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QUANTIFICATION OF ACTIVE PHARMACEUTICAL INGREDIENTS IN COMMERCIALLY AVAILABLE POLY PHARMACEUTICAL TABLETS BY MEANS OF DSC

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Abstract: Differential scanning calorimetry is the first line technique indispensable for industrial quality control laboratories and, next to many routine applications, could be used in quantitative assays. For this purpose, a relationship between the signal value of analyte (enthalpy change ΔH) and its concentration in the matrix is used. However, there are several limitations of its application, concerning solid state interactions between APIs, other APIs and/or coexisting excipients. With respect to their physical properties, it is known that amorphization state and/or permanent particle deformation can produce relatively large areas of interparticle contact and thus high particle-particle bonding forces. Finally, it may affect the DSC quantitative measurements. The problem was shown using commercially available, different poly component tablets containing ibuprofen in the presence of pseudoephedrine hydrochloride or paracetamol and coexisting excipients.

Keywords: differential scanning calorimetry, DSC, paracetamol, ibuprofen

Solid pharmaceutical preparations can be considered as heterogeneous systems consisting of one or more active pharmaceutical ingredients (APIs) and several excipients. In such blends physical interactions are quite common. Some of them are deliberately invoked to produce a certain effect, for example, to aid processing, modify drug dissolution (oral modified release) or distribution in the body (parenteral modified release drugs). Other interactions in solid phase are unintended, usually causing the problems. The essence of physical interactions is that interacting molecules are not modified in any way. In the other words: new molecules, in chemical meaning, are not created.

Most poly active component drugs, currently available on the market, belong to the group of nonsteroidal anti-inflammatory drugs (NSAIDs); a drug class also comprising combinations of antipyretics and/or analgesics (e.g., ibuprofen (IBU)) together with APIs from other pharmacological groups as antiallergics, sympathomimetics and antitussives. The physical interactions between active ingredients are rare. Considering ibuprofen for example, only few reports concerning incompatibilities with ketoprofen (1) and menthol (2, 3) were found. Much more publications are dealing with excipients. Magnesium stearate is commonly used in pharmaceutical manufacturing as a "flow agent" which helps ensure that the pressing process is smooth and the ingredients stay blended in the proper proportions. It was demonstrated (4) that the particles of magnesium stearate appear to adhere to the surfaces of the other components on mixing. All stearates were found to form simple eutectics with ibuprofen (5-9). Some interaction were also observed with polyvinylpyrrolidone (PVP) and calcium phosphate (8, 9). For other drugs new associative structures (8, 10) were reported when a surfactant, sodium dodecylsulfate, was added as well as interactions of lactose with drugs containing amino groups (11).

In our previous paper (12) we have discussed the use of DSC method in quantification of APIs in commercially available, one-component tablets. For this purpose, a relationship between the signal value of analyte (enthalpy change ΔH) and its concentration in the matrix was exploited. The scale of the problem was showed using commercially available different tablets of paracetamol (PAR). In the course of the studies it was shown that composition of the mixtures (in a meaning of used excipients), the way

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of their preparation (as non-micronized mixture, micronized mixture or pure raw analyte) and the weights of samples alter the final results of such measurements leading to different contents of PAR. It was also shown that there is no apparent direction of the observed differences, suggesting that the use of the DSC method for quantification of APIs in commercially available tablets should be assessed individually and requires appropriate empirical preliminary studies in each case.

The objective of the present study was to estimate the influence of interactions between two active agents, presented in the tablet, on their quantification. For that reason six commercially available tablets with IBU different in weight, type of excipients and composition, were determined by DSC method. Two calibration curves plotted from mixtures containing micronized and non-micronized starch (Starch 1500) with an increasing amounts of IBU were used. The micronization process was applied to modify the crystalline nature of mixtures under study. In this way the complex technological processes of their manufacturing were emulated. Appropriate calibration curves were further applied to calculate the final experimental contents of IBU (O_{DSC}) in the tablets and were compared with those declared (D) by the manufacturer using equation $A(\%) = [(O_{DSC}\text{-}D)/D]\times 100$.

EXPERIMENTAL

Materials

Ibuprofen powder – pure polymorphic form I with estimated melting temperature at $T_{onset} = 76.1^{o}C$ was obtained from Hubei Granules-Biocause Pharmaceutical Co., Ltd., China (LOT 400-0709065M). The corn starch Starch 1500 was from Colcorcon Ltd. UK (Lot 500075).

Ibuprofen is a low potency, high dose drug. Typical dose of IBU in one component drugs in Poland is 400 mg, however in two component drugs the dose does not exceed 200 mg.

The following two components tablets containing 200 mg of IBU per tablet and PAR were used: Metafen (325 mg of PAR) manufactured by Polpharma, Poland (LOT 016582), the mean weight of tablet 699.20 mg, composed of povidone, pregelatinized starch, microcrystalline cellulose, magnesium stearate; Nurofen Ultima (500 mg of PAR) manufactured by Reckitt Benckiser, Poland (LOT AB070), the mean weight of tablet 870.38 mg, composed of croscarmellose sodium, microcrystalline cellulose, anhydrous colloidal silica, magnesium stearate, stearic acid.

The following two components tablets containing 200 mg of IBU and 30 mg of pseudoephedrine hydrochloride were used: Acatar Zatoki manufactured by US Pharmacia Ltd., Poland (LOT U1107221), the mean weight of tablet 530.36 mg, composed of cellulose (Elcema P-100 and Elcema F-150), corn starch, pregelatinized starch, Guar gum, talc, croscarmellose sodium, crospovidone, colloidal silica, hydrogenated vegetable oil; Ibuprom Zatoki manufactured by US Pharmacia Ltd., Poland (LOT U1205401), the mean weight of tablet 544.08 mg, composed of cellulose (Elcema P-100 and Elcema F-150), corn starch, pregelatinized starch, Guar gum, talc, croscarmellose sodium, crospovidone, colloidal silica, hydrogenated vegetable oil; Modafen manufactured by Zentiva, Czech Republic (LOT 3230912), the mean weight of tablet 575.18 mg, composed of microcrystalline cellulose, lactose monohydrate, corn starch, pregelatinized starch, sodium lauryl sulfate, povidone 25, stearic acid, sodium carboxymethyl starch, anhydrous colloidal silica; Nurofen Zatoki manufactured by Reckitt Benckiser, Poland (LOT AH006), the mean weight of tablet 374.22 mg, composed of calcium phosphate, microcrystalline cellulose, povidone, croscarmellose sodium, magnesium stearate.

Sample preparation

Twenty tablets of each medical product under the study were individually weighed and ground in an agate mortar and pestle into fine powder.

The set of IBU mixtures with starch Starch 1500 (1000 mg each) at concentrations from 10% to 60% (corresponding to 0.50-3.0 mg of drug in the sample) were separately prepared, gently homogenized and divided. One part (500 mg) of received physical (non-micronized) mixture was ready for further experiments; the other was micronized in an agate mortar and pestle with some drops of methanol for 10 min.

Method

The principle of the method is a relationship between the signal value of IBU (enthalpy change ΔH) and its concentration in the matrix. For this purpose both of micronized and non-micronized sets of mixtures were measured by means of DSC. In this way two calibration curves with an increasing amounts of IBU were plotted. Appropriate calibration curves were further applied to calculate the final experimental contents of IBU (O_{DSC}) in the tablets and were compared with those declared (D) by the manufacturer using equation $A(\%) = [(O_{DSC}\text{-}D)/D]\times 100$.

Thermal analysis

The DSC measurements were performed in nitrogen atmosphere with a flow rate of 50 mL/min using EXSTAR DSC 7020 apparatus (SII Nano-Technology Inc.) calibrated with indium and tin, and equipped with DSC7020 electric cooling unit.

The samples of micronized and non-micronized mixtures of about 5.0 mg were accurately weighed in aluminium pans and sealed. The pans were equilibrated at 30°C for 15 min and thereafter the melting behavior was analyzed at heating rate of 10°C/min. All measurements were performed at least three times and averaged. The tablets were examined at least six times.

Validation of DSC method

The method was validated for specificity, linearity, precision, limit of detection, and limit of quantification as well (13). The calculations were made using statistical program STATISTICA v.10.

Specificity

Specificity of the method was assessed by comparing the DSC heating traces of raw IBU, raw excipients and obtained both micronized and non-micronized mixtures. The T_{onset}, T_{max} temperatures, and presence of new chemical individuals were taken into account.

Linearity

The calibration plots were constructed by analysis of seven (n = 7) different mixtures (both micronized and non-micronized), corresponding to content of IBU ranging from 0.50 mg to 3.00 mg. Determination of linearity was made *via* three replicates and assessed as

Table 1. Effects of mixture composition on the area of melting peak ΔH (averaged from three determinations). The differences between ΔH of IBU of non micronized and micronized mixtures (B) as a function of IBU concentration in the sample shows linear dependence: y = 41.27-19.98×X, r = 0.9976, r^2 = 0.9952.

Composition of the mixture	Content of IBU in the sample [mg]	ΔH of IBU* [mJ/mg]		B** [mJ/mg]
		Micronized mixtures	Non micronized mixtures	
IBU/starch	0.50	53.38	83.00	29.62
	1.00	130.50	153.00	22.50
	1.50	208.50	219.75	11.25
	1.75	241.5	249.08	7.58
	2.00	293.33	295.50	2.17
	2.50	370.00	360.00	-10.00
	3.00	435.00	416.00	-19.00

*ΔH was recalculated to the content of IBU in the sample; **differences between ΔH of non micronized and micronized mixtures

Table 2. Data validation of DSC method.

Validation parameters		Micronized mixtures	Non-micronized mixtures
Specificity		Specific	Specific
Slope ($a \pm S_a$)		154.94 ± 2.74	134.96 ± 2.68
Intercept ($b \pm S_b$)		-23.68 ± 5.27	17.59 ± 5.15
r		0.9992	0.9990
r^2		0.9984	0.9980
LOD [mg]		0.12	0.14
LOQ [mg]		0.37	0.41
Linearity [mg]		0.37 – 3.00	0.41 – 4.41
Precision (n = 6)	%RSD	1.95	2.07

Regression equation y = ax + b; S_a - standard deviation of slope; S_b - standard deviation of intercept.

a relationship between the area of DSC melting peak ΔH and content of IBU in mg per sample.

Linearity was reported as the linear calibration equations (y = ax + b) and the correlation coefficients r and r^2.

Limits of detection (LOD) and quantification (LOQ)

LOD and LOQ were calculated from the calibration curve slope (a) and the slope standard estimation error (S_e), using formulas: LOD = 3.3 × S_e/a and LOQ = 10 × S_e/a.

Precision

The repeatability of the method was determined by analysis of six (n = 6) replicates of samples from individual weighing. The study was done for one concentration level of 2.00 mg of IBU in the sample, and the results were expressed as the relative standard deviation (%RSD).

RESULTS AND DISCUSSION

The determined enthalpy changes ΔH of mixtures with increasing IBU contents (0.5 mg to 3.00 mg per sample giving the concentration from 10 to 60%) and starch, both micronized and non-micronized, are presented in Table 1.

One can see the differences between ΔH values. Within the range from 0.50 mg to 2.00 mg of IBU per sample (10 to 40%) the ΔH values of micronized mixtures were distinctly lower than corresponding non-micronized mixtures. For contents of IBU over 2.00 mg per sample (40%) the relationship was reversed and the micronized mixtures enthalpies were distinctly higher. Interestingly, the ΔH differences (labeled as B in Table 1) and concentration of IBU are linearly correlated with strong regression coefficient r = 0.9976 and r^2 = 0.9952 (y = 41.27 - 19.98 × X). At this point we can't comment this phenomenon.

In order to plot appropriate calibration curves, the obtained ΔH enthalpies of micronized as well as non-micronized mixtures as a function of the increasing weights of IBU in a constant sample weight (5.0 mg) were used. The validation data were summarized in Table 2. It thus demonstrated that developed method meets the acceptance criteria in the scope of specificity, sensitivity, linearity and precision.

Table 3 shows the melting onset and maximum temperatures (T_{onset}, T_{max}) of ibuprofen in tablets under study. With two exceptions (Metafen and Nurofen Ultima), the temperatures are comparable to pure raw IBU and ranging from 75.9°C to 76.2°C and 76.0°C to 76.2°C for T_{onset} and T_{max}, respectively. Metafen and Nurofen Ultima have significantly lower temperatures: 72.9°C, 76.8°C and 70.9°C, 75.4°C. It is interesting that they are both composed of IBU in the presence of paracetamol (PAR) and the concentrations of IBU per tablet are definitely lower than 29% and 23% while for the others are ranging from 34.77% to 53.43%.

The calculated calibration curves described above were applied to quantitative determinations of IBU. The final experimental contents O_{DSC} ± SD and A(%) are presented in Table 4.

For clarity of observation, all respective drugs under study were gathered in Table 5, to show which excipients could interfere with IBU. Components of particular importance were marked in the gray fields.

The content of IBU in presence of pseudoephedrine hydrochloride, in tablets (Acatar Zatoki and Ibuprom Zatoki) composed from starch, cellulose, croscarmellose sodium, colloidal silica, Guar gum, talc, crospovidone and hydrogenated vegetable oil were very close to those declared by the manufacturer. It suggests that there are no interactions between drug components and if they are, they

Table 3. The melting temperatures T_{onset} and T_{max}, enthalpy change ΔH and content of ibuprofen (IBU) in poly pharmaceutical drugs under study.

Analgesic	T_{onset} [°C]	T_{max} [°C]	ΔH [mJ/mg]	% IBU/tablet
Metafen	72.9	76.8	94.98	28.60
Nurofen Ultima	70.9	75.4	98.02	22.98
Acatar Zatoki	76.2	79.0	146.25	37.73
Ibuprom Zatoki	76.1	79.1	139.25	36.78
Modafen	75.9	79.2	130.50	34.77
Nurofen Zatoki	76.0	79.0	118.75	53.43
Pure Ibuprofen	76.1	79.0	130.00	-

Table 4. Quantification of IBU in tablets under study by means of DSC method, based on calibration curves obtained from micronized and non micronized mixtures.

Analgesic	IBU content (O_{DSC}) ± SD [mg/tablet]	A(%) [(O_{DSC}-D)/D]x100
	Micronized mixtures	
Metafen	143.95 ± 5.43	-28.02
Nurofen Ultima	153.25 ± 1.44	-23.38
Acatar Zatoki	205.44 ± 1.24	2.72
Ibuprom Zatoki	196.58 ± 4.27	-1.71
Modafen	186.17 ± 3.08	-6.91
Nurofen Zatoki	164.60 ± 4.26	-17.70
	Non micronized mixtures	
Metafen	122.50 ± 6.24	-38.75
Nurofen Ultima	122.70 ± 1.65	-38.65
Acatar Zatoki	203.42 ± 1.42	1.71
Ibuprom Zatoki	192.40 ± 4.90	-3.80
Modafen	178.56 ± 3.53	-10.72
Nurofen Zatoki	166.08 ± 5.32	-16.96

Table 5. The components of drugs under study. The presence of the ingredient in the drug was marked with "×"; respective excipients that could interfere with IBU are in the gray fields.

Drug name	Type of excipient													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Metafen	×	×	×	×										
Nurofen U.			×	×	×	×	×							
Acatar Z.		×	×		×	×		×	×	×	×			
Ibuprom Z.		×	×		×	×		×		×	×			
Modafen	×	×	×			×	×						×	×
Nurofen Z.	×		×	×	×							×		

1-povidone (PVP); 2-starch; 3-cellulose; 4-magnesium stearate; 5-croscarmellose sodium; 6-colloidal silica; 7-stearic acid; 8-Guar gum; 9-talc; 10-crospovidone; 11-hydrogenated vegetable oil; 12-calcium phosphate; 13-sodium lauryl sulfate; 14-lactose.

don't affect the final result. In other tablets consisting of pseudoephedrine hydrochloride the effect of stearates and PVP (Nurofen Zatoki, Modafen), calcium phosphate (Nurofen Zatoki), surfactans (sodium lauryl sulfate) as well as lactose (Modafen) were leading to moderate interactions. The strongest interactions can be observed for tablets composed from IBU in the presence of PAR where magnesium stearate, stearates and PVP were found.

CONCLUSIONS

The substances found in tablets often interact between themselves. The manufacturers generally provide an information on the type of excipients used during their production, however, usually only for main components and in most cases, there are no data concerning their concentrations. For that reason, it is difficult to estimate the influence of solid phase interactions on quantitative measurements. However, some general remarks are possible. The calculated statistical parameters of DSC method show that with several limitations it is possible to quantify API in poly pharmaceutical tablets. Under conditions that were used in the research, it was found that some excipients such as stearates, povidone, sodium lauryl sulfate as well as lactose could modify the measurement results in various ways. On

the other hand, the second active ingredient (both PAR and pseudoephedrine hydrochloride) doesn't seem to interfere. It should be emphasized that the described mutual solid state interactions can be observed during DSC measurements, while they do not change the quality of drug, they can sometimes alter the drug pharmacodynamics.

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