J Therm Anal Calorim (2012) 109:807–815
DOI 10.1007/s10973-012-2294-6

DSC and IR as supporting tools for identification of methylxanthines in solid dosage forms of drugs

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Bretsznajder Special Chapter

Abstract The purpose of this study was to learn, to what extent the DSC, FT-IR and Raman spectroscopy can be useful for evaluation of the quality of medicinal products, the composition of marketed pharmaceutical preparations. As many as twenty-seven commonly available medicinal products were chosen, of which the majority constitute the so-called over-the-counter drugs. As basic active pharmaceutical ingredients (APIs), the products contained methylxanthines: theophylline, diprophylline and caffeine. The study has shown that in many cases the three techniques can be useful for the detection of APIs in medicinal products. To reach this aim, well-shaped endothermic DSC peaks, appearing due to melting of the active constituents and the so-called matching factors of the FT-IR and Raman spectra related to those of API used as standards, were utilised. The results obtained by Raman spectroscopy were satisfying to a limited extent only. On the other hand, the matching factors were twice less effective than the results obtained by the FT-IR technique. In the case of the preparations with caffeine, the matching factors were several times less effective than those obtained by FT-IR. An exception to this rule are only medicinal products containing acetylsalicylic acid, whose matching factors were several times higher than those of FT-IR, but because of their low concentrations, it was impossible to detect the ingredient in the sample.

Keywords DSC · FT-IR · Raman spectroscopy · Methylxanthines · Medicinal products · Quality assessment

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Introduction

The safety of pharmacotherapy depends in a high degree on the quality of applied medicinal products. Pharmaceutical law requires control of compatibility of active substances, excipients and medicinal products with established standards. This obliges the drug manufacturers to check the entity and quality of all raw materials used during the production of pharmaceutical preparations, as well as to provide the control of the manufacturing process of pharmaceuticals, and of the final products [1, 2]. Particular requirements are provided by pharmacopoeias and they can also be found in regulations of the International conference on harmonization of technical requirements for registration of pharmaceuticals for human use (ICH) issued to unify the requirements obligatory for new drugs introduced to pharmaceutical market [3].

For proper investigation of substances and medicinal products it is necessary to use appropriate techniques of instrumental analysis. Recent literature screening shows the high interest in the use of thermoanalytical techniques, differential scanning calorimetry (DSC) and thermogravimetry (TG) for this purpose [4–6], as well as of spectroscopic techniques, IR spectroscopy with Fourier transformation (FT-IR), near-infrared spectroscopy (NIR) and Raman spectroscopy [7–10]. The fact illustrating the increasing role of these methods in drug studies, is incorporation of a monograph concerning IR spectroscopy into Polish Pharmacopoeia VI [11], and of a monograph on thermal analysis, near-infrared spectroscopy and Raman spectroscopy into Polish Pharmacopoeia VII [12], the latter being a translation of a monograph from the 5th European Pharmacopoeia.

It should be mentioned that actually required systems for controlling drug quality manufactured by pharmaceutical

industry are mainly focused on the quality study of a final product, which is a pharmaceutical preparation. Recent tendencies are directed to modification of this rule towards controlling the manufacturing process as well, thus providing basis for elimination of the control of a final product [13, 14]. Due to this, in the pharmaceutical industry efforts have been undertaken to introduce the above mentioned thermoanalytical and spectroscopic techniques enabling fast obtaining of results from small samples taken from the production line, as controlling steps of the production process in the real time. These are called Process analytical technologies (PAT). The application of PAT increases the possibility of controlling the production process and leads to appropriate quality of the final product.

Taking all above into consideration, the aim of this study is to learn, to what extent the selected instrumental techniques, DSC, FT-IR and Raman spectroscopy, can be useful for evaluation of the quality of substances and medicinal products. In practice, realization of this aim will be based on evaluation of potential use of the instrumental techniques to confirm the presence of a particular drug substance in a medicinal product containing an active substance and several pharmaceutical excipients. The study will be extended over the analysis of pharmaceutical preparations manufactured by various firms, but containing the same active substance at different levels. In this way, it will be possible to estimate the impact of excipients, their type and quantity, on the presence of an active substance in a pharmaceutical preparation by DSC, FT-IR and Raman spectroscopy techniques.

Experimental

Materials

A total number of twenty-seven commercially available medicinal products was analysed. These are as follows (manufacturers given in parentheses): Afonilum SR 375 (Abbott, Ludwigshafen, Germany); Apap Extra (US Pharmacia, Wroclaw, Poland); Aspirin Activ (Bayer HealthCare, Leverkusen, Germany); Cefalgin (Polfa, Pabianice, Poland); Coffecorn mite, Coffecorn forte (Filofarm, Bydgoszcz, Poland); Coffepirine (Marcmed, Lublin, Poland); Diprophyllinum, Kofepar (Pliva, Krakow, Poland); Etopiryna (Polpharma, Starogard Gdanski, Poland); Euphyllin long 200, Euphyllin long 300, Euphyllin CR (Altana Pharma, Konstanz, Germany); Grippostad C (Stada Arzneimittel, Bad Vilbel, Germany); Koferina, Kopiryna (Medicofarma, Radom, Poland); Panadol Extra, Solpadeine capsules, Solpadeine tablets, Coldrex MaxGrip C (GlaxoSmithKline Consumer Healthcare, Warsaw, Poland); Saridon (Roche, Warsaw, Poland); Theoplus 100 mg, Theoplus 300 mg (Pierre Fabre Medicament, Boulogne, France); Theospirex retard 150 mg, Theospirex retard 300 mg (Biofarm, Poznan, Poland); Theovent 100, Theovent 300 (GlaxoSmithKline Pharmaceuticals, Poznan, Poland).

The active pharmaceutical ingredients used in this study were as follows: acetylsalicylic acid, ethenzamide (Polpharma, Starogard Gdanski, Poland); ascorbic acid (Merck, Darmstadt, Germany); caffeine, theophylline (Sigma-Aldrich, Steinheim, Product of China); chlorphenamine maleate, phenylephrine hydrochloride (Aflofarm, Lodz, Poland); codeine phosphate (Pharma Cosmetics, Krakow, Poland); diprophylline (Polfa, Krakow, Poland); paracetamol, propylphenazone (Polfa, Pabianice, Poland).

The excipients, used as auxiliary constituents of the analysed medicinal products, were: microcrystalline cellulose, croscarmellose sodium (FMC Bio Polymer, Brussels, Belgium); corn starch (Sigma-Aldrich, St. Louis, USA); ethylcellulose, potato starch, sucrose (MP Biomedicals LLC, Illkirch Cedex, France); hypromellose, methylcellulose (Shin-Etsu Chemical Co., Tokyo, Japan); lactose (PPH Galfarm, Krakow, Poland); magnesium stearate (Sinochem, Jiangsu, China); povidone, stearic acid (Fluka, Poznan, Poland); sodium lauryl sulfate (Merck, Darmstadt, Germany); sodium starch glycolate (JRS Pharma, Rosenberg, Germany). All substances were used without further purification.

Methods

DSC scans were carried out on a heat-flux DSC, model 822^e (Mettler Toledo, Schwerzenbach, Switzerland) instrument, with a liquid nitrogen cooling system (Dewar vessel) and a STAR^e software. Samples under study, approx. 4 mg in weight were accurately weighed ($\pm$0.01 mg) and encapsulated in a 40 µl flat-bottomed aluminium pans with crimped-on lids. Measurements were performed over the temperature range of 25–300 °C at a heating rate of 10 °C min^{-1} under nitrogen stream at a flux rate of 70 ml min^{-1}. Each experiment was repeated at least in triplicate.

The FT-IR spectra were recorded on a Nicolet 380 FT-IR spectrometer (Thermo Fisher Scientific, Madison, WI, USA), with a DTGS KBr detector and an OMNIC software. The analysed samples were prepared as KBr pellets with the aid of a hydraulic press (Specac, Orpington, UK). Each pellet was prepared from a 1-mg sample and 100 mg of spectroscopy-grade KBr (Merck, Darmstadt, Germany). Measurements in triplicate were performed in the 4,000–400 cm^{-1} spectral region with spectral resolution of 4 cm^{-1} Before each measurement, background spectra was taken with average 16 scans.

The Raman spectra were recorded on a DXR SmartRaman spectrometer (Thermo Fisher Scientific, Madison,

WI, USA). The spectrometer was equipped with a Raleigh filter, CCD detector and the OMNIC software. The measurements were run in triplicate over the 3,413–99 cm^{-1} spectral range with the use of a 15-mW DXR 780 nm laser with a slit width of 25 μm. Exposure time was 1 s (twice).

Results and discussion

In order to check the utility of DSC, FT-IR and Raman spectroscopy as potential techniques enabling identification of the constituents of the medicinal products, twenty-seven commonly available pharmaceutical preparations were chosen, the majority of which constitute the so-called over-the-counter (OTC) drugs. As basic active pharmaceutical ingredients (APIs), the preparations contained three methylxanthines: theophylline (Afonilum SR 375, Euphyllin CR, Euphyllin long 200, Euphyllin long 300, Theoplus 100 mg, Theoplus 300 mg, Theospirex retard 150 mg, Theospirex retard 300 mg, Theovent 100, Theovent 300), diprophylline (Diprophyllinum) and caffeine (Apap Extra, Aspirin Activ, Cefalgin, Coffecorn forte, Coffecorn mite, Coffepirine, Coldrex MaxGrip C, Etopiryna, Grippostad C, Kofepar, Koferina, Kopiryna, Panadol Extra, Saridon, Solpadeine capsules, Solpadeine tablets). Besides caffeine, the preparations contained also large amounts of paracetamol, 200–500 mg (Apap Extra, Cefalgin, Coldrex MaxGrip C, Grippostad C, Kofepar, Panadol Extra, Saridon, Solpadeine capsules, Solpadeine tablets); acetylsalicylic acid, 300–500 mg (Aspirin Activ, Coffepirine, Etopiryna, Koferina, Kopiryna); propylphenazone, 150 mg (Cefalgin, Saridon); ascorbic acid, 150 mg (Coldrex MaxGrip C, Grippostad C); ethenzamide, 100 mg (Etopiryna, Koferina); and smaller amounts of codeine phosphate, phenylephrine hydrochloride and chlorphenamine maleate. The analysed products are mainly used as analgesics, antipyretics and anti-inflammatory medicines. Moreover, those containing theophylline and diprophylline have also been used as anti-asthmatics.

The analysed products were in solid drug forms such as dragées, classical tablets (coated and uncoated), tablets with prolonged action, and capsules filled with powders, pellets or granulates with modified (prolonged) release. All the preparations studied contained besides the active substances also up to 11 excipients, ensuring optimal activity of the medicinal products from the point of view of pharmacotherapy. During classical chemical analysis, the excipient is separated from APIs, which is a time- and work-consuming process. Perhaps the application of DSC, FT-IR, and Raman spectroscopy could allow for elimination of this step of analytical procedure.

Drug manufacturers generally provide information on the type of excipients used during production of a given medicinal product; however, there are cases where the information is given only for main excipients, and there is lack of the most important knowledge on the proportions these excipients are present in the medicinal product. Also, while interpreting the results obtained by DSC, FT-IR and Raman spectroscopy techniques it is worth consideration the fact that these substances influence the shape of the DSC curves as well as the IR and Raman spectra.

DSC

The results of DSC analyses of the APIs are shown in Table 1 and presented graphically in Fig. 1. The analysis of these data indicates that the mean temperature values of the DSC peaks due to melting of the drug substances are

Table 1 Active pharmaceutical ingredients contained in the studied medicinal products

No.	Active pharmaceutical ingredients	Melting point/°C		Transition heat/J g^{-1}
		[2]	DSC data	
1	Theophylline	270–274	271.20	−161.83
2	Diprophylline	160–165	158.24	−130.37
3	Caffeine	234–239	235.08	−110.10
4	Paracetamol	168–172	168.64	−183.99
5	Acetylsalicylic acid	Ca 143	142.75	−164.17
6	Ascorbic acid	Ca 190 °C with decomposition	191.61	−244.18
7	Propylphenazone	102–106	103.43	−107.39
8	Ethenzamide	Not found	130.68	−192.61
9	Codeine phosphate	227.5	182.23	−17.50
			243.40	−151.63
10	Phenylephrine hydrochloride	Ca 143	143.12	−155.58
11	Chlorphenamine maleate	130–135	135.76	−121.95

consistent with those reported by Polish Pharmacopoeia VIII [2], which confirms high purity of these compounds. The exceptions are diprophylline and codeine phosphate, for which small differences have been noticed between the DSC data and the literature values. Consequently, strong and narrow endothermic peaks of APIs would constitute a basic criterion for identification of these substances in the pharmaceutical preparations.

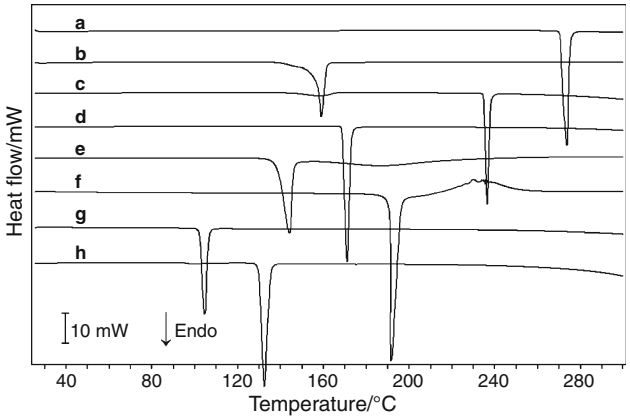

Fig. 1 DSC scans of active pharmaceutical ingredients (*a*) theophylline, (*b*) diprophylline, (*c*) caffeine, (*d*) paracetamol, (*e*) acetylsalicylic acid, (*f*) ascorbic acid, (*g*) propylphenazone and (*h*) ethenzamide

However, preliminary evaluation of the DSC curves of the 27 medicinal products has shown a high impact of the API contents recalculated into the mass unit of a dragée, tablet or capsule, on the possibility of identification of a constituent in a preparation. The data in Table 2 calculated on the basis of the dose of a drug substance and the mean tablet mass designed for 10 units of dragées, tablets or capsules, have shown that particular medicinal products can be significantly differentiated by the percentage contents of an active pharmaceutical ingredient. Among the three methylxanthines studied, the preparations contained higher amounts of theophylline (42.51–94.45% of the tablet mass), next of diprophylline (56.17%), and the lowest amounts of caffeine, which was present in the range of 3.36–10.00% of the tablet mass.

Table 2 Results of the investigation of methylxanthines by DSC, FT-IR and Raman techniques

No.	Medicinal products	Dose of API/g	Average tablet mass/g	Content of API in tablets/%	Melting point DSC/°C	Transition heat DSC/J g^{-1}	Matching factor FT-IR/%	Matching factor Raman/%
1	Theoplus 100	0.100	0.163	61.34	262.23	−48.83	98.51	44.81
2	Theoplus 300	0.300	0.510	58.82	261.25	−42.23	98.68	46.76
3	Theovent 100	0.100	0.181	55.24	264.12	−58.76	98.15	44.55
4	Theovent 300	0.300	0.500	60.00	270.60	−77.82	98.11	44.70
5	Theospirex retard 150	0.150	0.180	83.33	270.09	−116.36	98.59	42.65
6	Theospirex retard 300	0.300	0.359	83.56	269.80	−121.23	98.79	47.13
7	Euphyllin long 200	0.200	0.268	74.62	270.18	−94.29	89.60	55.92
8	Euphyllin long 300	0.300	0.404	74.25	272.17	−103.67	98.20	52.76
9	Euphyllin CR	0.250	0.588	42.51	143.58	−63.08	92.34	51.18
10	Afonilum SR 375	0.375	0.397	94.45	270.81	−152.34	99.01	68.35
11	Diprophyllinum	0.200	0.356	56.17	162.75	−81.24	60.80	62.00
12	Apap Extra	0.065	0.650	10.00	163.12	−123.92	9.46	9.79
13	Kofepar	0.065	0.696	9.33	163.83	−131.77	13.04	3.69
14	Panadol Extra	0.065	0.686	9.47	163.91	−122.51	14.20	3.13
15	Cefalgin	0.050	0.695	7.19	82.30	−46.75	18.07	5.38
16	Saridon	0.050	0.651	6.68	139.14	−21.74	16.87	3.08
17	Solpadeine, capsules	0.030	0.625	4.80	167.59	−136.67	15.87	2.11
18	Solpadeine, tablets	0.030	0.651	4.60	166.87	−123.49	7.44	4.95
19	Grippostad C	0.025	0.395	6.32	152.58	−105.67	12.64	2.57
20	Coldrex MaxGrip C	0.025	0.743	3.36	162.79	−102.32	5.02	2.88
21	Kopiryna	0.050	0.541	9.24	132.73	−121.50	2.69	9.53
22	Coffepirine	0.050	0.548	9.12	124.97	−135.45	1.03	8.63
23	Aspirin Activ	0.050	0.647	7.72	134.07	−122.61	0.37	8.31
24	Etopiryna	0.050	0.594	8.41	76.95	−83.68	6.42	11.95
25	Koferina	0.050	0.542	9.22	81.04	−56.35	2.41	11.44
26	Coffecorn forte	0.100	0.296	33.78	225.55	−37.40	78.29	15.07
27	Coffecorn mite	0.025	0.401	6.23	220.75	−67.08	42.60	18.24

Interpretation of the DSC curves of the theophylline tablets has shown that the average temperature of the DSC peak characteristic of the melting of this methylxanthine falls within the range of 269.80–272.17 °C. The DSC peak of theophylline overlaps endothermic peaks assigned to the melting of this drug substance present at very high amounts (74.62–94.45%) in the tablets of Afonilum SR 375, Theospirex retard 300 mg, and Euphyllin long 200. This confirms the presence of theophylline in the sample.

There are interesting DSC curves of four preparations (Fig. 2), exhibiting additional peaks originating from the excipients present. Probably they are associated with lactose present in high amounts. These curves have quite different shapes, especially when compared with those of other preparations containing theophylline. However, due to high concentration of the excipient they are very similar to each other. The DSC peak assigned to the melting of theophylline is seen in the preparations Theoplus 300, Theoplus 100 and Theovent 100, and it is shifted towards lower temperature by about 10 °C, and emerging in the range of 261.25–264.12 °C.

A special case among these preparations are the tablets of Euphyllin CR. Irrespective of the fact that they have 42.51% of theophylline, there is no peak in the DSC curve confirming the presence of the drug substance. At the same time, a signal appearing around about 200 °C, is characterised by a stronger intensity than that of the corresponding peaks of other preparations. This can be a proof of its shift towards the lower values and of overlapping the DSC peak of lactose.

Inspection of the DSC curve of the Diprophyllinum preparation shows that an endothermic peak emerging over the temperature range corresponding to the melting of diprohylline (160–165 °C), can be used for its identification. There is also an additional signal at 147.73 °C, appearing in the DSC curve of this preparation, which results probably from the presence of one of the excipients.

In contrast to the two above-mentioned methylxanthines, the presence of caffeine was not confirmed in any of the 16 medicinal products containing this substance. Over the characteristic for the melting of this compound temperature range of 234–239 °C, there were no endothermic DSC peaks, as seen also in Fig. 3. The reason for this can be a too low content of caffeine in these tablets in relation to their mass or the impact of other constituents, drug substances or excipients, on the shape of the DSC curves. It should also be mentioned that part of the medicinal products contain besides caffeine, also paracetamol in the amount of 35.97–80.00% of the tablet mass, acetylsalicylic acid (50.51–82.12%), ascorbic acid (4.04–37.94%), propylphenazone (21.58–23.04%), ethenzamide (16.84–18.45%), and small amounts of codeine phosphate, phenylephrine hydrochloride and chlorphenamine maleate (0.63–1.28%). For this reason, in other preparations containing caffeine it was much easier to identify peaks due to the melting of these substances than those of methylxanthine.

The substance, which occurs in high amounts in the analysed medicinal products, is paracetamol. The peak due to its melting appears over the range of 152.58–167.59 °C. These values are lower than the literature ones (Table 2). This can be due to interaction with other constituents of these preparations or eutectic formation between caffeine and paracetamol [15, 16]. It has also been demonstrated that all the preparations having not only caffeine, but also paracetamol, are characterised by specific shape of the DSC curves, as depicted by curves c–f in Fig. 3.

The Cefalgin and Saridon tablets contain identical concentration of APIs (caffeine, paracetamol, and propylphenazone), but they are produced by different manufacturers, and due to this they differ by the kind and the contents of the

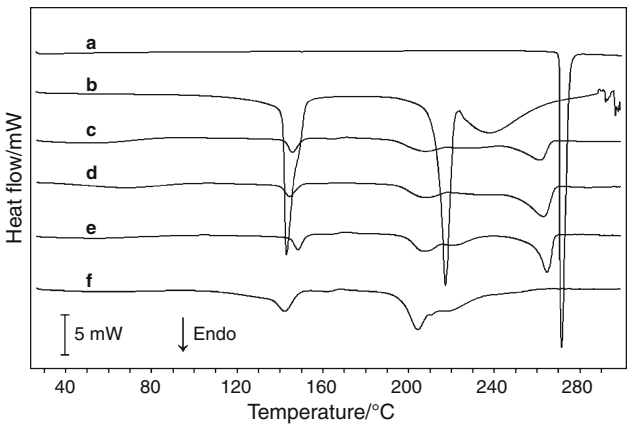

Fig. 2 DSC scans of medicinal products containing lactose (*a*) theophylline, (*b*) lactose, (*c*) Theoplus 300 mg, (*d*) Theoplus 100 mg, (*e*) Theovent 100 and (*f*) Euphyllin CR

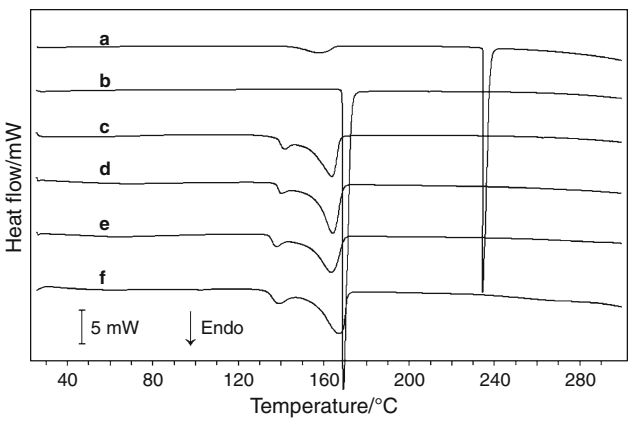

Fig. 3 DSC scans of medicinal products containing caffeine and paracetamol (*a*) caffeine, (*b*) paracetamol, (*c*) Apap Extra, (*d*) Kofepar, (*e*) Panadol Extra and (*f*) Solpadeine (capsules)

excipients. Their DSC curves in Fig. 4 show broadened peaks of a low intensity which are difficult for interpretation. There is no clear signal originating from paracetamol, which is present in these preparations as a dominating constituent (in 35.97–80.00%). However, there is no endothermic peak assignable to the melting of propylphenazone. Probably, the three drug substances and the excipients cause overlapping of these thermal effects associated with the transitions occurring in the constituents, which makes impossible identification of characteristic DSC peaks of the melting of the APIs. On the other hand, the literature data suggests eutectic formation in the mixtures of paracetamol and caffeine, and of paracetamol and propylphenazone [16].

FT-IR spectroscopy

The FT-IR spectra offer valuable information enabling identification of the bulk chemicals. For this reason, the FT-IR spectra of methylxanthines were registered, and based on the literature data, characteristic peaks in the spectra were correlated with the group frequencies corresponding to particular types of vibrations occurring in a molecule of the studied compound [17, 18]. Taking into consideration the complex chemical composition of the medicinal products, it is reasonable to expect that their spectra will be the consequences of the effects of interaction of the infrared radiation with all constituents of a dragée, tablet or capsule. Based on this, it was decided to resign from correlation of particular absorption bands in the FT-IR spectra of medicinal products to specific groups of methylxanthine, but instead the so-called matching factor was designed, which determines in per-cents the degree of matching of the spectrum of a medicinal preparation to that of methylxanthine. This was the basis of confirmation of the API's presence in the analysed medicinal product.

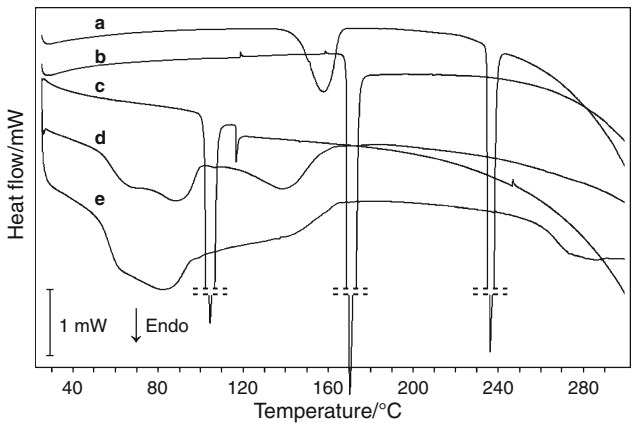

Fig. 4 DSC scans of medicinal products containing caffeine, paracetamol and propylphenazone (*a*) caffeine, (*b*) paracetamol, (*c*) propylphenazone, (*d*) Saridon and (*e*) Cefalgin

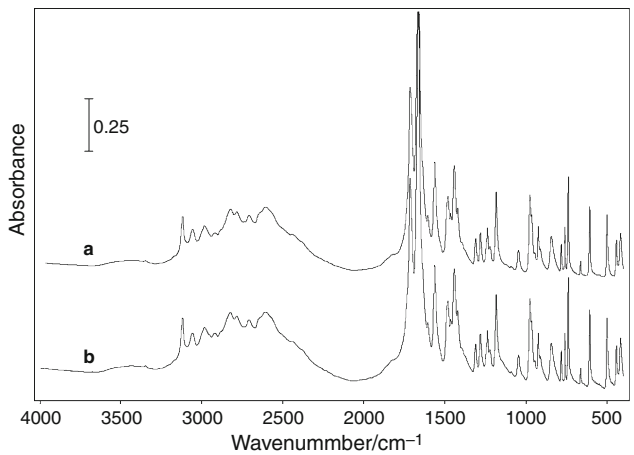

Fig. 5 FT-IR spectra of (*a*) theophylline and (*b*) Theospirex retard 300 mg

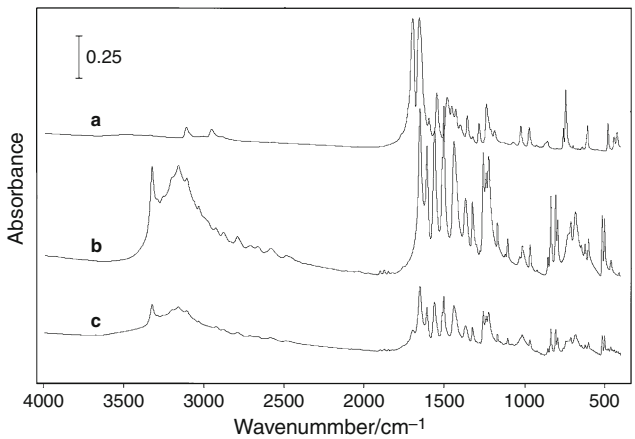

Fig. 6 FT-IR spectra of (*a*) caffeine, (*b*) paracetamol and (*c*) Panadol Extra

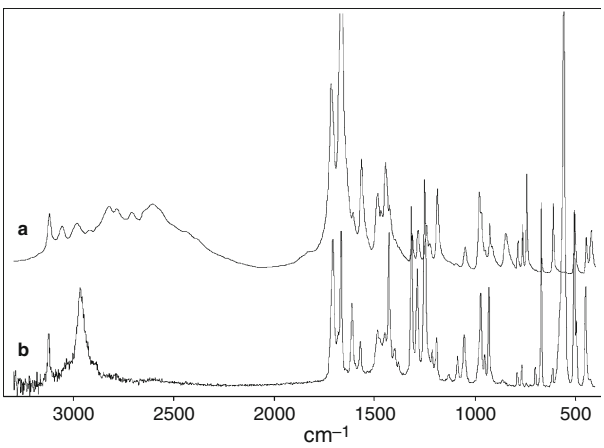

Fig. 7 IR and Raman spectra of theophylline in bulk (*a*) FT-IR and (*b*) Raman

Computer-generated values of the matching factors for all the pharmaceutical preparations studied are compiled in Table 2. An analysis of these data has shown that for theophylline, which is the dominant constituent in the preparations, the matching coefficients of particular FT-IR spectra of the medicinal products with this methylxanthine to the spectrum of the theophylline fall within the range of 89.60–99.01%. This indicates that the spectra of these preparations nearly overlap that of theophylline, as illustrated in Fig. 5. The highest similarity to the spectrum of theophylline shows the tablets of Afonilum SR 375. It is worth emphasizing that in spite of the relative low contents of this methylxanthine in the tablets of Theoplus and Theovent (55.24–61.34%), the matching factors of the spectra for these preparations to the FT-IR spectrum of theophylline exceed 98%.

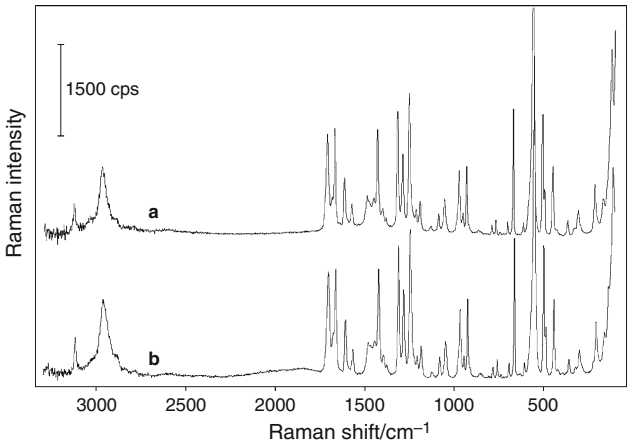

Fig. 8 Raman spectra of (*a*) theophylline and (*b*) Theospirex retard 300 mg

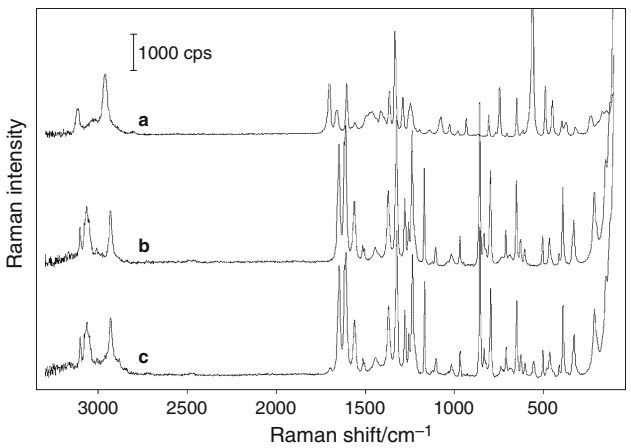

Fig. 9 Raman spectra of (*a*) caffeine, (*b*) paracetamol and (c) Panadol Extra

The matching factor for the FT-IR spectrum of the Diprophyllinum tablets in relation to diprophylline as the reference substance is equal to 60.80% with the concentration of the active substance in the preparation of 56.17%. The spectra of the tablets with this methylxanthine to a large extent overlap the API's spectrum, while the small differences in the shape of both spectra probably result from the influence of excipients present in the medicinal product.

In the tablets of caffeine its contents is too low to generate any similarity with the FT-IR spectra of these preparations to those of the API's. The spectra of the preparations with caffeine significantly differ from those of methylxanthine used for comparison, and the matching factors are very low falling in the range of 0.37–18.07%. An exception provide the dragées of Coffecorn forte containing 33.78% of caffeine with a matching factor higher than in other cases, equal to 78.29%. This suggests that some of the excipients present in this preparation are inactive for IR radiation.

Except for caffeine, the analysed preparations contain also higher quantity the other drug substances, which influence the shape of their spectra. Since in nine preparations with paracetamol and in five preparations with acetylsalicylic acid, the active ingredients are present at

Table 3 Matching factor of medicinal products with caffeine and paracetamol to the FT-IR and Raman spectra of paracetamol

No.	Medicinal products	Content of paracetamol in tablets/%	Matching factor FT-IR/%	Matching factor Raman/%
1	Apap Extra	76.92	71.10	23.62
2	Kofepar	71.84	67.43	22.63
3	Panadol Extra	72.89	68.53	22.44
4	Cefalgin	35.97	63.95	19.84
5	Saridon	38.40	64.71	19.28
6	Solpadeine, capsules	80.00	68.43	21.63
7	Solpadeine, tablets	76.80	67.66	22.57
8	Grippostad C	50.63	69.43	24.29
9	Coldrex MaxGrip C	67.29	67.26	24.50

Table 4 Matching factor of medicinal products with caffeine and acetylsalicylic acid to the FT-IR and Raman spectra of acetylsalicylic acid

No.	Medicinal products	Content of acetylsalicylic acid in tablets/%	Matching factor FT-IR/%	Matching factor Raman/%
1	Kopiryna	73.94	99.41	62.75
2	Coffepirine	82.12	99.48	73.57
3	Aspirin Activ	77.28	99.54	80.15
4	Etopiryna	50.51	92.53	67.21
5	Koferina	55.35	95.21	64.60

high concentrations, the matching factors were determined for all preparations with these APIs. The results presented in Tables 3 and 4 and shown in Fig. 6 reflect high matching factors for these medicines. Consequently, they can be useful for identification of paracetamol and acetylsalicylic acid in these medicinal products.

Raman spectroscopy

Both FT-IR and Raman spectroscopy are complementary techniques. A spectral band corresponding to the particular type of vibration in a molecule in Raman spectrum will be hardly visible or it will not be visible in the FT-IR spectrum, and vice versa. Combining these techniques allows for a detailed and reliable analysis of a sample. For instance, as shown in Fig. 7, overlapping the FT-IR spectrum with Raman spectrum of diprophylline indicates that both spectra are not identical, and the signals appear at different wave numbers, depending on the method applied for recording of the spectrum. The signals corresponding to the same type of vibration either are shifted relative to each other and differ in their intensity, or they have no reflection in the spectrum obtained by the other technique. It depends mainly on the type of bonds in a molecule, which are assigned to particular bands of the spectrum.

The high concentration of theophylline in the analysed preparations is reflected in the matching factors for these medicinal products, which fall within the range of 42.65–68.35%. This indicates the relatively high compatibility of the Raman spectra of medicinal products with the theophylline spectrum as is illustrated in Fig. 8. However, when comparing the data of Table 2, the matching factors obtained by the of FT-IR and Raman spectroscopy, it can be concluded that in the case of the Raman spectroscopy they are rather less satisfying.

The matching factor of the Raman spectrum of the Diprophyllinum tablets in relation to those of diprophylline equals to 62.00%, which is comparable to the data obtained by the FT-IR technique. However, similarly as in the case of DSC and FT-IR analyses, the low concentration of caffeine in the preparations is reflected by low matching factors of the Raman spectra of the preparations in relation to the methylxanthine's spectrum (2.11–18.24%). The analysis of the Raman spectra shown in Fig. 9 and the data compiled in Table 3 indicate that not satisfying results were obtained when matching the Raman spectra of medicinal products to the spectrum of paracetamol as API. The matching factors for these preparations fall in the range of 19.28–24.63%, which have no practical meaning from the point of identification of a constituent in a commercially available pharmaceutical preparation. An opposite conclusion can be drawn from the data compiled in Table 4 for acetylsalicylic acid.

Conclusions

The performed study on 27 commercial pharmaceutical preparations has shown that in many cases the DSC, FT-IR and Raman spectroscopy techniques can be useful for detection of the presence of active pharmaceutical ingredients in medicinal products. To achieve the purpose of this study, well-shaped endothermic DSC peaks, appearing due to melting of the active constituent and the so-called matching factors of the FT-IR and Raman spectra to the spectrum of API used as a standard, were utilised.

The factor, which decided the utility of these techniques for identification of an active substance, is its contents in the preparations. In practice, with the exception of the DSC analysis of Euphyllin CR tablets, in all medicinal products with theophylline and diprophylline it was possible to detect API using of DSC, FT-IR and Raman spectroscopy. The identification of caffeine was not possible due to its low concentration, in the range of several per-cent. However, an attempt to identify two other APIs, paracetamol and acetylsalicylic acid, occurring in the preparations with caffeine could be done by using DSC and FT-IR, for which the matching factors were satisfying. It must also be stated that identification of the remaining APIs in the samples, was impossible.

When comparing the three studied techniques, it can be concluded that the results obtained by Raman spectroscopy were satisfying to a small extent only, but the way of performing the measurements using this technique was

quite simple and did not require any preliminary preparation of a sample for analysis. However, the matching factors were twice lower as compared to those obtained after application of the FT-IR technique. In the case of the preparations with caffeine, the matching factors are several times lower than those obtained by FT-IR. The exceptions to this rule are only medicinal products containing acetylsalicylic acid, for which their matching factors appeared to be several times larger than those for FT-IR, but because of their low concentrations, it was impossible to detect the constituent in the sample.

References

1. European Pharmacopoeia 5. Strasbourg: Council of Europe; 2005.
2. Polish Pharmacopoeia VIII. Warsaw: Ministry of Health; 2008.
3. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH. http://www.ich.org/home.htlm. Accessed 16 Sep 2011.
4. Macedo RO, Do Nascimento TG. Quality control of thiabendazole pre-formulation and tablets by TG and DSC coupled to the photovisual system. Thermochim Acta. 2002;392–393:85–92.
5. Gomes APB, Correia LP, da Silva Simoes MO, Macedo RO. Development of thermogravimetric method for quantitative determination of ketoconazole. J Therm Anal Calorim. 2008;91:317–21.
6. Lappalainen M, Karppinen M. Techniques of differential scanning calorimetry for quantification of low contents of amorphous phases. J Therm Anal Calorim. 2010;102:171–80.
7. Sasic S, Ozaki Y, editors. Raman, infrared and near-infrared chemical imaging. Hoboken: Wiley; 2010.
8. Vergote GJ, Vervaet Ch, Remon JP, Haemers T, Verpoort F. Near-infrared FT-Raman spectroscopy as a rapid analytical tool for the determination of diltiazem hydrochloride in tablets. Eur J Pharm Sci. 2002;16:63–7.
9. Roggo Y, Degardin K, Margot P. Identification of pharmaceutical tablets by Raman spectroscopy and chemometrics. Talanta. 2010;81:988–95.
10. Tanase C, Odochian L, Apostolescu N, Pui A. TG-FTIR analysis applied to the study of thermal behaviour of some edible mushrooms. J Therm Anal Calorim. 2011;103:1079–85.
11. Polish Pharmacopoeia VI. Vol. 1. Warsaw: Ministry of Health; 2002.
12. Polish Pharmacopoeia VII. Vol. 1. Warsaw: Ministry of Health; 2006.
13. Vajna B, Farkas I, Szabo A, Zsigmond Z, Marosi G. Raman microscopic evaluation of technology dependent structural differences in tablet containing imipramine model drug. J Pharm Biomed Anal. 2010;51:30–8.
14. Hausman DS, Cambron RTh, Sakr A. Application of on-line Raman spectroscopy for characterizing relationships between drug hydration state and tablet physical stability. Int J Pharm. 2005;299:19–33.
15. Tkachenko ML, Zhnyakina LE, Kosmynin AS. Physicochemical investigation of paracetamol—caffeine solid mixtures. Pharm Chem J. 2003;37:430–2.
16. Bi M, Hwang S-J, Morris KR. Mechanism of eutectic formation upon compaction and its effects on tablet properties. Thermochim Acta. 2003;404:213–26.
17. Szczepaniak W. Instrumental methods in chemical analysis. 5th ed. Warsaw: WNT; 2008 (in Polish).
18. Silverstein RM, Webster FX, Kiemle DJ. Spectroscopic methods for identification of organic compounds. 2nd ed. Warsaw: PWN; 2007 (in Polish).