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Thermal analysis methods for pharmacopoeial materials*

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Abstract: Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) are commonly used for purity and solvent determinations, polymorphism studies and quantitative analysis. These methods are now simple to carry out. Furthermore, automation with robotics allows the use of DSC as a routine control. It is proposed to introduce DSC and TGA in pharmacopoeial monographs as a replacement or alternative to routine melting-point determinations and loss on drying assays. Furthermore, polymorphism and purity may be determined, which is often lacking in monographs. Results of many commercial batches or reference substances of pharmacopoeial raw materials and examples of the use of DSC robotics for quality control are given.

Introduction

Quantitative thermal analysis methods have been used in pharmaceutical analysis for more than 20 years. Their advantages for studies of polymorphs, solvates and hydrates and for the purity determination and quantification of volatile compounds in raw materials have been demonstrated [1–4]. They are described as general methods in the pharmacopoeia but their use is described only in a few monographs for purity (USP) or for determining the loss on drying of reference substances, for example, bromocriptine (USP). Several authors [5–9] have suggested the use of thermal analysis for loss on drying assays and melting-point determination.

The precision of instrumentation, computer calculations and calibrations and especially robotics allow analysts to consider these techniques as valuable in routine control. Furthermore, additional information about polymorphism and purity may be obtained at the same time. This is specially important since many substances may show polymorphism [10, 11].

The purpose of this paper is to discuss the use of DSC (power compensation or heat flux) as an alternative method to melting-point determination, and TGA as an alternative method for the determination of loss on drying in monographs.

Instrumentation

DSC-2 and the DSC-7 robotic system (Perkin–Elmer) were used for differential scanning calorimetry (DSC) measurements and the thermobalance TGS-2 (Perkin–Elmer) was used for thermogravimetric determinations.

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Results

Differential scanning calorimetry

Calibration. As for those instruments used to determine melting point, DSC instruments must be calibrated.

Table 1 gives a summary of standard substances for melting-point calibration. Table 2

Table 1
Standards for thermoanalysis

Temperature (°C)	Substance
38.84*	Mercury
0.0*	Water
26.87*	Diphenylether (phenoxybenzene)
29.77*	Gallium
36.32*	1,3-Dioxolan-2-one
48 *c*,*e*	Benzophenone
52.0,* 52‡	4-Nitrotoluene
58.08*	Succinonitrile
69.0§	Azobenzene
69.2†	Biphenyl
80.5,* 80‡	Naphthalene
83.0§	Vanillin
95.1,* 95,‡ 96§	Benzil
99.9 *a*	Phenanthrene
114.2,* 116,§ 114‡	Acetanilide
122.4,* 122‡	Benzoic acid
128,† 128.7 (ICTA)	Potassium nitrate (II–I)
136,§ 134.7	Phenacetin
147.6,* 147.1 *b*, 147‡	Diphenylacetic acid
151.4 *a*	Adipic acid
156.6	Indium
165,§ 163.2	Benzanilide
166§	Sulphanilamide
166.0 *c*	Rubidium nitrate(transition)
183.6,* 183‡ *a*, *b*	Anisic acid
193§	Sulphapyridine
192§	Salophen
210§	Dicyandiamide
210.4,* 209.0 *a*, 210‡	2-Chloro-anthraquinone
215.8 *d*	Anthracene
228 *c*	Rubidium nitrate(transition)
229§	Saccharin
232.0,* 231.9†	Tin
237§	Caffeine
246.2,* 245.3 *a*, 246‡	Carbazole
263§	Phenolphthalein
271.4 *d*, 271.3 *c*	Bismuth
285.2,* 284.6 *a*, 285‡	Anthraquinone
300,† 299 (ICTA), 299.4 *c*	Potassium perchlorate(transition)
321.1,* 320.9c	Cadmium
327.5*	Lead
334 (ICTA)	Potassium nitrate(transition)
419.6,* 419.4†	Zinc

*D. Ambrose and L. Crovini, *Recommended Reference Materials for the Realization of Physicochemical Properties* (K. N. Marsh, Ed.), Blackwell Scientific, Oxford.

†*NBS Standards for DSC, DTA, Catalog* 1988–1989.

‡*NBS Standards for Melting Points, Catalog* 1988–1989.

§*WHO Standards for Melting Points.*

a, See ref. 7; *b*, see ref. 12; *c*, see ref. 13; *d*, see ref. 14, *e*, see ref. 15.

Table 2
Comparison of DSC melting points of pure substances (T_o pure substance calculated by the purity program) given by two instruments at a heating rate of 1°C min^{-1}

Substance	WHO melting point (°C)	Perkin–Elmer DSC-2 (°C)	Mettler TA 3000 (°C)	Purity (%)
Azobenzene	69	68.4	68.0	99.9
Vanillin	83	82.1	81.6	99.8–99.9
Benzil	96 (NBS 95)	95.4	94.7	99.9
Acetanilide	116 (NBS 114)	114.6	114.0	99.95
Phenacetin	136	134.8	134.4	99.92
Benzanilide	165	163.2	162.6	99.93
Sulphanilamide	166	164.4	164.6	99.8–99.9
Salophen	192	191.3	191.4	99.7
Sulphapyridine	193	190.8	190.9	99.85
Dicyandiamide	210	208.9	208.9	99.7–99.8
Saccharin	229	227.6	227.9	99.92
Caffeine	237	235.4	235.9	99.98
Phenolphthalein	263	261.5	262.0	99.85
Standards:				
Naphthalene	80	80.0		
Benzoic acid	122.4	122.1		
Indium	156.6	156.6		
Adipic acid	151.4	151.1		
Diphenylacetic acid	147	146.4		
Bismuth	271.3	269.2		
Zinc	419.5	417.1		

shows a comparison of results from two instruments with substances of WHO standard melting points.

The two instruments give the same results after purity correction.

Figure 1 gives examples of calibration for DSC-2 and DSC-7 robotic systems (onset values).

The results show that most measured melting points below 200°C are within 1°C of the theoretical values. The deviation increases to 2°C at 420°C. For 200–400°C, the corresponding temperature correction has to be made. Some standards are questionable (literature value and purity).

For calibration it is proposed that NBS or ICTA standard metals and standards with certified purity >99.9% be used; for example, NBS standards for 4-nitrotoluene, succinonitrile, azobenzene, biphenyl, naphthalene, benzil, acetanilide, benzoic acid, diphenylacetic acid, adipic acid, indium (>99.9999%), anisic acid, 2-chloroanthraquinone, tin, bismuth, anthraquinone, potassium perchlorate, cadmium, lead, zinc.

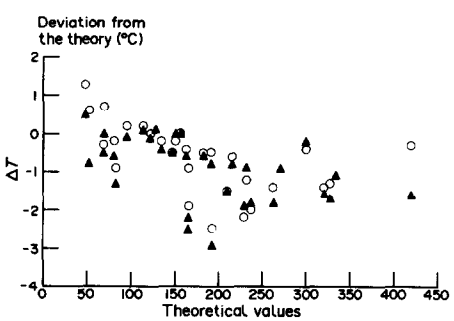


Figure 1
Comparison of calibration of two instruments WHO, ICTA, commercial sources. ▲ DSC normal: DSC-2, 10°C min^{-1} calibrated with In and Zn. ○ VSP pan: DSC-7 robot 2°C min^{-1} calibrated with In and Zn.

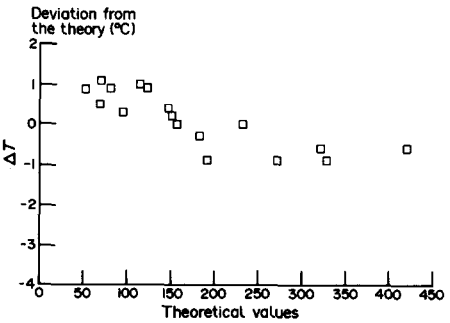


Figure 2
Comparison of proposed standards. □ USP pan: DSC-7 robot 2°C min^{-1} calibrated with In and Sn.

The proposed reference standards were scanned after calibration of the DSC-7 with indium and tin. Figure 2 gives the results; the values found are within ±1°C of the theoretical values.

In conclusion, for more precise melting-point determinations a standard in the temperature range of the melting point can be measured and the value corrected. This is simple with a robotic system.

Polymorphism. Polymorphism is generally not detectable in melting-point experiments.

Figure 3 illustrates the transition of a drug substance that occurs before the melting point and does not affect the classical melting-point result.

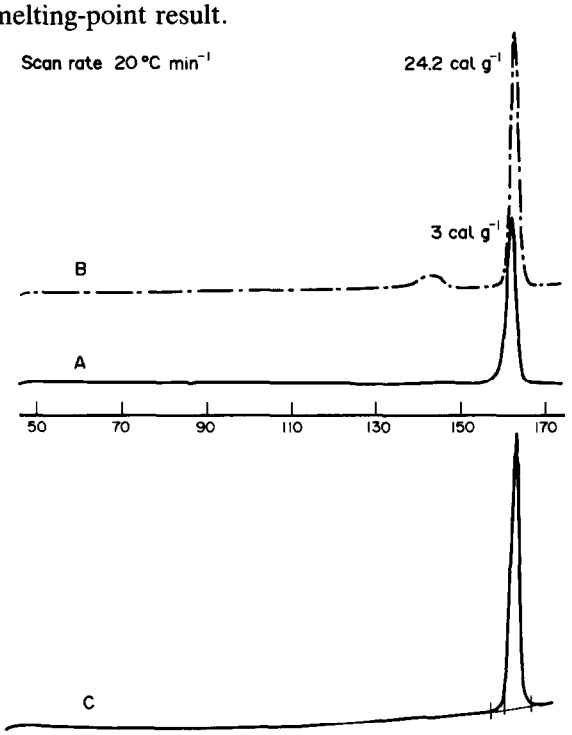


Figure 3
Transition solid → solid before the melting of the usual form. The transition energy is at about 3 cal g^{-1} and is unchanged at 20, 10 or 2.5°C min^{-1}. The melting point result is not affected by this transition. Curve A: batch 1, usual form. Curve B: batch 2 with transition before melting. Curve C: batch 1 after heating until 150°C and cooling. The transition is irreversible.

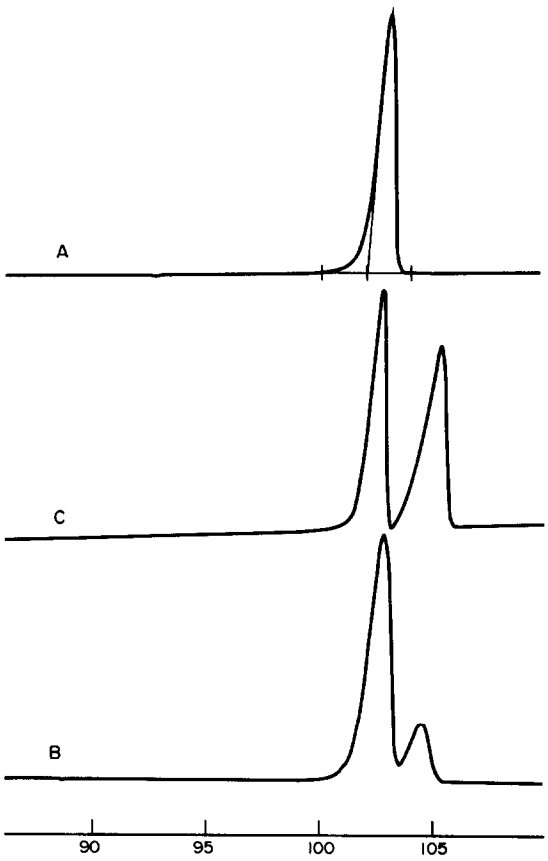
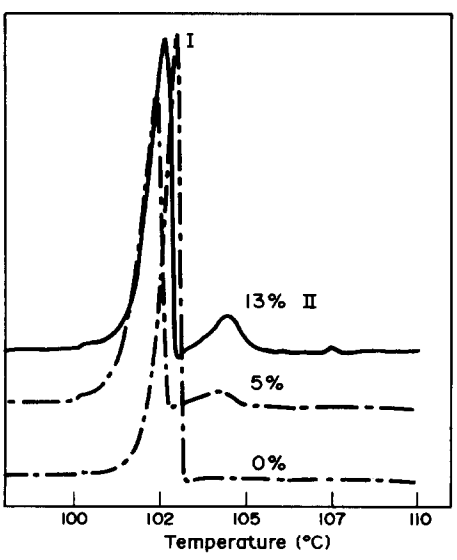
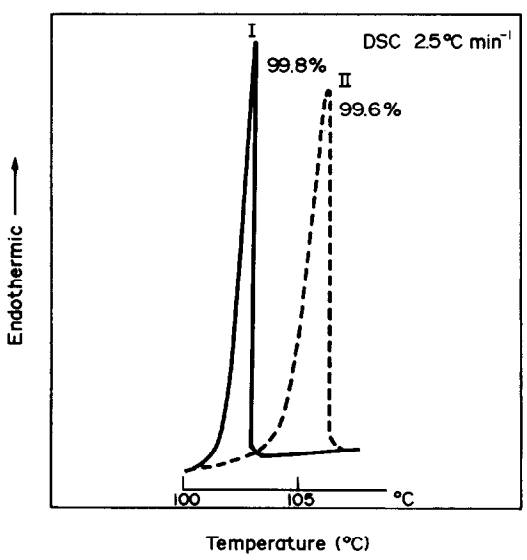


Figure 4
DSC scans of propyphenazone: A, pure form I; B, batch B containing higher melting form II; C, batch B after isothermal treatment for 2 days at 100°C: faster transition by isothermal treatment at 102°C.



DSC scans of three mixtures



DSC scans of pure modifications

Figure 5
Melting behaviour of propyphenazone. Current batches may contain small amounts of the crystalline modification II, leading to a higher melting point.

Figures 4 and 5 illustrates the results for propyphenazone. Batch B did not fulfil the melting requirements. The observed high melting point was not due to a higher purity of the sample but to a small amount of the higher melting form. A *slow* transition before the melting point can be induced by isothermal treatment. The transition occurs only if the metastable form is present.

Owing to the high quality of thermal exchange in DSC equipment, a fast heating rate may be used, allowing detection of melting, crystallization or amorphous → liquid → crystallization processes below the melting point. Geheno *et al.* [9] gave the example of carbamazepine the low melting form of which is not detected by the melting point determination; the transformation occurs below the starting temperature. The authors observed such behaviour, for example, for butylhydroxyanisole, temazepam, aspartame and mannitol.

Melting-point determination. The results of DSC melting points of commercial batches or reference substances of pharmacopoeial raw materials are given in Table 3. The table gives also for comparison the measured pharmacopoeia melting point and the requirement of the pharmacopoeia.

Some but not all results are in excellent agreement with literature or melting point measurements, demonstrating the need for a case-by-case validation.

Melting-point determination for low melting substances is of particular interest (e.g. phenol, 41°C; lauric acid, 43°C; hexadecanol, 47°C). Furthermore, the DSC experiments are carried out in an inert atmosphere to prevent oxidative decomposition during the melting process and therefore allowing reproducible measurements (e.g. saccharose). Results with different heating rates are also given demonstrating that for ideal substances like caffeine, acetanilide, adipic acid, amino-antipyrine, benzoic acid and mannitol, the same melting point is obtained by DSC with a 10, 5 or 2°C min^{-1} heating rate.

The use of different heating rates with a robot allows detection of non-ideal melting points. The robotic system is particularly useful for such validation experiments. Table 4 gives typical results for ideal melting compounds for which the melting point and the purity are independent of the heating rate.

Purity assessment. Table 3 also shows DSC purity results for raw materials, mostly described in a pharmacopoeia. Purity determination is possible in most cases, even for substances which melt with some decomposition (nitrogen atmosphere) or those with a low melting point like phenol.

DSC allows the determination of melting enthalpy. The melting depression due to impurities is proportional to this value, demonstrating that the setting of the same limits of melting range is not always valuable.

For lignocaine (lidocaine) hydrocholoride, ΔH = 16 kJ mol^{-1}; for chloramphenicol, ΔH = 36 kJ mol^{-1}.

In a substance with a melting enthalpy of approximately 30 kJ mol^{-1}, 2% of impurities would depress the melting point by only 1°C. A typical example is the case of different batches of β-hydroxypropyltheophylline complying with the melting-point range requirement, but for which PSA and DSC analysis revealed 0 to 5% of impurities [1].

Use of robotics. The robotic system DSC-7 allows analysis of 48 samples with specific heating, cooling and calculation programs.

Typical standard deviations for melting-point determinations are given in Table 5 for Physostigmine base and butalbital.

Table 3
DSC melting points of pharmacopoeial raw materials

Substance	DSC melting point (°C)	Heating rate (°C min^{-1})	Requirement (°C)	Pharmacopoeia melting point (°C)	Pharmacopoeia	Comments
Acetanilide	115.0	10	113–115		USP	99.97%
	114.4	2				
	114.8	2				
Acetaminophen	168.6	10	168–172		USP	
Adipic acid	151.2	2.5	151–155		USP	
	151.4	5				
	151.4	10				
Allobarbital	172.2	10		171.7	Ph.Eur	99.75%
	173.1	2				
Amino-antipyrine	108.4	10	108–110	107.8	USP	99.9%
	108.6	2				
Antipyrine	110.9	5	110–112.5	111.9	USP	99.9%
Anisic acid	182.5	2				
Ascorbyl palmitate	112.9	5	107–117		USP	99.4%
Ascorbic acid	192	20	190–192		USP	
Aspartame			246–247	236		Polymorphism
Azobenzene	69.1	2	about 68	68.1	USP	99.9%
	69.0	5				
	68.8	10				
Benzanilide	163.3	2				99.9%
Benzoic acid	122.5	2.5	121–124		USP	99.9%
	122.5	5				
	122.4	10				

Table 3
Continued

Substance	DSC melting point (°C)	Heating rate (°C min^{-1})	Requirement (°C)	Pharmacopoeia melting point (°C)	Pharmacopoeia	Comments
Benzophenone	49.5 49.5 48.6	2.5 5 10	48.5		USP	
Benzethonium hydrochloride	163.2 160.9	10 2	158–163	159.9	USP	99.0%
Benzocaine mesylate	149.0	5	145–151	149.3		99.9%
Butalbital	139.0	2.5	138–141	138.9–139.8	USP	99.9%
BHA	40.7/53	5	48–55	54.8	USP	Polymorphism
BHT	70.9	5	about 70		Ph.Eur.	99.95%
Caffeine	236.0 236.4 236.2 236.9	2.5 5 10 2	235–237.5		USP	99.9%
Carbamazepine	194.6	10	190–193			
Cetylpyridinium chloride	83.3	10	80–84		USP	
Chloramphenicol	150.6 150.6	10 2	149–153	148.9	USP	USP ref. 99.73%
Chlorpheniramine	131.8	2	130–135		USP	
Chlorthalidone	219.5		about 220 >215	218	BP USP	
Cholesterol	147.5	5	147–150		USP	
Denatonium benzoate	172.5	10	164–168	169–170	NF	99.5%
Dexamethasone acetate	232.0	10	none		USP	99.0%

Diazepam	131.2	5	131–135		USP	99.95%
Ethyl-*p*-hydroxy benzoate	114.8	10	116		Ph.Helv.	99.9%
Haloperidol	150.9	2	147–152 147–151	150.8	USP BP	
Hexadecanol	47.0	10				99.1%
Hydrocortisone	222.0	5				
Hydrochlorothiazide	265.1	10	none		USP	99.5%
Indapamide	163.9	10	Merck: 160–162			
Lauric acid	42.9	2.5	none			99.8%
Lignocaine hydrochloride	68.7	2	66–69		USP	Ref USP
Lobeline hydrochloride	191.7	10	none			
Mannitol	164.9 165.1	5 2.5	165–169	167.1	USP	99.9% Polymorphism
Nifedipine	171.4	2.5	171–175	172.3	USP	99.7%
Niacinamide (nicotinamide)	128.9 129.3 128.7	10 2 2	128–131	129.3	USP/Ph.Eur.	99.99%
Methyl-*p*-hydroxy benzoate	125.8 126.0	5	125–128		USP/Ph.Eur.	99.8%
Oxybuprocaine hydrochloride	159.0	10	aprox. 158	159.2	USP	99.7%
Phenacetin	135.0	2	134–137		USP	99.97%
Paracetamol	168.9	2	168–172		USP	
Phenol	41.4	2.5	none	USP	99.5%	
Pindolol base	170.3	1.25	169–173	170–171	USP	99.99%
Prednisolone acetate	241	20	237–239 dec.			Decomp.

Table 3
Continued

Substance	DSC melting point (°C)	Heating rate (°C min $^{-1}$)	Requirement (°C)	Pharmacopoeia melting point (°C)	Pharmacopoeia	Comments
Progesterone	130	5	126–131		USP	99.9% Polymorph.(121)
Propyl-*p*-hydroxy-benzoate	96.0	10	96–99		Ph.Helv.	99.8%
Propyphenazone	102.6	1.26	102–106		Ph.Helv.	99.9%(Form I) Polymorphism
Saccharose	226.8	5	none		Ph.Helv.	99.95%
Salicylic acid	158.0	10	158–161		USP	99.9%
Sorbic acid	133.1	10	133–136		BP	
Sulphapyrine	190.8	1	190–192		USP	99.85%
Temazepam	159.4	2.5	157–163	158.8		99.9% Polymorphism
Timolol maleate	200.8 196.2	10 2	none		USP	99.2%
Tetrathyl-thiurandisulphide	71.7 71.6	10 2		71.2		
Thiomersal	237	20	none		USP	
L-Threoninol	60.7	2.5				
Triamterene	329.1	10	none		USP	ref. USP
Urea	134.5	2.5	132–135 132–134		USP BP	
Vanillin	82.4	2	81–83	81.4	BP	99.95%
D-Xylose	152.5 150	5 5	none		USP	99.2%

Table 4
Influence of heating rate on melting point

Heating rate (°C)	Melting point (°C)	SD	Purity (%)
DSC-2 for pindolol (n = 7 for SD)			
1.25	170.3	0.11	99.99
2.5	170.40		
5	170.38		
10	170.46		
DSC-7 with robot for a new raw material (n = 5)			
1.25	125.85	0.34	99.7
2.5	125.75	0.44	99.6
5	126.2	0.33	99.6

Table 5
Reproducibility of results obtained by the DSC-7 robot of Perkin–Elmer

Physostigmine base: heating rate, 5°C min^{-1}; ΔH = 33 kJ mol^{-1}

Weight	Onset (°C)	Purity
2.197	104.3	99.69
2.196	104.1	99.64
2.109	104.1	99.64
2.109	104.2	99.65
2.188	104.2	99.60
2.222	104.15	99.66
2.186	104.1	99.60
1.110	104.1	99.70
3.153	104.0	99.70
4.241	104.2	99.69

Mean = 104.15°C; SD = 0.08; RSD = 0.08%; n = 10.

Butalbital: heating rate, 2.5°C min^{-1}; ΔH = 25 kJ mol^{-1}

1.583	139.0	99.84
1.561	138.9	99.85
1.578	138.9	99.88
1.540	138.9	99.90
1.527	138.8	99.90
1.537	139.2	99.86
1.519	139.0	99.88
1.070	139.0	99.88
2.098	139.0	99.84
3.069	139.1	99.88
4.047	139.4	99.96
5.082	139.3	99.96

Mean = 139.04°C; SD = 0.18; RSD = 0.13%; n = 12.

Thermogravimetric analysis (TGA)

TGA presents many advantages in comparison with a loss on drying assay owing to the principle of the determination. Loss on drying assays are isothermal. In the TGA dynamic method, the change of weight vs the temperature is plotted. Therefore, the true loss of weight will always be obtained. The conditions of the isothermal loss on drying

assay are best optimized. Artefacts due to degradation or sublimation in isothermal assays are avoided. For example for malonic acid, TGA, water and solvent determinations <0.1% values were obtained but isothermal determination lead to 0.1–0.5% values due to decomposition. Entrapped solvent is evolved only during melting. TGA allows its determination, even if decomposition begins just after melting. This solvent is not determined in the isothermal method.

Unexpected solvates or hydrates may be manufactured. Often the isothermal temperature of the classical method is too low to determine bonded water or the solvent. This is always determined by TGA.

TGA which gives exact dihydration or desolvatation steps, may be used as an identification pattern for many drugs and excipients. It requires only traces of samples which is a great advantage for expensive materials or for references substances (e.g. bromocriptine ms in USP). TGA is also valuable for determining the volatile part of an aroma, for compositional analysis, kinetic analysis or for studying solid–liquid or solid–vapour equilibria. As the carrier gas can be chosen, experiments can be strictly well controlled.

Table 6 gives typical relative standard deviations for the thermogravimetric analysis of a monohydrate, for a substance with entrapped solvent not detected by the isothermal loss on drying assay and for tablets containing hygroscopic excipients.

Figure 6 demonstrates the good correlation between loss on drying, TGA and water

Table 6
Examples of relative standard deviations (RSD) for thermogravimetry

A monohydrate of a drug substance	mean value $\bar{x}_7$: 3.81%	RSD = 2.0%
An entrapped solvent	mean value $\bar{x}_9$: 0.54%	RSD = 15%
A tablet	mean value $\bar{x}_6$: 4.48%	RSD = 1.9%

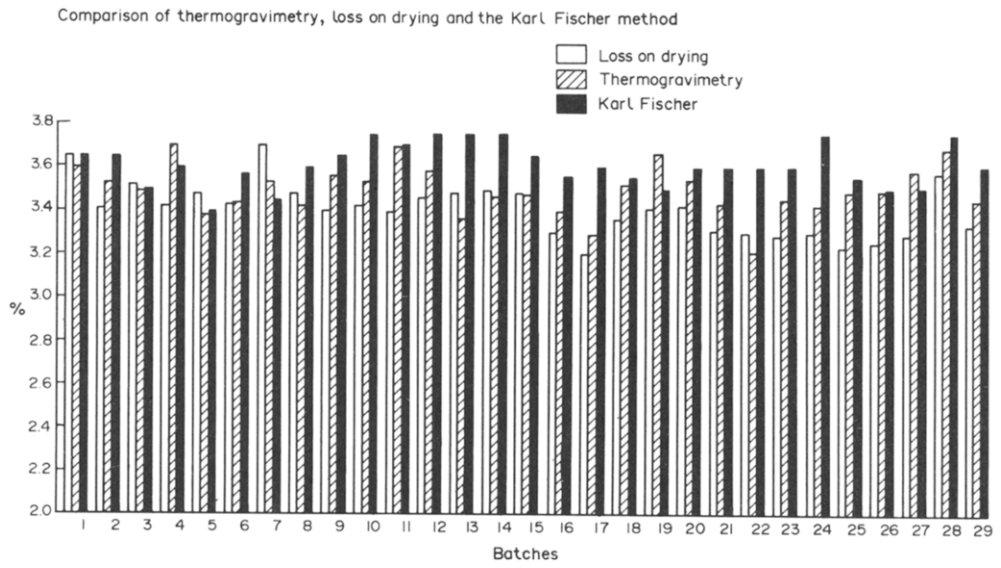


Figure 6
Comparison of thermogravimetry, loss on drying and the Karl Fischer method.

content for a monohydrate. Thermogravimetric values, loss on drying results and water determinations are compared for 29 different batches. For most batches the discrepancy is less than 10% of the values.

Conclusions

DSC and TGA are accurate methods of analysis which can be used as alternatives to classical melting-point determination and loss on drying assay as routine methods in pharmacopoeia monographs.

For the DSC the correlation with the classical melting-point determinations has to be validated in each case. The replacement of the classical melting-point determination in monographs by DSC would be a big advantage; DSC is more precise, quick and gives in the same run information about purity and polymorphism.

With robotics, DSC analysis allows more rapid analysis, and higher analytical reliability. A scan at 20°C min^{-1} or a 10°C heating rate is suggested for polymorphism or solvate detection and a specific heating rate, for example 2 or 5°C min^{-1}, for melting point and purity determination.

TGA analysis can replace every isothermal loss on drying experiment. The method requires very small samples and is very accurate. Furthermore it gives information about the type of bonding of the solvent. More precise results are obtained since wrong isothermal determinations may result from decomposition or from the lack of detecting solvate or entrapped solvent under the isothermal conditions of the monograph.

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