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Thermal analysis and calorimetric methods in the characterisation of polymorphs and solvates

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Abstract

The definitions and thermodynamic background for interpreting thermal analysis data are presented in this review. Most drug substances and excipients which have been reported to display polymorphism and pseudo-polymorphism are referenced.

The influence of experimental parameters and substance parameters on thermoanalytical data are presented. The limits and advantages of thermal methods and combined techniques are discussed. Examples describing the use of solution calorimetry and microcalorimetry are given. Thermal methods are unique in providing knowledge of thermodynamic data, for producing modifications and for distinction between polymorphs, solvates and impurities. The methods require only a small amount of material. However, for complex polymorphic behaviour, other techniques have to be used in addition. Kinetic data can be calculated in some situations. Thermal analysis methods are generally limited to routine quantitative analysis of polymorphism. Microcalorimetric techniques are useful complements for the study of polymorphism and pseudo-polymorphism and in certain cases for quantitative determinations.

Keywords: DSC; MDSC; ODSC; Polymorphism; Pseudo-polymorphism; Solvate

1. Introduction

Polymorphism is the tendency of a substance to crystallise into different crystalline states. The solid forms of the same compound are called polymorphs or crystalline modifications. Polymorphs show the same properties in the liquid or gaseous state but they behave differently in the solid state. The best known examples of polymorphism is carbon, which can exist in the form of graphite or as diamond.

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In the solid state, the atoms of a molecule may be arranged in one of seven fundamental crystalline forms: triclinic, monoclinic, orthorhombic, tetragonal, trigonal, hexagonal or cubic. All the crystalline forms, which are known in organic or inorganic chemistry, may be encountered. The amorphous state is characterised by crystallisation in a non-ordered, random system, related to the liquid state. The name "glassy state" is given to amorphous products which liquify by undergoing a glass transition. The term "amorphate" has been used recently.

Differences in the visual or morphological appearance of a substance do not necessary reflect polymorphism. Crystallisation of the base cells may occur in three different directions. A compound can produce crystals with different morphologies (habits) without changing the crystalline structure by preferentially growing in different directions.

Different solid phases, which may occur during crystallisation or galenical processes, are polymorphs, amorphous phases or solvates which form as the result of compound formation with the solvent. Water is a component of our atmosphere and the formation of hydrates is a special type of solvation. The expression pseudo-polymorphism applies to hydrates and solvates.

It has been suggested that almost all organic compounds exist in different solid states [1,2]. The most important reviews are given in Refs. [1–21].

Because all the physicochemical characteristics of the solid state are implied in polymorphism and pseudo-polymorphism, the pharmaceutical industry is confronted with this behaviour. The main properties affected are melting and sublimation temperatures, heat capacity, conductivity, volume, density, viscosity, crystal hardness, crystal shape, colour, refractive index, solubility, dissolution rate, stability, hygroscopicity and solid state reactions.

The effect of polymorphism on bioavailability is the most important consequence if the bioavailability is mediated via dissolution [11]. The oldest known example is chloramphenicol palmitate. Some other cases include novobiocin, griseofulvin, carbamazepine, aspirin and ampicillin. This behaviour is correlated with different dissolution rates. The polymorphism of excipients [13] may also play an important role in bioavailability as demonstrated by the loss of bioavailability of suppositories due to polymorphic transformation of the excipient during storage [7,9,13]. The process of transformation on one polymorph into another is a phase transition, which may also occur on storage or during processing. If the phase transition is reversible, the two polymorphs are enantiotrops. If the phase transition is irreversible, the two polymorphs are monotrops.

Amorphous states may appear in some proportion in each crystallisation or drying process. Typically obtained during lyophilisation, spray-drying, granulation, grinding or milling, the amorphous form is responsible for the higher reactivity of some batches. It gives rise to major problems with activity and stability [10]. Amorphous forms generally tend to crystallise in the presence of moisture (e.g. indomethacin, lactose). However, some drug substances undergo a transition from an ordered crystalline state to an amorphous one [10]. The presence of the amorphous fraction leads to the uptake of moisture in certain batches and thus to deviation in the content of the dosage form.

Batch-to-batch reproducibility also affects storage behaviour, milling ability and crystalline transitions during processing of the dosage forms. For instance, cephalexin, chloramphenicol, digoxin, spironolactone, sulphathiazole, barbiturates, sulphanilamide, carbamazepine, chlorpropamide, cefalotin, fostedil, phenylbutazone, piroxicam and sorbitol are reported to undergo transition during drying, grinding, milling and tabletting. Takahashi demonstrated the influence of excipients, of compression and of the type of mill for fostedil [22]. Chan and Doelker found that most substances undergo transition under trituration [23].

These processes are particularly important if the drug substance is a solvate or a hydrate and partially loses its structure through processing as do, for example, hydrates of theophylline [19,24], cefixime [25] or caffeine [26,27]. Byrn [6] described several cases of such phenomena. Hydrate formation has been observed during wet granulation, pelletisation or after storage of tablets or capsules. For example, theophylline, caffeine, codeine, nitrofurantoin, chlorpromazine, oxytetracycline or phenobarbital [18,28].

In order to obtain a better bioavailability, solid disperison in polyvinylpyrrolidone (PVP) or cyclodextrin is often proposed for the dosage form. In many cases recrystallisation to a less soluble form has been observed. Crystallisation of drug substance from injectables, solutions or creams occurs frequently [10,29].

Chemical stability in the solid state is strongly correlated with batch-to-batch reproducibility [10,30]. Even the photostability may be concerned. For instance, different photochemical stabilities were observed for two crystalline modifications of frusemide [31]. For ethoxycinnamic acid, two polymorphs give different photochemical degradation products; the third modification was stable [32].

In development, it is mandatory to solve problems to polymorphism before pivotal trials. A typical case history follows. The initial batches produced crystallised as a crystalline modification A. Preformulation studies demonstrated the occurrence of several forms and, especially, the thermodynamically stable crystalline modification B. In scaling up the production of later batches, it was no longer possible to obtain form A. Large differences in the dissolution rates (of the substance and of the clinical capsules) were observed. Therefore, the formulation of the capsules with the crystalline form B had to be optimised. Moreover, stability studies of two batches of form A were performed in parallel. The results demonstrated that nuclei representing between 2% and 5% of B in one batch were sufficient to induce solid–solid transformation of A to B (about 20% after 1 year at 30°C). The other batch of pure form A, stored in parallel, showed no changes [10,145].

2. Polymorphism/pseudo-polymorphism studies in pharmacy

Investigating the polymorphic behaviour of drugs and excipients is an important part of preformulation work. Table 1 summarizes all cases of polymorphism and pseudo-polymorphism of drug substances that were found in the literature. In 1990, Borka and Haleblian [21] published a summary of the literature. Table 1 includes

Table 1
Drug substances with polymorphic or pseudo-polymorphic behaviour

Name	Ref.	Name	Ref.
Acebutolol hydrochloride	[21]	Arecoline hydrochloride	[20]
Aceclidine hydrochloride	[21]	Asparaginase	[21]
Acedapsone	[21]	Auranofin	[21]
Acemetacin	[21,33]	Azaperone	[21]
Acetamide	[21]	Azelastine hydrochloride	[46]
Acetaminophen	[3,34]	Azintamide	[20]
Acetazolamide	[21,35]	Aztreonam	[47,48]
Acetohexamide	[3,21]	Bacampicillin	[49]
21-Acetoxypregnelonone	[21]	Baclofen	[21]
β-Acetyldigoxin	[21]	Bamethan sulphate	[20]
DL-*O*-Acetylpantolacton	[21]	Bamipine hydrochloride	[21]
Acetylsalicylic acid	[21]	Barbital	[3,50]
Acetylsulisoxazole	[21]	Barbiturates	[21]
Adenosine derivative	[36]	Barbiturates azo deriv.	[51]
Adiphenine hydrochloride	[21]	Benactyzine	[21]
Ajmaline	[21]	Bendroflumethiazide	[52]
Allantoin	[21]	Benoxaprofen	[21]
Allobarbital	[21]	Benperidol	[21,53]
Allopregnane-3β, 20α-diol	[12]	Bentiromide	[41]
5-Allyl-barbituric acid deriv.	[21]	Benzamide	[3]
Alprenolol hydrochloride	[21]	Benzilic acid esters	[21]
Amcinonid	[37]	Benzocaïne	[54]
Amiloride hydrochloride	[38]	Benzoylbenzoxazolidininone	[21]
Amino-acids	[39]	Benzopyran deriv.	[55]
p-Aminobenzoic acid	[21]	Benzoxalethiol	[20]
Amikacin disulphate	[40]	Berberine hydrochloride	[21]
Aminopenicillanic acid deriv.	[21]	Betadrenol hydrochloride	[21]
Amiperone	[41]	Betamethasone acetate	[21,56]
Amiflamine	[42]	Bilamide	[20]
Amisometradine	[21]	Biotine	[21]
Amitriptyline hydrochloride	[21]	Biperiden	[20]
Amobarbital	[21]	Bitoscanate	[21]
Amoxilline	[19]	Bolandiol dipropionate	[21]
Amphetamine sulphate	[21]	Bromisoval	[21]
Ampicillin	[21]	Bromopride	[21]
Amylocaïne hydrochloride	[20]	Bromovalerylurea	[21]
Amrinone	[21]	Bromperidol	[57]
Androstane-diol deriv.	[21]	Brompheniramine maleate	[21]
Androstane-dione deriv.	[21]	Brotizolam	[41]
Androstanolone	[21,41,43]	Brucine	[20]
Androstene-diol deriv.	[21]	Buclosamide	[20]
Androstene-dione deriv.	[21]	Bumetanide	[21]
Androsterone	[44]	Bupicomide	[58]
Anilamate	[21]	Bupivacaine hydrochloride	[21]
Anthranilic acid	[21]	Bupranolol hydrochloride	[21]
Anthraquinone carboxylic acid	[45]	Busulphan	[19]
Aprindin hydrochloride	[21]	Buspirone hydrochloride	[58]
Aprobarbital	[21]	Butacaine hydrochloride	[21]
Apronalide	[21]	Butallylonal	[21]

Table 1 (continued)

Name	Ref.	Name	Ref.
Butinoline	[21]	Clodantoin	[21]
Buthalital sodium	[21]	Clofenamide	[21]
Butobarbital	[21]	Clominorex	[21]
Butoxycaine hydrochloride	[21]	Clomipramine hydrochloride	[21]
Butropipazone	[21]	Clonidin hydrochloride	[21]
Caffeine	[21,26]	Clorindanol	[21]
Calcium gluceptate	[21]	Clotrimazol	[21]
Calcium lactate	[19]	Codeine	[20]
Calcium panthotenate	[19]	Corticosterone	[21]
Camphoric acid deriv.	[59]	Cortisone acetate, enanthate	[21]
Captopril	[60]	Coumaphol	[21]
Caramiphen hydrochloride	[20]	Cresols	[21]
Carazolol	[21]	Cromoglycate disodium	[83]
Carbamazepine	[19,21,61–66]	Cyclandelate	[21]
Carbocromen hydrochloride	[21]	Cyclobarbital	[21]
Carbromal	[21]	Cyclobutyrol sodium	[21]
Cefactor	[67]	Cyclopenthiazide	[84]
Cefaloridin	[19]	Cyclophosphamide	[21,85]
Cefalotin sodium	[21,68,69]	Cyheptamide	[21]
Cefamandole	[19]	Cyproheptadine hydrochloride	[21]
Cefazolin	[21]	Danthron	[21]
Cefixime	[25]	Dapsone	[21]
Celiprolol hydrochloride	[70]	Dehydroandrosterone	[21]
Cephalexin	[21,71]	Dehydroepiandrosterone	[21]
Cephaloglycin	[21]	Deoxycorticosterone propionate	[21]
Cephaloridine	[21]	Deserpidine	[21]
Cetraxate hydrochloride	[72]	Dexamethasone acetate	[21]
Chenodeoxycholic acid	[21]	Dexamethasone palmitate	[86]
Chloralhydrate	[21]	Diacetylmorphine	[21]
Chloramphenicol + deriv.	[21]	Diatrizoic acid	[21]
Chloramphenicol palmitate	[20,21,73,74]	Diazepam	[19]
Chlorbenzoamine dihydrochlor.	[21]	Dibromsalicyl	[21]
Chlordiazepoxide hydrochloride	[21]	Diclofenamide	[21]
Chlorethyl aminouracil	[21]	Diclofenac	[87]
Chlormidazole hydrochloride	[21]	Diclofenac aminosalicylate	[88]
Chloroacetamide	[21]	Didrovaltrate	[21]
Chlorphenoxamin hydrochloride	[20]	Diethylamine salicylate	[21]
Chlorpropamide	[21,75]	Diethylstilbestrol	[21]
Chlorpromazine hydrochloride	[76]	Difenoxin hydrochloride	[89]
Chloroquine diphosphate	[21,,77,78]	Diflunisal	[21]
Chlorquinaldol	[21]	Digitoxin	[21]
Chlortestoterone	[21]	Digoxin	[21,90,91]
Chlortetracycline hydrochloride	[21]	Dihydroergotoxin ms	[92]
Chlorthalidone	[21]	Dimethoxanate hydrochloride	[21]
Chlolesterol and esters	[21,79]	Dioctyl sodium sulphosuccinate	[21]
Choline chloride	[21]	Diphenadione	[93]
Cibenzoline succinate	[80]	Diphenidol	[94]
Cimetidine	[21,81,82]	Diphenylamine	[20]
Cinnamic acid	[21]	Diphenylhydantoin	[21]
Clenbuterol hydrochloride	[21]	Diphenylmethane disulphonamide	[21]

Table 1 (continued)

Name	Ref.	Name	Ref.
Diphenylprorenamine	[21]	Flumetramide	[21]
Diprophylline	[20]	Fluocortolone pivalate + salts	[21]
Dipyramidol	[21]	Flucocortisol acetate	[21]
Disopyramide	[21]	Fluorohydrocortisone acetate	[21]
Dobutamine hydrochloride	[95]	Fluprednisolone	[21]
Dormovit	[21]	Fluogestone acetate	[21]
Doxylamine succinate	[96]	Fluspirilene	[21]
Droloxifene	[97]	Fosinoprilsodium	[109]
Droperidol	[21]	Fostedil	[21,22]
Embramine hydrochloride	[21]	Furaltadone	[21]
Emedastine difumarate	[98]	Furosemide (Frusemide)	[110–113]
Emetine hydrochloride	[19,85]	Gepirone hydrochloride	[21]
Enalapril maleate	[21,99,100]	Glafenine	[21]
Enoxamine	[101]	Glibenclamid	[21,114]
Ephedrine	[20]	Glibornuride	[21]
Epiandrosterone	[20]	Glimidine (Glycodiazine)	[21]
Eprozinol hydrochloride	[21]	Glucose	[19]
Ergometrine tartrate	[20]	Glutethimide	[21]
Ergotamin tartrate	[19]	Gramicidin	[21]
Erythritol	[3]	Griseofulvin	[21]
Erythromicin + estolate	[21,85]	Guaiphenesin	[21]
Estramucine	[102]	Guanoxyfen sulphate	[21]
Estradiol + salts	[21]	Halofenate	[21]
Estradiol esters	[21]	Haloperidol	[20]
Estrone	[20]	Heptabarbital	[21]
Etacrynic acid	[21]	Heptaminol hydrochloride	[21]
Etafedrine hydrochloride	[21]	Heptolamide	[113]
Ethallobarbital	[21]	Heroin (diacetylmorphine)	[21]
Ethambutol dihydrochloride	[21]	Hexachlorophene	[20]
Ethionamide	[19]	Hexobarbital	[21]
Ethinyl estradiol	[21,103]	Histamine	[19]
Ethyl biscoumacetate	[21]	Histidine + salts	[21]
Ethyl gallate	[21]	Homatropin hydrochloride	[21]
Etidocaine hydrochloride	[21]	Hydrochlorothiazide	[115]
Etiocholane deriv.	[21]	Hydrocortisone + salts	[21]
Etofilline	[21]	Hydroflumethiazide	[21]
Etoposide	[104]	Hydroxyphenylretinamide	[21]
Famotidine	[105]	Hydroxyprocaine hydrochloride	[21]
Felodipine	[106]	Hydroxypropyl theophylline	[18,92]
Fenbufen	[41]	Hyoscamine hydrochloride	[20]
Fendiline hydrochloride	[21]	Hyoscine *n*-butylbromide	[116]
Fenoctimine sulphate	[21]	Hyoscyamine sulphate	[19]
Fenoterol hydrobromide	[21]	Ibuprofen	[117–121]
Fenproporex	[21]	Ibuprofen lysinate	[122]
Fenretinide	[21,30]	Imidazopyridine deriv.	[123]
Fluanisone	[57]	Imidolin hydrochloride	[21]
Flucabril	[21]	Imipramine hydrochloride	[21]
Flucloxacillin	[107]	Indalpin	[37]
Fludrocortisone acetate	[21]	Indigo	[21]
Flufenamic acid	[21,108]	Indomethacin	[21,124,125,126]

Table 1 (continued)

Name	Ref.	Name	Ref.
Inositol nicotinate	[21]	Methazole amide	[21]
Iopamidol	[127]	Methisazone	[142]
Iopanoic acid	[128,129]	Methoin	[21]
Iprindole hydrochloride	[21]	Methoxsalen	[21]
Isoajmalin	[21]	Methotrexate	[143]
Isomethadone hydrochloride	[21]	Methoxyphenylacetylosin	[144]
Isoniazid	[20]	Methylandrostanediol	[21]
Isoprenaline sulphate	[19]	Methylestradiol	[21]
Isothiourea deriv.	[130]	Methyldopa	[19]
Ketoconazole	[19]	Methylnitrovinylimidazole	[21]
Ketotifen hydrogen fumarate	[131]	Methylphenylbarbituric acid	[21]
Khellin	[21,132]	Methylprednisolone + acetate	[21]
Levobunol	[113]	Methylsulphanilysulphanilamide	[21]
Levodopa	[19]	Methyltestoterone	[21]
Levomepromazine hydrochloride	[62]	Metoclopramide + hydrochloride	[21]
Lidocaine hydrochloride	[20]	Metofenazate hydrochloride	[21]
Lisinopril	[133]	Metolazone	[21,4,145]
Loperamide	[134]	Metronidazole benzoate	[21,146]
Lorazepam	[21,135,136,137]	Methylcinnamic acid	[21]
Lorcainide hydrochloride	[21]	Mexiletine hydrochloride	[21,147]
Losartan	[138]	Miconazole	[148]
Mafenide hydrochloride	[21]	Midodrin hydrochloride	[149]
Mandelic acid	[21]	Minoxidil hydrochloride	[21]
Maprotiline hydrochloride	[21]	Miokamycin	[150]
Mebendazole	[139]	Moclobemid	[37]
Medrogestone	[21]	Mofebutazone	[151,152]
Medetomidine hydrochloride	[140]	Moperone	[21]
Mefenamic acid	[21]	Mopidamol	[21]
Mefenorex hydrochloride	[21]	Morphine	[21]
Mefruside	[21]	Mupirocin	[153]
Menadione	[20]	Nabilone	[21]
Menthol	[21]	Nafagrel hydrochloride	[154]
Mepacrine hydrochloride	[21]	Nafcillin	[21]
Mephernesine	[20]	Nafoxidin hydrochloride	[21]
Mephentermine sulphate	[20]	Naftifine hydrochloride	[58]
Mephesin carbamate	[21]	Nalidixinic acid	[21]
Mepivacaine hydrochloride	[21]	Nicametate dihydrogencitrate	[21]
Meprobamate	[21,141]	Nicardipine hydrochloride	[155,156]
Mercaptopurine	[21]	Nicergoline	[157]
Mestranol	[21]	Nicocodin	[21]
Metahexamide	[21,37]	Nicotinamide	[21]
Metalazon	[21]	Nifedipine	[21]
Metamphetamine	[21]	Nifenalol hydrochloride	[21]
Metaraminol bitartrate	[21]	Niflumic acid	[21]
Metenolone	[21]	Nimodipin	[158]
Metformin hydrochloride	[21]	Nitrendipin	[21]
Methadone	[21]	Nitroflurmethan	[21]
Methallenestril	[21]	Nitrofurantoin	[21,159,160,161]
Methamphetamine hydrochloride	[21]	Nordazepam	[162]
Methandriol + salts	[21]	Norethisterone	[21]

Table 1 (continued)

Name	Ref.	Name	Ref.
Norfenfrine hydrochloride	[20]	Phenytoine	[178]
Norfloxacin	[163,164]	Phthalysulphathiazole	[21]
Norleucine	[20]	Pilocarpin nitrate	[19]
Norpseuodohedrin hydrochloride	[21]	Pimethixen	[18]
Nortriptyline hydrochloride	[165]	Pimozide	[21]
Noscapin hydrochloride	[19]	Pindolol	[21]
Novobiocin	[21]	Pipamperone	[21]
Noxiptylin	[21]	Pipemidic acid	[179]
Nystatin	[21]	Piperazine	[19]
Ouabain	[21]	Piperylon	[92]
Oxaceprol	[21]	Pipobroman	[21]
Oxamniquine	[21,166,167]	Piribedil	[21]
Oxazepam	[168]	Piroxicam	[21,180–183]
Oxeladin citrate	[21]	Pirprofen	[21]
Oxetacine	[21]	Polycaine hydrochloride	[21]
Oxohexyltheobromide	[21]	Praziquantel	[21]
Oxprenolol hydrochloride	[21]	Prazosin hydrochloride	[184,185]
Oxyclozanide	[21]	Prednisolone + acetate	[21,186]
Oxypendyl hydrochloride	[21]	Prednisone	[21]
Oxyphenbutazone	[169]	Prenoxdiazine hydrochloride	[21]
Oxytetracycline	[21]	Primidon	[19]
Pantolactone	[21]	Proadifen hydrochloride	[21]
Paracetamol	[21,170]	Probucol	[21]
Paratoine	[20]	Progesterone	[21,187,188]
Parsol 1789	[21]	Proline	[21]
Paroxetine hydrochloride	[171]	Promethazine	[20]
Penbutolol sulphate	[21]	Propallylonal	[21]
D-Pencillamine	[21]	Propantheline bromide	[21]
Penicillin G	[172]	Propanolol hydrochloride	[21]
Pentamidine isethionate	[173]	Propipocaine hydrochloride	[20]
Pentazocine	[174]	Propylhexedrine hydrochloride	[20]
Pentobarbital	[21]	Propyphenazone	[4,18,21,145]
Pentoxytylline	[21]	Promethazine	[20]
Penoctone bromide	[21]	Propallylonal	[21]
Pethidine hydrochloride	[21]	Propantheline bromide	[21]
Phenacaine	[20]	Propanolol hydrochloride	[21]
Phenacetine	[20]	Proscar	[122]
Phenadoxone hydrochloride	[21]	Prothionamide	[21]
Phenazine	[21]	Prothipendyl hydrochloride	[20]
Phenazopyridine	[20]	Proxibarbal	[21]
Phenelzine dihydrogensulphate	[21]	Proxyphylline	[21]
Phenethylammonium bromide	[175]	Pseudo-ephedrine hydrochloride	[20]
Phenformin hydrochloride	[21]	Psilocin	[21]
Phenmetrazine + salts	[21]	Psilocybin	[21]
Phenobarbital	[21,176]	Pyramidon	[189]
Phenpromethamine hydrochloride	[21]	Pyrazinamide	[21]
Phensuximide	[21]	Pyrantel tartrate	[21]
Phentermine hydrochloride	[21]	Pyridine deriv.	[190]
Phenylbutazone	[21,29,177]	Pyrimidine bases	[21]
Phenylpropanolamine hydrochloride	[20]	Pyrimidone deriv.	[191]

Table 1 (continued)

Name	Ref.	Name	Ref.
Pyridoxal hydrochloride	[192]	Sulphamoyldiaminoazobenzene	[21]
Pyrithyldione	[21]	Sulphaanilamide	[21]
Quercetin	[20]	Sulphanilamidomethoxypyrimidine	[21]
Quinine salts	[21]	Sulphanylxylamide	[21]
Raclopride tartrate	[42]	Sulphapyrazole	[21]
Ramantidine	[42]	Sulphapyridine	[21]
Renytolin hydrochloride	[21]	Sulphaproxiline	[200]
Reserpin	[21]	Sulphathiazole	[21,201–204]
Resorantel	[20]	Sulphathiourea	[21]
Resorcinol	[21]	Sulphatriazine	[21]
Riboflavin	[21]	Sulphazamet	[3]
Rifampicin	[21]	Sulphisoxazole	[3]
Rotenone	[21]	Sulphonamides	[21]
Salbutamol	[20]	Sulphormetoxine	[21]
Salicylic acid	[21]	Sulindac	[205]
Scopolamine hydrochloride	[20]	Suloctidil	[21]
Secbutobarbital	[21]	Sulpiride	[21]
Sodium ampicillin	[21]	Tamoxifen citrate	[21]
Sodium cromoglycate	[21]	Terconazole	[41]
Spiperone	[21]	Temazepam	[206]
Spironolactone	[21,193]	Terfenadine	[207,208]
Spiramycin	[194]	Terpin hydrate	[20]
Stadacacin	[21]	Testoterone + salts	[21]
Stanozolol	[21]	Tetracaine hydrochloride	[12,21,209]
Steroid hormones	[21]	Tetracycline	[21,101]
Streptomycin sulphate	[20]	Tetrazolate deriv.	[210]
Stiripentol	[195]	Thebacon hydrochloride	[21]
Succinylsulphathiazole	[19,22]	Theobroma oil	[21]
Sulphabenzamide	[21,196–198]	Theophylline	[21,28,211,212]
Sulphacetamide	[21]	Thialbarbital	[21]
Sulphacarbamide	[21]	Thiamine salts	[21]
Sulphacetamide	[21]	Thiamphenicol + salts	[21]
Sulphachlorpyridazine	[21]	Thiopental	[21]
Sulphadiazine	[21]	Thiosinamine	[20]
Sulphadicramide	[21]	Thiothyr	[21]
Sulphadimidine	[21]	Tiamizide	[21]
Sulphaethidole	[21]	Ticlopidine hydrochloride	[21]
Sulphafurazole	[21]	Tilidine hydrochloride	[21]
Sulphaguanidine	[21]	Timolol maleate	[21]
Sulphalene	[21]	Tinidazole	[21]
Sulphamerazine	[21]	Tiocarilde	[21]
Sulphamethizole	[21]	Tobramycin	[213]
Sulphameter	[20]	Tobucarine hydrochloride	[19]
Sulphamethonium hydrochloride	[20]	Tolbutamie	[21,214,215]
Sulphamethoxazole	[21]	Tolpropamine hydrochloride	[21]
Sulphamethoxydiazine	[21]	Tramazoline hydrochloride	[21]
Sulphamethoxypyridiazine	[21]	Tranilast	[216]
Sulphamethylthiazole	[21]	Trazodone hydrochloride	[217]
Sulphametrole	[21,199]	Triamcinolone diacetate	[21]
Sulphamoxole	[21]	Trimethoprim	[21]

Table 1 (continued)

Name	Ref.	Name	Ref.
Trimetozine	[21,218]	Usninic acid	[20]
Triparanol	[21]	Varbromal	[221]
Tromantadine hydrochloride	[21]	Verapamil hydrochloride	[19]
Trospium hydrochloride	[21]	Vesulong	[20]
Tyramine	[20]	Vinbarbital	[20]
Uracil	[219]	Vitamin A acid	[3]
Uradipil	[21,220]	Voluntal	[20]

their review and completes it. Other summaries, including details on the number of phases, have been published [6,13,19,62,222].

Table 2 gives examples of polymorphism and pseudo-polymorphism of excipients. A great number of publications deal with lactose, magnesium stearate, sorbitol, mannitol, cellulose and fats. Polymorphism of excipients has also been reviewed [13].

For drug substances as well as for excipients, thermal analysis is particularly suited for the study of polymorphism and pseudo-polymorphism and is now used as a routine basis in preformulation work or in the quality control of drugs. The

Table 2
Excipients with polymorphic or pseudo-polymorphic behaviour

Excipient	Ref.
Adeps solidus	[21]
Amylodextrins	[21]
Aspartam	[13]
Butylhydroxyanisole	[13]
Calcium oxalate	[226–228]
Calcium phosphates	[224,225]
Cellulose	[229]
Chenodeoxycholic acid	[21]
Cyclodextrins	[230]
Fatty acids, fatty alcohols	[13]
Glycerides	[9,13,231–239]
Glyceromonostearate	[240]
Glycine + hydrochloride	[21]
Hydrogenated canola oil	[241]
Lactose	[21,13,242,243]
Lipids	[244]
Menthol	[21]
Magnesium stearate	[13,223,245,246]
Paraffin	[247]
Saccharose (sucrose)	[248–250]
Sorbitol	[13,251–256]
Stearic acid	[257]
Suppository bases	[7,233–238]

introduction of robotics considerably increases the advantages of differential scanning calorimetry (DSC) and thermogravimetry (TG). Modulated DSC (MDSC) or oscillated DSC (ODSC) and high resolution TG allow a better interpretation of overlapping thermal events. Combined techniques such as heat controlled FTIR or heat controlled X-ray diffractometry make interpretations of thermodynamic relationships easier. Microcalorimetry (isoperibol, adiabatic or isothermal), which is now very sensitive, is being used increasingly. Thermomicroscopy [20] remains a useful technique for the better understanding of heat processes.

3. Thermodynamic and kinetic aspects of polymorphism and pseudo-polymorphism

3.1. Polymorphs: enantiotropy and monotropy

Precise knowledge of thermodynamic stability and relationships between different solid phases of a drug substance is a prerequisite for understanding the crystallisation process. At the beginning of the crystallisation, depending on the supersaturation and the solubility curves of each polymorph or pseudo-polymorph, the first crystal is formed as the most soluble form. Then, for thermodynamic reasons, it is converted to the less soluble form.

The relative positions of the solubility curves are determined by the phase diagram of the solid phases which is governed by the Gibbs' phase rule

$$v = C - 2 - \Phi \tag{1}$$

where v is the number of variance of the system, C the number of constituents and Φ the number of phases.

In the case of polymorphism $C = 1$ if two phases are present (e.g. two solid phases) and if the pressure and the temperature vary, the variance is unity. If the pressure or if the temperature is fixed the variance is zero. It is necessary to know the equilibrium curves between the solid forms under the influence of humidity, temperature and pressure in order to predict changes for storage, stability, compatibilities and production processes.

Phase diagrams of pressure versus temperature illustrate the different equilibrium curves of the transitions solid–solid or solid–liquid or solid–gas. Fig. 1 illustrates the two different types of phase diagrams corresponding to enantiotropy and monotropy. For each form, there is a solid–liquid equilibrium curve and a solid–vapour equilibrium curve. If the liquid–vapour equilibrium curve (CD in (Fig. 1(a)) meets the two solid–vapour curves after the point of intersection of the solid–solid equilibrium curve, there will be a solid I $\leftrightarrow$ solid II equilibrium curve (BF in Fig. 1(a)) and a reversible transition point I $\leftrightarrow$ II at a specific pressure. This case is known as enantiotropy. At the transition point, the free energy of the two forms is the same. AB is the equilibrium solid I–vapour, BC the equilibrium solid II–vapour, FB the equilibrium solid I–solid II, FC the equilibrium solid II–liquid and CD the equilibrium liquid–vapour (Fig. 1(a)). The term monotropy applies in the case of an irreversible transition from one form to another. Monotropy is

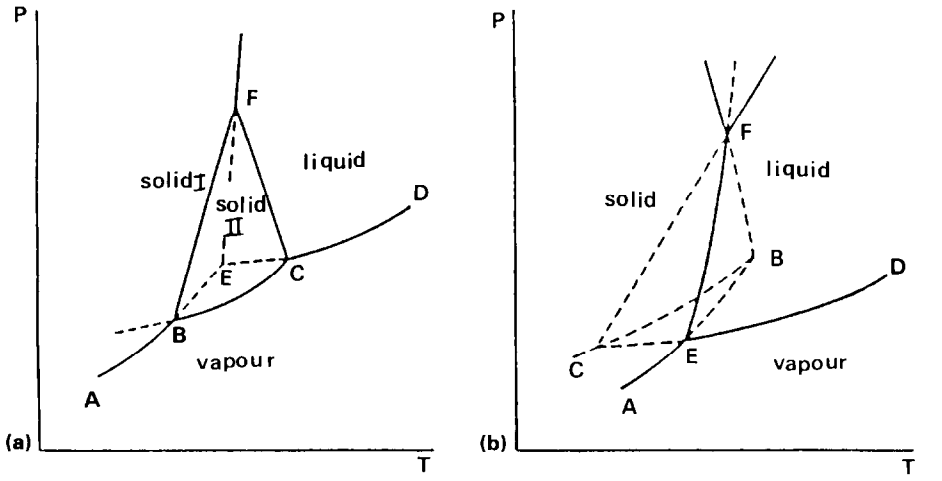


Fig. 1. Phase diagram for a single component with polymorphic behaviour: (a) enantiotropy; (b) monotropy.

bound to the existence of metastable thermodynamic forms. The liquid–vapour curve crosses the solid I–vapour curve before the points B and C. In Fig. 1(b), the equilibrium curves are AE for solid I–vapour, FE for the solid–liquid equilibrium and ED for the liquid–vapour equilibrium. In both cases the dashed curves represent metastable curves.

Knowing the relationship between the thermodynamic quantities H (enthalpy), G (free energy), S (entropy) and T (temperature), it is often simple to represent equilibrium states by plotting the free energy G as a function of the temperature for each form. If the two curves intersect before the melting point, there is reversibility, i.e. enantiotropy, and if the reverse is true, there is monotropy (Fig. 2).

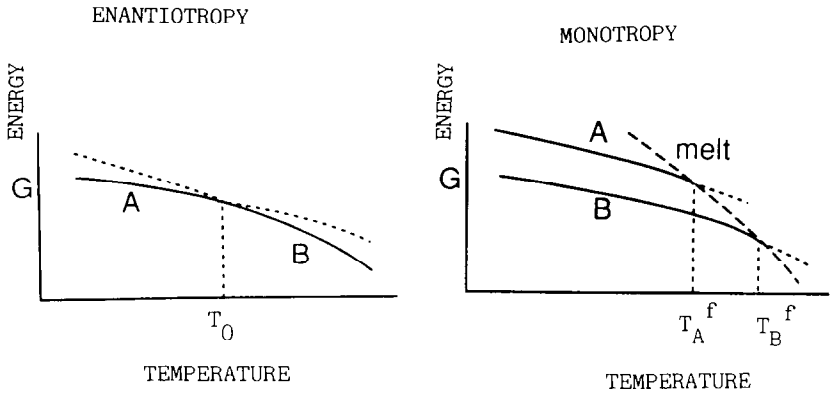


Fig. 2. Relationship between Gibbs energy G and temperature for two modifications in the cases of enantiotropy and monotropy.

In the case of monotropy, the higher melting form is always the thermodynamically stable form. In the case of enantiotropy the lower melting form is the thermodynamically stable form at temperatures below the transition point and the higher melting form is the thermodynamically stable form at temperatures above the transition point. The relationship between the melting enthalpies of two solid phases, A and B, (ΔH_f^A and ΔH_f^B) and the heat of transition, ΔH_t is

$$\Delta H_t = \Delta H_f^A - \Delta H_f^B \tag{2}$$

The transition point can be measured by thermal analysis, solubility measurements or by a combination of measurements of solubilities and melting enthalpies.

The form which is thermodynamically stable at the temperature and pressure of measurement is that which has the lowest free energy and the poorest solubility. For each modification, Eq. (3) is valid.

$$\log C = \frac{-\Delta H_{diss}}{RT} + K \tag{3}$$

where C is solubility, T is the temperature in kelvin, R is the gas constant, ΔH_{diss} is the heat of dissolution (or heat of solution) in the solvent and K is a constant. In the case of enantiotropy both modifications have the same solubility at the transition point.

The apparent enantiotropic transition point may differ in solvents (mediated solvent transition) or in the solid state for kinetic reasons. Solvents, impurities or scale changes may have drastic influences on the kinetic process in crystallisation. Nuclei, particle size, impurities, residual solvents and excipients may influence kinetics in the final formulation.

There may be a considerable energy barrier involved in moving from a metastable to a stable state. The activation energy for the transition of a solid phase to the other phase is a kinetic parameter, which may be prohibitively high. Such an example is diamond relative to graphite at room temperature; diamond is kinetically stable although thermodymamically metastable. A pharmaceutical example is the γ form of metolazone which does not transform during storage although it is the highly insoluble α form which is the thermodynamically stable form [4,10,145].

The manufacture of different polymorphic forms, the determination of the stable modification and the knowledge of monotropy or enantiotropy are the initial studies in preformulation work. Since kinetics is an important factor, studies of mixtures with known composition are important in solubility experiments and also in DSC experiments. Metastable states often make interpretations difficult. It is not only unstable forms which show monotropic behaviour that seem to be stable at room temperature. In the case of enantiotropy, a high melting form may also not revert to a low melting form on cooling.

If two polymorphs differ in melting points by 25 to 50°C, in the case of monotropy, the lower melting form will be very difficult to crystallise. The smaller the difference in the two melting points, the more easily the unstable or metastable form may be obtained. Supercooling and superheating are good ways to produce metastable or unstable forms. The kinetic curves of the rate of transition as a

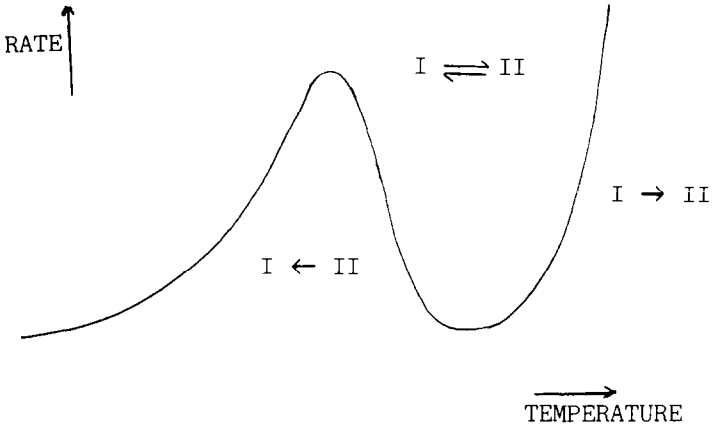


Fig. 3. Temperature dependence of the transition rates for a typical first order transition between a low temperature polymorph I and high temperature polymorph II.

function of temperature, is schematically given in Fig. 3. Near the transition point, the rate is minimal but it increases at higher or lower temperatures. By fast cooling, the rate of transition in the opposite direction may have a maximum and may decrease again and a metastable form is obtained. Transitions in the solid state are correlated with the crystalline structures of each form. Reversible transitions are generally displacive and metastable modifications, apparently stable, undergo a reconstruction transition, which involves a major reorganisation of the crystal structure (e.g. diamond).

From DSC measurements, the melting point, the melting enthalpy and perhaps the transition point may be measured. The plots of the thermodynamic quantities H (enthalpy) and G (free energy) clarify relationships between the polymorphs. Figs. 4 and 5 show such plots and also show the DSC curves, which may be obtained in monotropy or in enantiotropy, with a stable state or a metastable state. For correct interpretation of DSC curves, it is extremely important to remember these curves, because both kinetics and thermodynamics play roles.

Table 3 is a summary of the thermodynamic rules established by Burger [5] in order to help to distinguish between monotropic and enantiotropic transitions.

3.2. Amorphous state

Amorphous forms (amorphates) generally undergo a glass transition, which is a transition of the second order with a change in the specific heat C_p. Crystallisation to the crystalline form is exothermic. Pharmaceutically, the use of glasses or glassy mixtures is attractive because of their enhanced dissolution rate and bioavailability [258,259]. However, depending on the temperature of the glass transition, which may be lowered by the presence of excipients or humidity acting as plastifiers, it is difficult to prevent crystallisation.

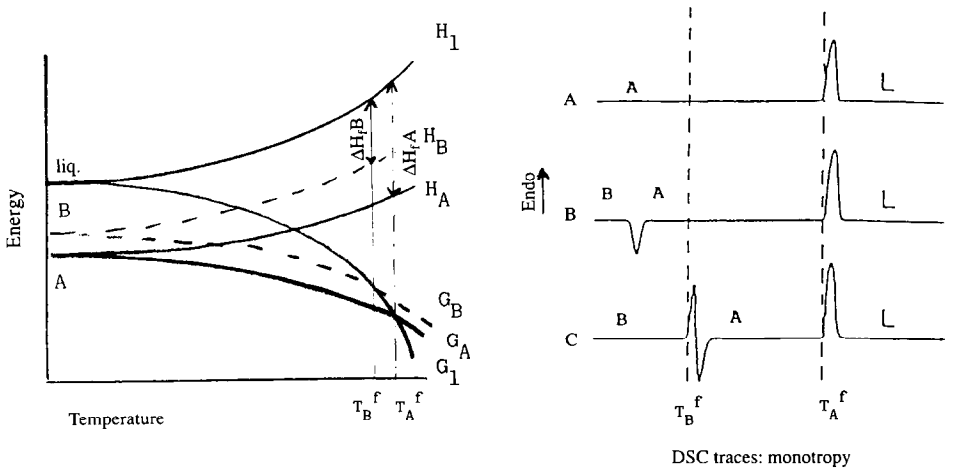


Fig. 4. Energy diagrams showing H (melting enthalpy) and G (free energy) for monotropic polymorphism and the corresponding DSC curves: T_0 is the temperature of the transition A to B; T_A^f is the melting temperature of A; T_B^f is the melting temperature of B. DSC scans: A, the thermodynamically high melting form A melts; B, the low melting form undergoes an exothermic transition into A; C, B melts and A crystallizes from the melt, then A melts.

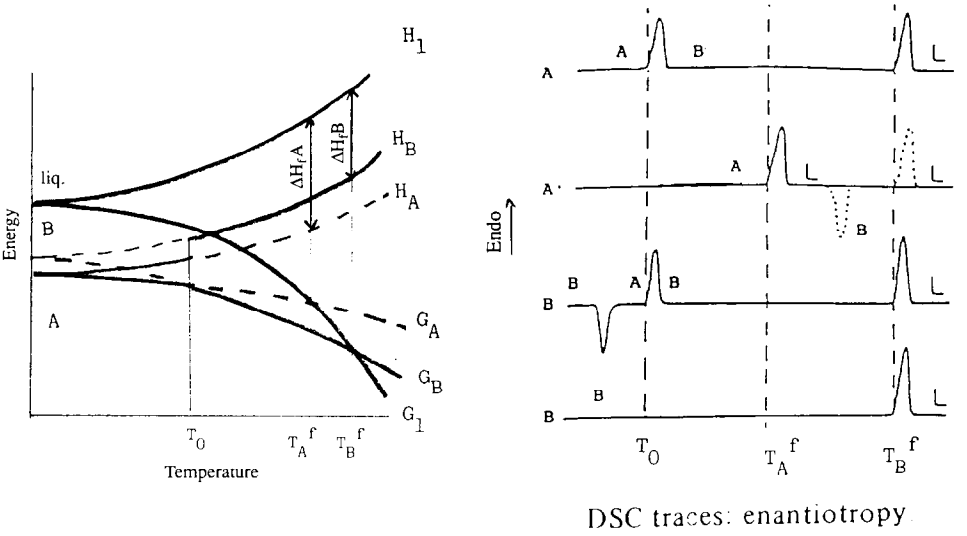


Fig. 5. Energy diagrams showing H (melting enthalpy) and G (free energy) for enantiotropic polymorphism and the corresponding DSC curves: T_0 is the temperature of the transition A to B; T_A^f is the melting temperature of A; T_B^f is the melting temperature of B. DSC scans: A, endothermic solid–solid transition into B, then B melts or A melts and eventually B crystallises from the melts. B, is at room temperature and a spontaneous exothermic transition into A occurs or B melts.

Table 3
Thermodynamic rules for polymorphic transitions according to Burger [5]; I is the higher melting form

Enantiotropy	Monotropy
Transition < Melting I	Transition > Melting I
I Stable > Transition	I always stable
II Stable < Transition	
Transition reversible	Transition irreversible
Solubility I higher < Transition	Solubility I always lower than II
Solubility I lower > Transition	
Transition II → I endothermic	Transition II → I exothermic
$\Delta H_f^I < \Delta H_f^{II}$	$\Delta H_f^I > \Delta H_f^{II}$
IR peak I before II	IR peak I after II
Density I < Density II	Density I > Density II

Relatively stable amorphous forms have been studied for ampicillin, bacitracin, betamethasone, chlorphrenamine hydrochloride, erythromycin, ethylmorphine, imipramine hydrochloride, indomethacin, neomycin sulphate, nystatin, oxyphenbutazone, oxytetracycline hydrochloride, sodium cromoglycate, rifampicin, spiramycin, sorbitol, succinylsulphathiazole, tetracycline hydrochloride, lactose, saccharose and glucose.

Table 4 gives examples of the glass transitions of some drug substances and excipients.

3.3. Pseudo-polymorphism

In the case of solvates, phase diagrams of temperature versus concentration of the solvent (or water) at a given pressure are used for binary systems. In the case of different hydration levels, the most hydrated form will be the stable form at the lowest temperature. The schematic solubility curve of calcium chloride hydrates is given, as an example, in Fig. 6. A pharmaceutical example is ouabaine which is obtained from water as ouabaine · $9H_2O$ at 0–15°C, ouabaine · $8H_2O$ at 15–28°C

Table 4
Examples of glass transitions of drug substances or excipients

Substance	Glass point/°C	Ref.	Substance	Glass point/°C	Ref.
Chloramphenicol	28	[258]	Paracetamol	24	[258]
Glutethimide	0	[258]	Phenobarbitone	42	[176]
Griseofulvin	89	[258]	Sorbitol	4	[13]
Indomethacin	41	[258]	Frusemide	44/54	[111]

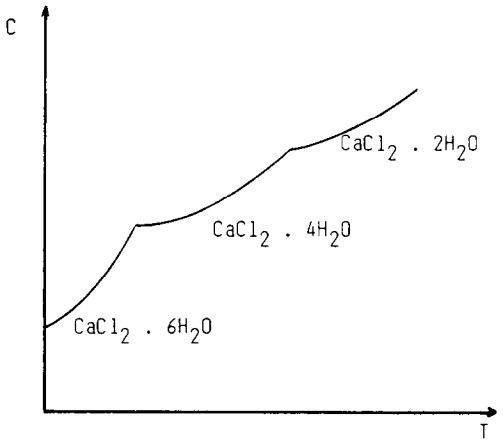


Fig. 6. Schematic solubility curve of calcium chloride hydrates: C is the concentration and T the temperature.

and ouabaine · $2H_2O$ at 28–90°C. In addition, ouabaine · $4.5H_2O$, $4H_2O$ and $3H_2O$ may be obtained from mixtures of water with other solvents. Ouabaine anhydrate is crystallised from ethanol at high temperatures.

It is impossible to ignore solvate formation in crystallisation processes. A solvate may first be crystallised and then transformed into a solvent free form during drying. The form obtained may be thermodynamically stable or metastable which leads to erroneous interpretations. If hydrate formation occurs only in water and if no transition of the anhydrous form to hydrate occurs at high relative humidity levels ($RH \geq 80\%$), the anhydrous form will be preferred, but if the hydrate is formed by the influence of the humidity ($RH \leq 65\%$), such as for example theophylline, caffeine, the choice of the form to be formulated is more difficult.

There are more than 90 hydrates described in the USP monographs. A great number of solvates have been reported, especially for steroids and antibiotics. Cortisone acetate and dexamethasone acetate form 10 different solvates [19]. Solvates and hydrates are best distinguished from polymorphs by the combination of DSC and TG applied to the desolvatation process.

3.4. Nomenclature for polymorphs and pseudo-polymorphs

There is no international conventional system. Roman numerals I, II, . . . , are very often used. According to Halcblian and McCronc [1], form I should be the form most stable at room temperature. Other authors use the range of the melting points [5,19]. Form I has the highest melting point. This system is not satisfactory because full data are sometimes not available and generally further work brings the discovery of new forms. Another classification is the alphabetic classification in the order of discovery. In the past the Greek alphabet (α, β) was used, particularly for fatty acids, alcohols, esters and glycerides. However a clear distinction between

polymorphs and pseudo-polymorphs has to be made, for example, S_A, S_B for solvates A or B or H_A or H_B for the hydrated forms A or B.

4. DSC and TG curves

This section briefly describes the type of curves which may be obtained and the limitation of thermal analysis.

4.1. Types of curves

Polymorphism

Type 1. A solid–solid transition occurs before the melting point of the high melting form. This transition is exothermic for monotropy and endothermic for enantiotropy. No loss of mass is detected by TG. The purity calculation on the melting peak of the high melting form is not affected by this transition if the transition occurs far below this melting.

Fig. 7 shows data for tolbutamide. The transition point is far below the melting point of the high melting form. Fig. 8 shows the case of penicillamine. The transition energy is very low and the transition occurs just before melting. Table 5 gives some examples of endothermic solid–solid transitions measured by DSC.

Type 2. Some substances have two melting points. After the melting of the lower melting form, crystals of the higher melting form grow from the melt, giving rise to

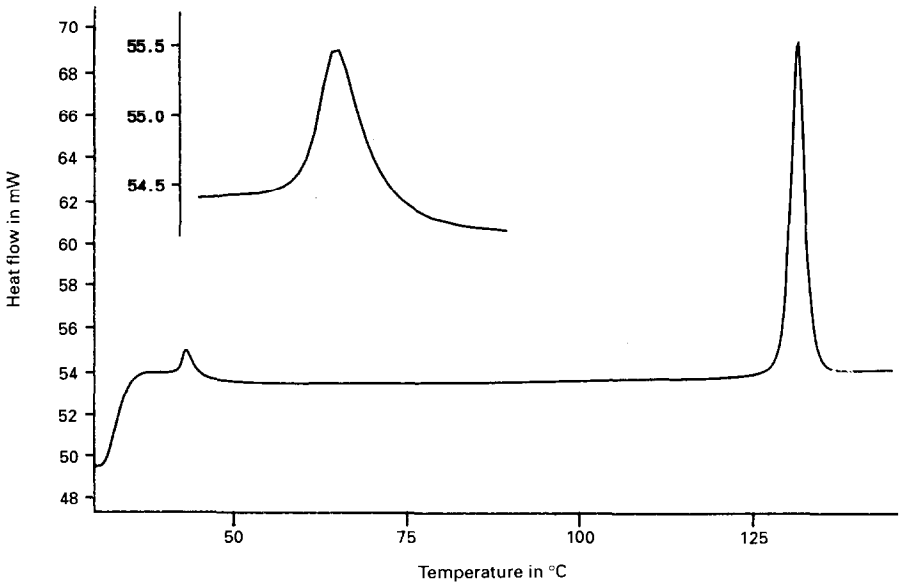


Fig. 7. DSC scan of tolbutamide showing an enantiotropic endothermic transition and subsequent melting.

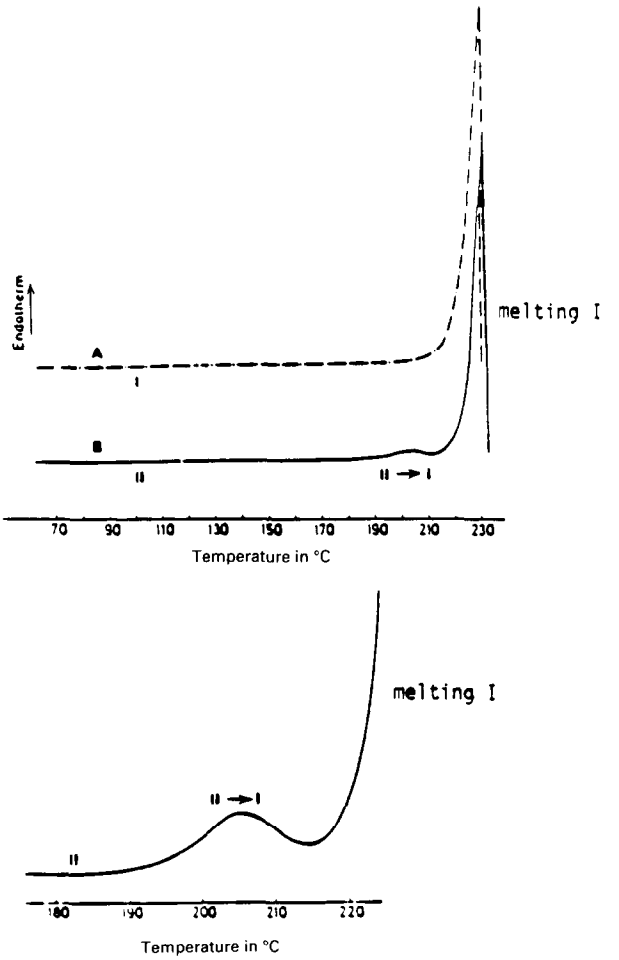


Fig. 8. Enantiotropic transition of penicillamine in the solid state prior to melting: A, batch A; B, batch B. The scale of (b) is $\times 10$ that of (a).

an exothermic peak on the DSC scan. Then the higher melting modification melts, giving a second endothermic peak (Fig. 9). Such a DSC scan can correspond to a monotropy or to an enantiotropy. The sample may be a pure form or a mixture.

The TG curve is extremely valuable in preventing misinterpretation of such curves. McCauley [122] described the DSC curve of phthalysulphathiazole, which presented such a DSC curve with two endothermic peaks separated by an exothermic peak. The TG curve demonstrated a strong decomposition during the first melting. The resulting degradation product then recrystallised and melted at higher temperatures. If an isomerisation takes place, then only the analytical data of the product obtained allows an accurate interpretation.

Table 5
Some examples of enantiotropy with an endothermic transition in DSC

Substance	T_t/°C	ΔH_t	T_f^I/°C	ΔH_f^I	Ref.
Acetazolamide	20.5	1.7 kJ mol^{-1}	263		[35]
Caffeine	141	4.1 kJ mol^{-1}	236	21.6 kJ mol^{-1}	[27]
Carbamazepine	160	3.3 kJ mol^{-1}	189	26.4 kJ mol^{-1}	[64]
Ibuprofen lysinate	64.7	7 J g^{-1}	180	94.7 J g^{-1}	[259]
Indalpin	65		163		[37]
Metoclopramide	125		147		[12]
Proscar	230	11 J g^{-1}	257	88 J g^{-1}	[205]
Succinic acid	140		190		[5]
Tolbutamide	40	8–9 J g^{-1}	128	93 J g^{-1}	[300]

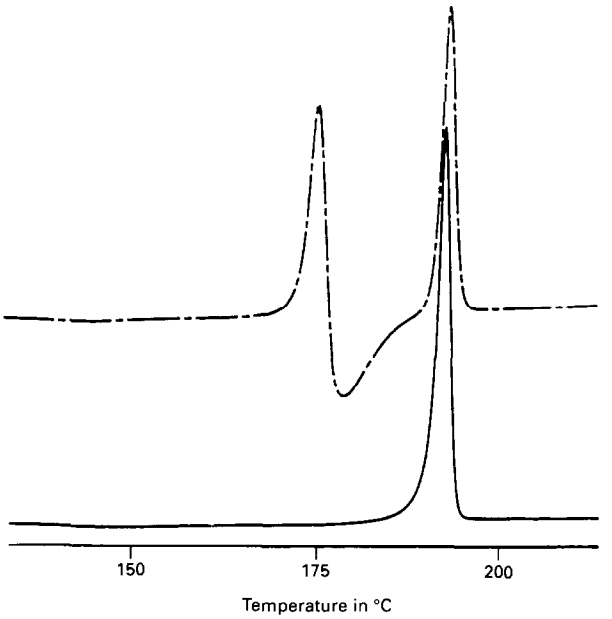


Fig. 9. DSC curve of polymorphs with dual melting because of the crystallisation of a new form which melts at higher temperature: · · , batch 1; ——, batch 2.

Type 3. Each crystalline modification has a melting peak and no conversion between modification occurs (Fig. 10).

No conclusion can be made concerning the thermodynamic stability at room temperature from only one DSC scan of type 2 or 3. Further studies are necessary and will be discussed later.

Amorphous state

In the glassy amorphous state, substances may undergo a glass transition, followed by an exothermic crystallisation and a subsequent melting endothermic

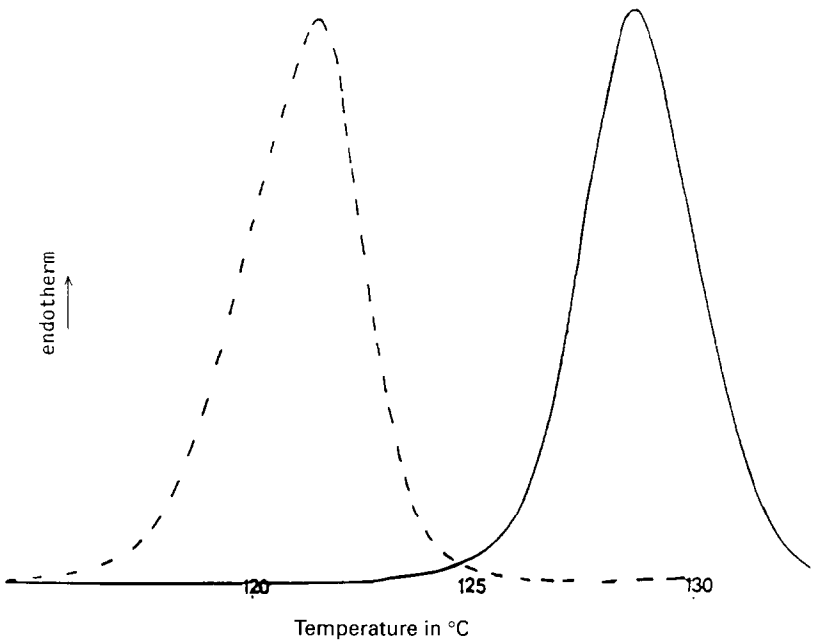


Fig. 10. Curves obtained where each crystalline modification has its own melting peak. No transition occurs during heating in solid state or liquid state (via crystallisation).

peak as demonstrated in Fig. 11. In certain cases, crystallisation to the crystalline form may not happen.

Pseudo-polymorphism

Type 1. Desolvation or dehydration occurs in the solid state with an endothermic peak. The position and the energy of this endothermic peak depend on the phase diagram of two components, the drug substance and the solvent and the stability of the component formed. For instance the different DSC behaviour of the hydrates of two different ergot alkaloids is demonstrated in Fig. 12. In the first case the solvate was totally transformed to the solvent free form at approximately 100°C. In the second case the solvent was not eliminated before 140–150°C.

DSC and TG are particularly useful in the study of hydrates with dehydration steps at low temperature. The reversibility of the process is difficult to avoid in X-ray or IR analysis if the measurements are not done in the absence of moisture resulting in scans of the hydrated form.

Type 2. The dehydration or desolvation process occurs during the melting or after the melting of the solvate (Fig. 13). In such cases, the solvate melts first and the solvent is eliminated from the liquid phase. The observed exothermic transition is due to the crystallisation of the solvent-free form from the melt. Then the melting

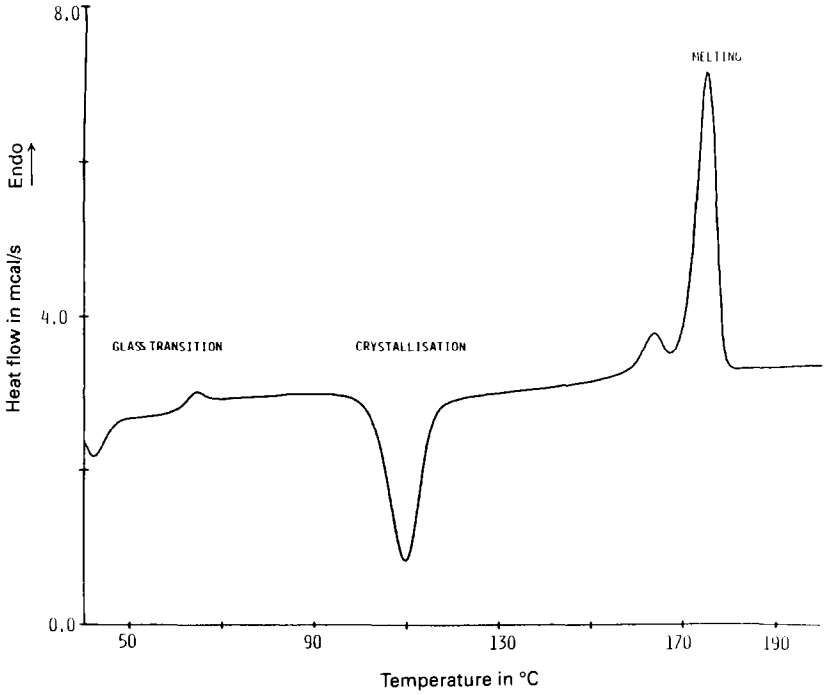


Fig. 11. Typical DSC scan of an amorphous form with glass transition followed by crystallisation and melting. This is the trace for L-polylactic acid.

peak of the solvent-free form is observed. In certain cases melting of the solvate and desolvation of the solid phase may overlap.

Type 3. Different polymorphic forms of the solvate with the same chemical composition may exist. This was demonstrated for two solvates with dioxane of oxazepam [168], for two hydrates of succinylsulphathiazole [19], for two hydrates of nitrofurantoin [160,161] or for three monohydrates of tranilast [216]. McCauley et al. [260] found that the transition point between two enantiotropic dihydrated forms of a drug substance was at 37°C. In the author's experience polymorphism shown by hydrated forms is frequent. Fig. 14 shows such a case for a drug substance which undergoes an enantiotropic transition in the anhydrous state. This form was very hygroscopic and transformed to the trihydrate H_I at room temperature. The DSC scan of this trihydrate shows a dehydration peak in the solid state. The subsequent portion of the scan is equivalent to the original anhydrous form. After storage for several months in a tropical climate (30°C/75% RH), a second trihydrate H_{II} is obtained. The same trihydrate H_{II} is also obtained by crystallisation in water or after equilibration of the original anhydrous form with its saturated aqueous solution. The DSC scan of this trihydrate differs from the first one because the dehydration gives rise to a new anhydrous form. This interpretation was

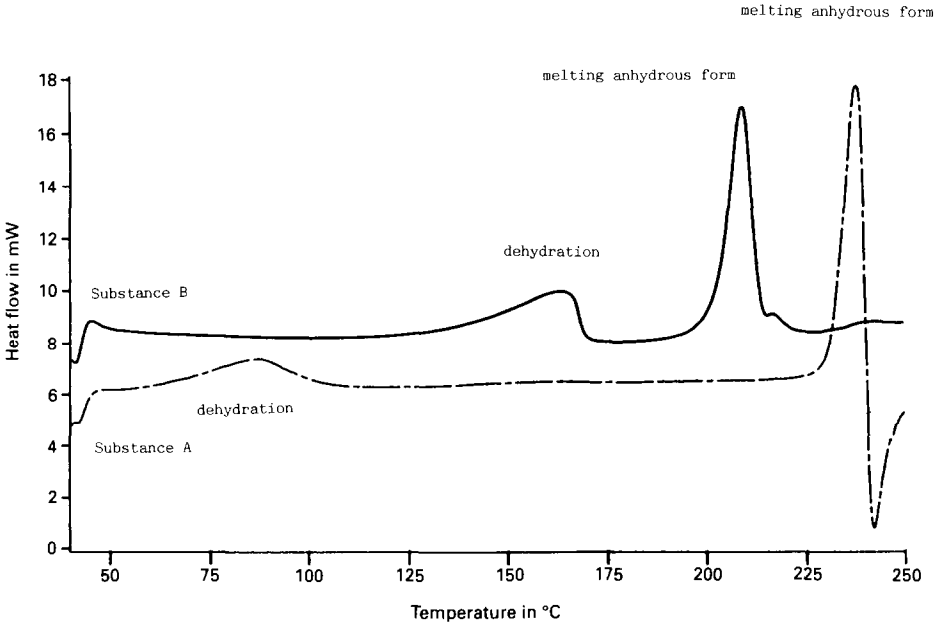


Fig. 12. DSC scans of the hydrates of two different ergot alkaloids with different dehydration temperatures.

confirmed by X-ray Guinier de Wolff diagrams, purity analysis, Karl Fischer and TG [18].

In studies of hydrates, several steps of dehydration should be considered. The combination of DSC and TG allows a specific identification, as demonstrated in Fig. 15, for two batches of calcium sulphate declared to be identical. Not only has ouabain several hydrates; some other examples are 1/4 and 1/2 hydrates of digoxin [91], hemi-, mono- and dihydrates or cephalexin and sesqui-, di-, hemipenta- and pentahydrates of norfloxacin [164].

4.2. Limitations of DSC analysis

Mannitol is an excipient very often used as support for lyophilisation. The author obtained four different modifications and could identify three of them with literature data (IR, X-ray, DSC). DSC scans of three forms were identical. DSC was able to distinguish only one form [13].

Fig. 16 demonstrates the need for additional studies on a drug substance. Since some decomposition occurs during melting, high heating rates were necessary. The lower melting form A has a slightly higher melting energy and a slightly slower dissolution rate. It is not hygroscopic, in contrast to form B. In equilibrium experiments in the presence of alcohols, B reconverts to A. Therefore, it is a case of enantiotropy and A is the stable form at room temperature.

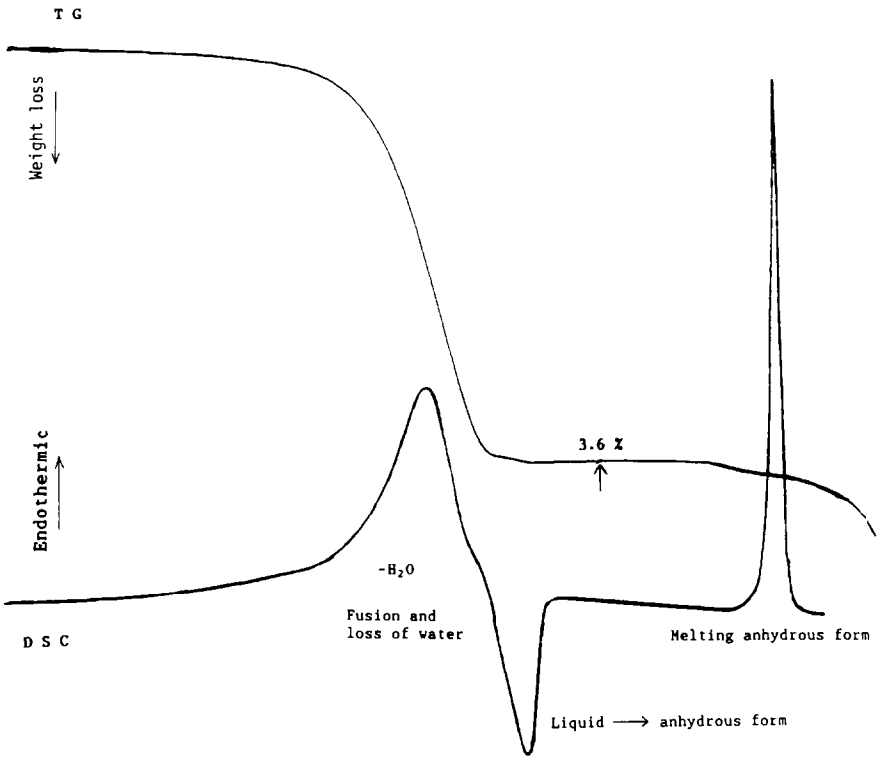


Fig. 13. DSC and TG scans of a substance in which dehydration occurs just after melting and the anhydrous form crystallises from the melt.

If substances such as midodrin hydrochloride [149] decompose and do not display a melting point, DSC is unsuitable for the study of polymorphism.

In the example given in Section 1, the transformation of batch was observed only in the presence of nuclei of the stable form. In this case, both forms A and B had distinct melting peaks. DSC scans of laboratory mixtures of both modifications showed two peaks. It was hoped to quantify each form in the batch while undergoes a transformation after storage. The DSC scans of samples stored were broad and the two peaks were not separated. This case demonstrates how difficult it is to predict the real behaviour of mixtures of polymorphs because of kinetic factors [10].

4.3. Better understanding of polymorphic materials using oscillating DSC (or modulated DSC)

With DSC or ODSC, an oscillating time temperature wave is applied with simultaneous heating (or cooling) at a constant rate. This allows the separation of the parent DSC signal (obtained using Fourier transform analysis) into two distinct components, the specific heat C_p (reversible) component and the kinetic (irreversible) component. This information allows for better interpretation of DSC

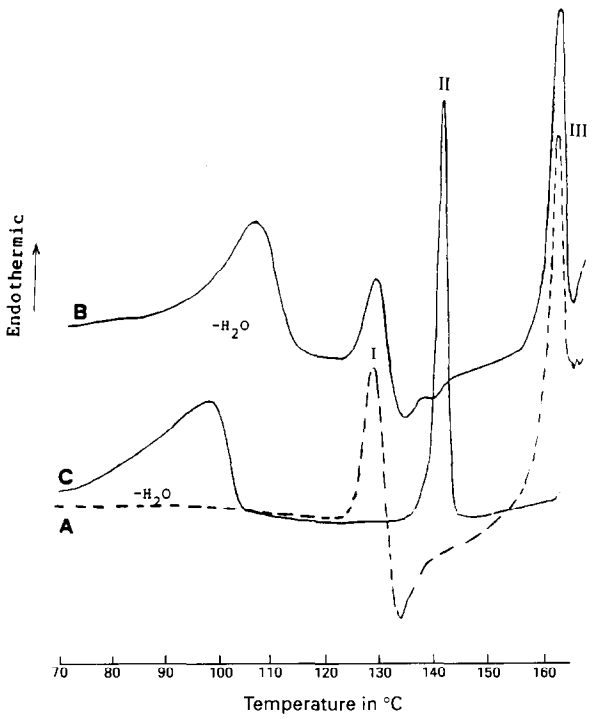


Fig. 14. Case of polymorphism of trihydrate. The anhydrous form has three modifications. Two modifications are enantiotropic. Curve A, dual melting of the anhydrous for; curve B, trihydrate H_I; curve C, trihydrate H_{II}.

events which overlap. For example a desolvation (irreversible) will be seen on the kinetic curve. Fusion will be seen on the C_p component. Crystallisation will be seen on the kinetic component [261,262].

4.4. High resolution TG

The heating rate is slowed down during a mass loss transition and increased when there is no mass loss. Overlapping mass loss events are better separated [261].

5. Factors influencing DSC and TG curves

This factors influencing the DSC and TG curves are responsible for misinterpretations as described by several authors [206,263–266].

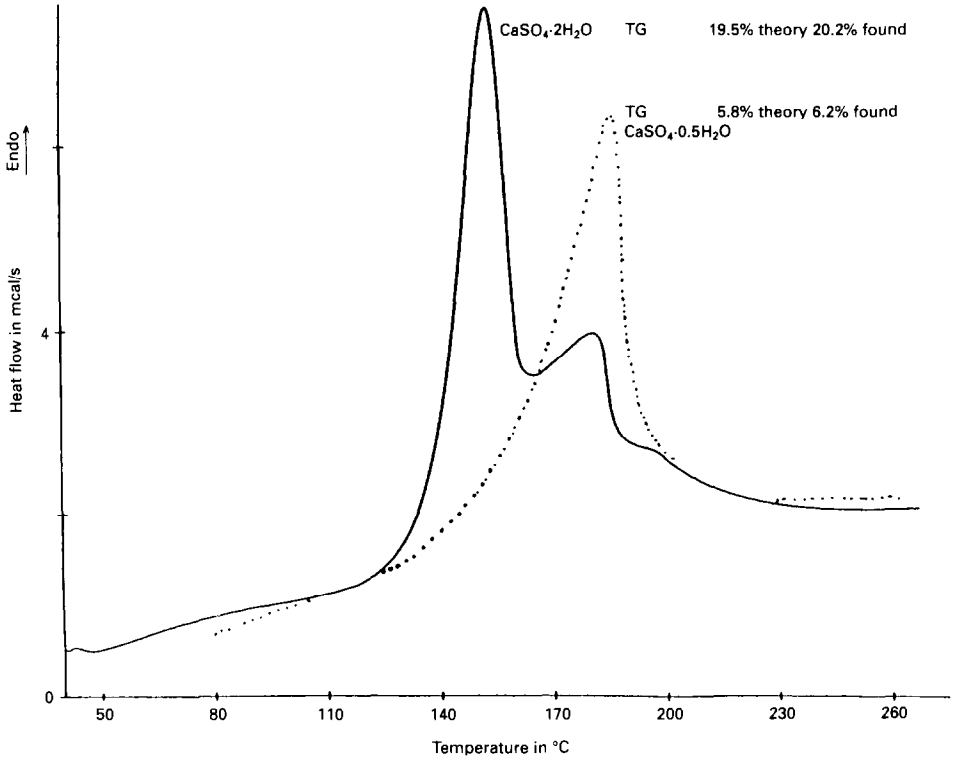


Fig. 15. DSC curves of two batches of calcium sulphate declared as identical. The first one is calcium sulphate dihydrate. The second is calcium sulphate hemi-hydrate.

5.1. Influence of experimental factors

The heating rate in DSC and TG and also the sample mass have a direct influence on the resolution of thermal events, and this influence is dependent on the instrumentation (thermal lag).

Polymorphism

Reversible solid–solid transition, as seen in tolbutamide, is not greatly influenced by the heating rate and is an exception. Generally, the heating rate has a strong influence on the kinetics and on the resolution of two peaks. A quick heating rate allows the melting of the lower melting form to be obtained. If the heating rate is too quick, so that no time is given for the recrystallisation from the melt of the higher melting form, a single melting peak of the low melting form is obtained. Such an example is given for temazepam in Fig. 17 [206]. At medium heating rate, the melting peak of the low melting form is followed by the melting peak of the high melting form. Only at slow heating rates does the recrystallisation exotherm of the liquid in the high melting form appear. Fig. 17 also illustrates the influence of

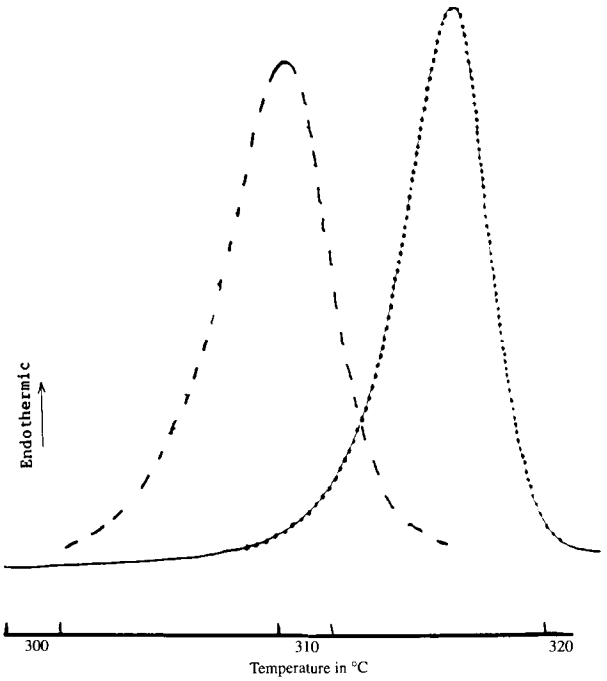


Fig. 16. Polymorphic behaviour of a benz-isoquinoline hydrochloride. Modification A is the stable form.

	Modification A	Modification B
Melting temperature/°C	304	311
ΔH/kcal mol^{-1}	12	11
Time in min for 90% dissolution:		
pH 1.2	3	4
pH 7.5	3	6
Particle size (more than 99%)/μm	194	80
Mass gain/%		
1 day 92% RH	0%	3.2% (hydrate)
1 month 92% RH	0%	3.2% (hydrate)
Transition in alcohols	A	B → A

the sample mass. The smaller the sample, the better is the resolution of the instrument and the transition is quicker.

The transition of temazepam was studied in more depth. It corresponded to monotropy. The exothermal monotropic transition, which should occur, was not detected in the DSC scan.

The DSC scans of an enantiotropic transition of tetracaine hydrochloride behave very similarly [209]. At a high heating rate a dual melting was observed; at a lower heating rate the solid–solid enantiotropic transition was observed. Such cases have been described in the literature, for example for carbamazepine [63].

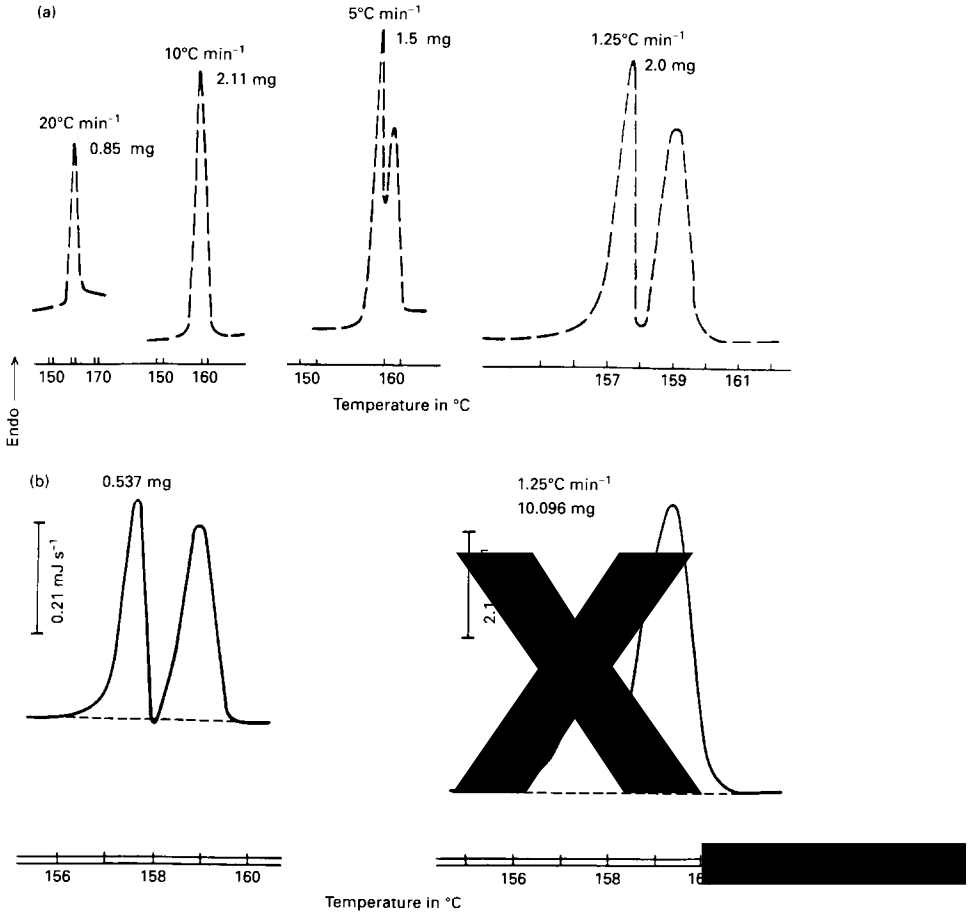


Fig. 17. Influence of (a) the heating rate and (b) the sample mass on the DSC scan of a metastable form of temazepam.

Unfortunately, if substances decompose under melting, a slow heating rate is not feasible and may give rise to artefacts. Exothermic degradation was observed before the melting peak of an ergot alkaloid when the DSC curve was recorded under air [206]. In order to avoid such problems, the use of nitrogen is recommended for all DSC experiments.

It may be that the solid–solid transition does not appear because of its very small enthalpy. In these cases, the decrease in the heating rate leads to the total transformation to the high melting form without detecting any transition in the DSC scan. The melting enthalpy rule of Burger is very helpful (Table 3). If the high melting form has the lower melting enthalpy, both forms are enantiotrophs and if the high melting form has the higher melting enthalpy, they are monotrophs.

Butylhydroxyanisole displays polymorphism [13]. Depending on the heating rate two peaks with different ratio were observed. In order to use the melting enthalpy rule, both forms have to be prepared. For that purpose a quick heating rate allowed the author to calculate the first enthalpy (103 J g^{-1}) because only one melting peak was obtained. Then, in order to calculate the enthalpy of the high melting form, the sample was tempered at 60°C and totally transformed into the high melting form. The melting enthalpy was found to be 87 J g^{-1}. This is also a case of enantiotropy. Within a few days the high melting form converted to the stable form at room temperature.

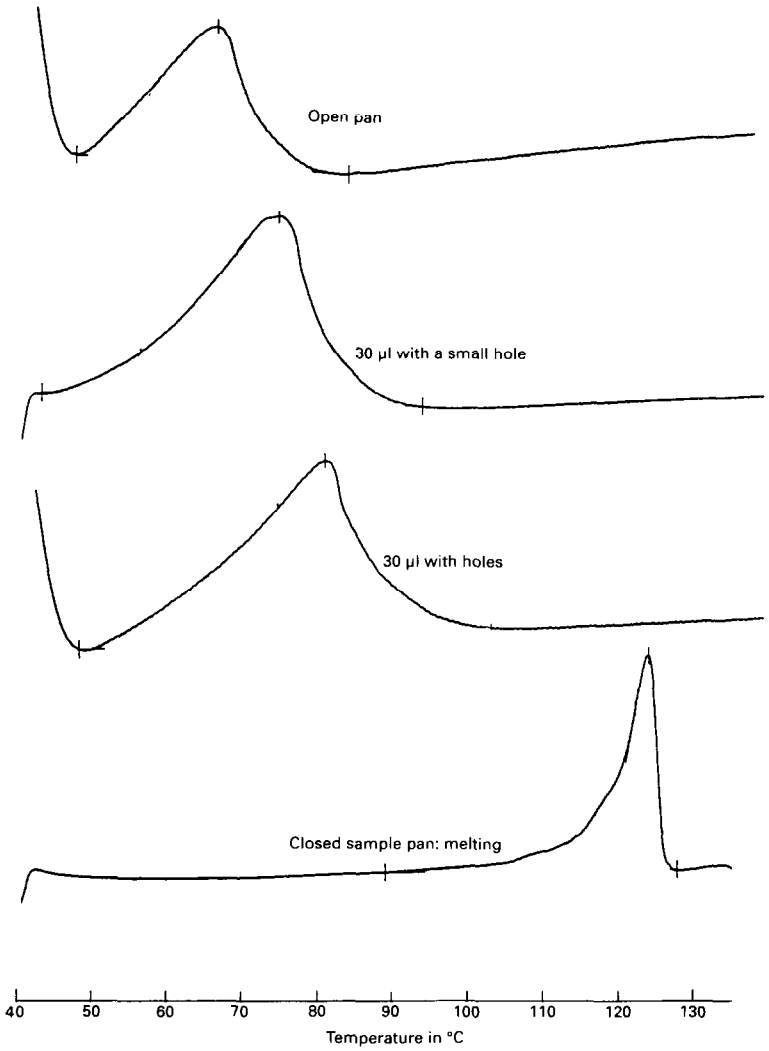


Fig. 18. Influence of the design of the pan on the DSC scan of a dihydrate. The same conditions were used for each run; heating rate was 5 K min^{-1}.

Amorphous state

Because the signal of the glass transition is proportional to the heating rate, a high heating rate is better. Generally, several cycles are suitable in order to eliminate the moisture and the thermal history of the sample. For crystallisation and melting events, on the contrary, slow heating rates are better, in order to allow quantitative data to be obtained.

Pseudo-polymorphism

The most spectacular influence is that of the sample pan type. In DSC experiments, different types of pan may be used. In hermetically sealed pans, the solvent cannot escape and remains in the pan. In this pan, the melting peak of the solvate may be observed if the pan does not open under the pressure of the vapour. If a small pin-hole is made in the cover of the pan, or if a crimped pan is used, the solvent can escape and the DSC curve will depend on the heating rate and the flow gas. In some cases, both melting of the solvate and desolvation in the solid state happen, which gives two endothermic peaks.

Fig. 18 demonstrates the influence of the pan. If the pan is open, dehydration occurs at approximately 70°C from the solid. If a cover with a pin-hole is used, the solvent is eliminated slowly. If a sealed sample pan is used, the solvent is not eliminated in the solid state and the dihydrate melts. Fig. 19 shows the DSC scans of a hydrate and the anhydrous form in two types of pan. If, for quality control, the sealed pan has been chosen, one must ensure a good sealing process in order to

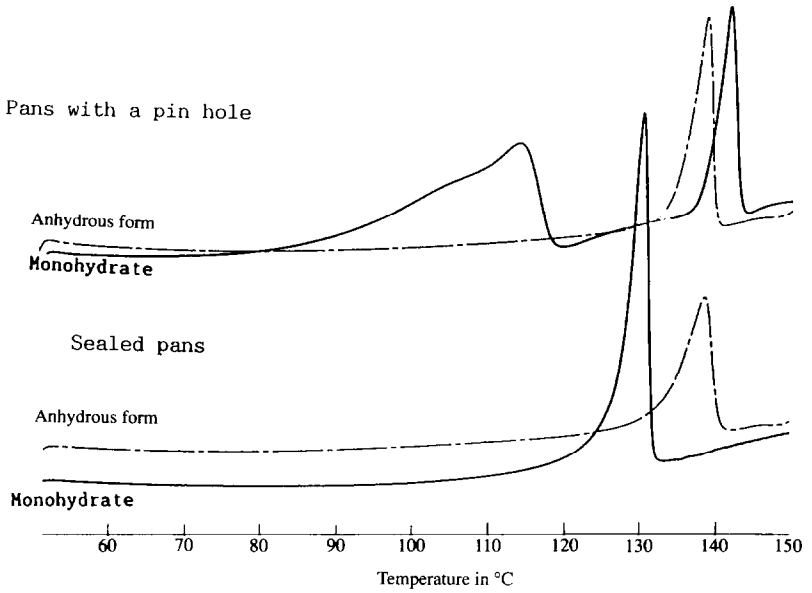


Fig. 19. Influence of the sample pan type on DSC curves of the monohydrate and of the anhydrous form obtained using sealed pans and pans with a pin-hole.

avoid artefacts. The presence of solvent or water as vapour around the crystal in the atmosphere of the pan may induce metastable solvate-free forms and also the amorphous state. This explains the discrepancies observed in the literature for interpretation of DSC curves and comparison with TG (for which open pans are generally used) or comparison with heat controlled X-ray or heat-controlled IR experiments.

Heating rates, sample size and the use of the derivative curves of TG (DTG) allow the optimisation of the separation of overlapping steps of desolvation or dehydration.

5.2. *Influence of the sample*

Particle size, impurities, crystal shape and nuclei of polymorphs are the main factors affecting the kinetics of phase transitions.

Amorphous state

The glass transition of amorphous forms is deeply influenced by impurities which play the role of plasticisers. For example the glass transition is generally strongly dependent on the amount of water. Therefore, it is recommended that the values of the glass transitions of the first DSC scan and of a second one after elimination of the solvent be compared if the measurement of the glass transition of anhydrous amorphate is desired. Amorphous substances are hygroscopic. The presence of moisture lowers the glass transition point, and consequently the crystallisation temperature in the crystalline form.

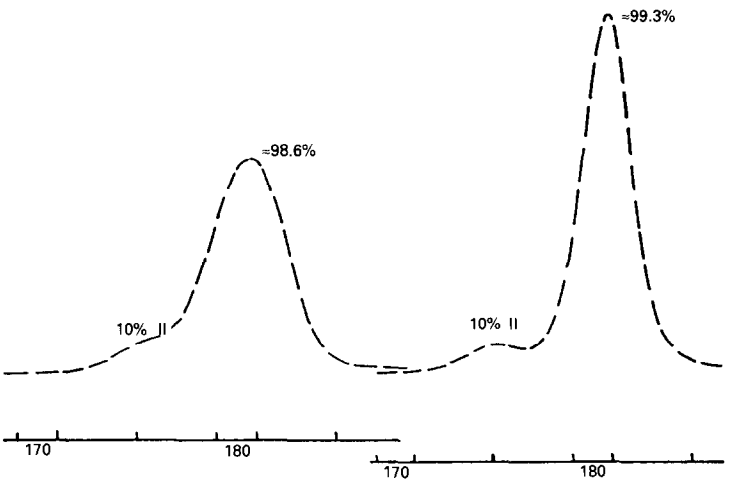


Fig. 20. Influence of the chemical purity of the sample on the resolution of polymorphs (mixtures of form I and form II, 90:10 m/m with samples of form I of different purity) by DSC.

Polymorphism

The influence of impurities on polymorphic behaviour may be drastic. The case of a drug substance for which only one form was obtained in all screenings for polymorphisms has been described by the author. In order to validate the DSC purity analysis, a mixture with a given impurity was manufactured by evaporation of a solution. A new metastable form was obtained, which did not appear in the similar experiment carried out with the pure batch [18].

Fig. 20 shows the influence of the chemical purity of the sample on the separation of two crystalline modifications. Because impurities decrease the melting point and have a broading effect on the peak shape, the DSC scan will not permit a distinction between polymorphs if their melting points are very close. Thermomicroscopy is a very useful instrument in identifying such cases.

Fig. 21 demonstrates the role of nuclei of the thermodynamically stable form on the DSC scans of the metastable forms. The DSC of the two modifications A and B of a drug substance, at all heating rates and also with isothermal tempering,

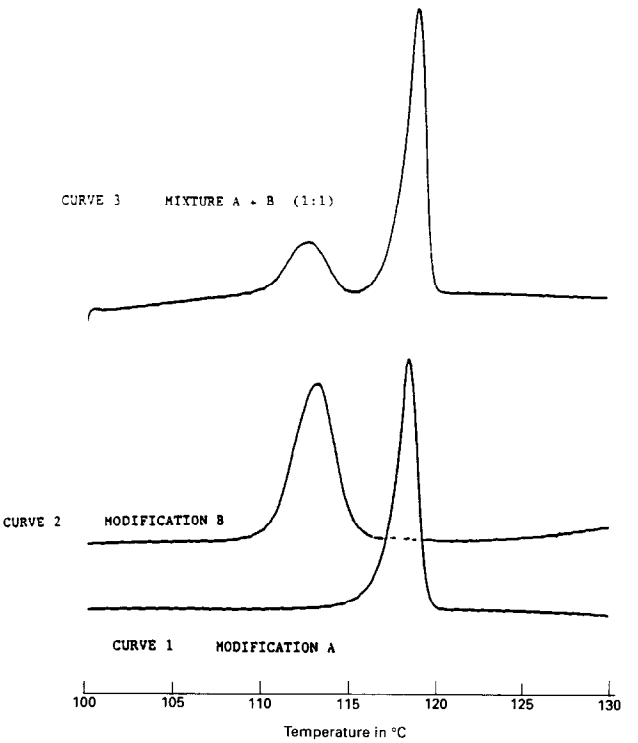


Fig. 21. Effect of nuclei of the DSC curves. Example of a drug substance with two modifications A and B; each modification has a sharp melting curve. Curve 1, modification A with ΔH_A 90 J g^{-1}, onset at 118°C; curve 2, modification B with ΔH_B^A 93 J g^{-1} and onset at 111°C; curve 3, mixture A + B (1:1). Measured value for ΔH_A is 68 J g^{-1} and theoretical value is 45 J g^{-1}. It may be concluded that part of modification B is transformed into modification A prior to its melting only in the mixture.

could not demonstrate the presence of a transition of A into B or B into A. It could be deduced from the melting positions and enthalpies that the low melting for was the stable form at room temperature; however, the melting enthalpies differ by only 3%. Therefore, DSC scans were performed by using mixtures of both modifications. Comparing the melting enthalpies of the mixture with the melting enthalpy of both modifications, it was observed that the corresponding peak of the high melting form B was higher than expected (68 J g^{-1} compared with the theoretical value of 45 J g^{-1}). This fact demonstrated that some transition of A into B occurred before the melting of B in the mixture. The influence of nuclei of crystalline modifications has also been studied for gepirone hydrochloride [267].

Fig. 22 deals with propyphenazone and demonstrates both the role of manufacture and of the heating rate. The DSC scan of batch 1 of manufacturer 1 did not show transitions of form I into form II until the slow heating rate of 1.2 K min^{-1} was used. Batch 2 of manufacturer 2 gave irreproducible DSC scans due to transitions at higher heating rates. Impurities or solvent, or amorphous portions or some amount of form B kinetically play a role in the transition which was almost completely achieved for batch 2.

Different metastable or stable modifications may be obtained from the melt. If no method other than DSC is used, wrong interpretations may be made. Fig. 23 concerns a drug substance which shows that after melting, two different higher melting forms can grow from the melt. Depending on the crystallisation and drying of the samples, form B or form C may appear after the melting of A. The transitions of this drug substance were studied in depth. A and C were found to be enantiotrophs. B was a monotroph. The X-ray diagrams of the three samples presented in Fig. 23 did not differ significantly.

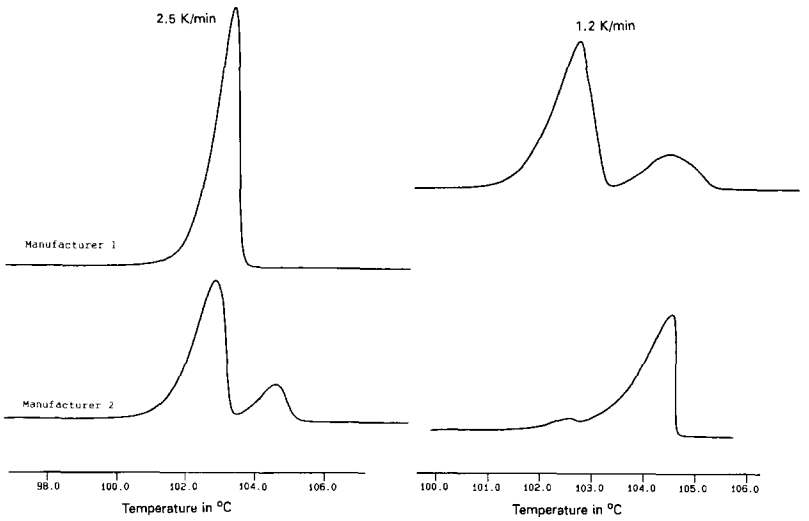


Fig. 22. DSC scans of propyphenazone demonstrating the influence of the heating rate and of the origin of the sample. The transition in the high melting form is quicker for the batch of manufacturer 2.

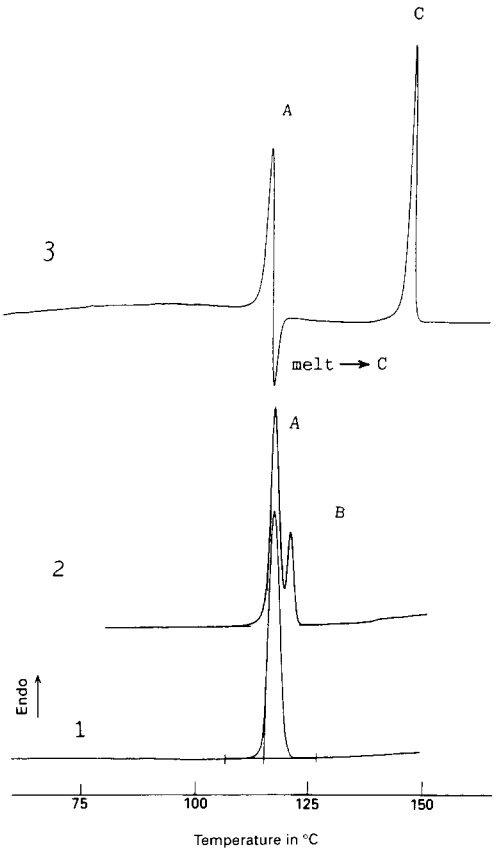


Fig. 23. DSC scans of three batches of a drug with the same X-ray diffraction pattern showing different behaviour after melting. Two different metastable forms (B or C) may appear from the melt of A.

Pseudo-polymorphism

In addition to the influence of experimental factors, the particle size is a most important factor which plays a role in the dehydration onset.

Fig. 24 deals with a very hygroscopic drug substance. In order to manufacture the dihydrate, crystallisation experiments were undertaken in different alcohol/water mixtures. DSC and TG very rapidly allowed differentiation between the hydrate and a solvate formed with ethanol.

5.3. Determination of the transition point by combination of DSC with solubility measurements

When the melting points of two modifications are within 2–3°C of each other or when the energy of transition is too small, DSC cannot give any indication of the transition temperature.

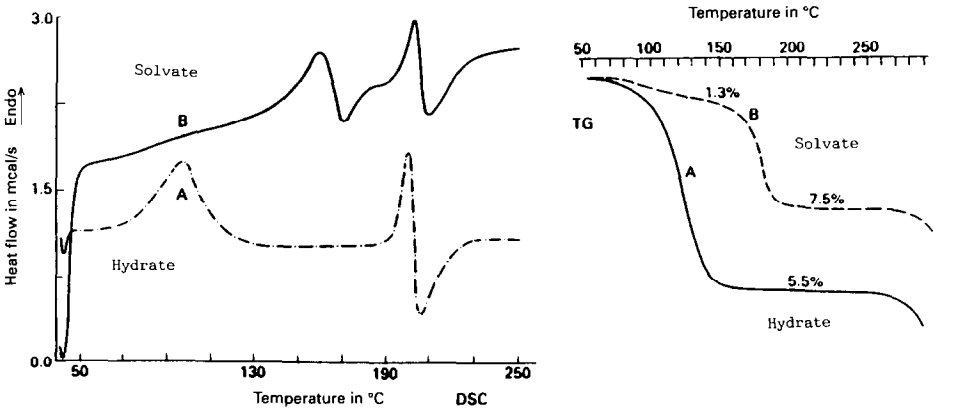


Fig. 24. Differentiation between hydrate (curve A) and solvate (curve B) by comparing the position of dehydration and desolvation peaks and by comparing TG results.

The enantiotropic transition temperature may be calculated from thermodynamic calculations because at the transition point, both modifications have the same solubility.

$$RT \ln x_A = \Delta H_f^A (T_0^A - T)/T_0^A \quad (4)$$

$$RT \ln x_B = \Delta H_f^B (T_0^B - T)/T_0^B \quad (5)$$

where ΔH_f is the melting enthalpy of A or B and T_0 is the melting point of A or B.

At the transition temperature T_t, Eqs. (4) and (5) are simplified to

$$T_t = \frac{T_0^A T_0^B (\Delta H_f^A - \Delta H_f^B)}{\Delta H_f^A T_0^B - \Delta H_f^B T_0^A} \quad (6)$$

For carbamazepine, Behme and Brooke [64] determined this temperature to be 71°C while in DSC the transition at 2 K min^{-1} was observed at approximately 150°C. A value of 73°C was obtained by intersection of the van't Hoff plots of the solubility curves in 2-propanol [64].

If the DSC shows only a solid transformation, knowing T_t, the melting point of the lower melting form can also be deduced.

6. Manufacture of modifications

DSC is very useful, due to its facilities for heating and cooling, in inducing the formation of metastable forms. Furthermore, pure forms may be obtained using tempering (isothermal holding).

Fig. 25 concerns β-hydroxy-propyltheophylline. After heating just above the melting point and cooling, the second heating curve shows a new metastable form which, after melting, undergoes a crystallisation to a third modification. In this example, the scan was obtained only with an impure sample [206].

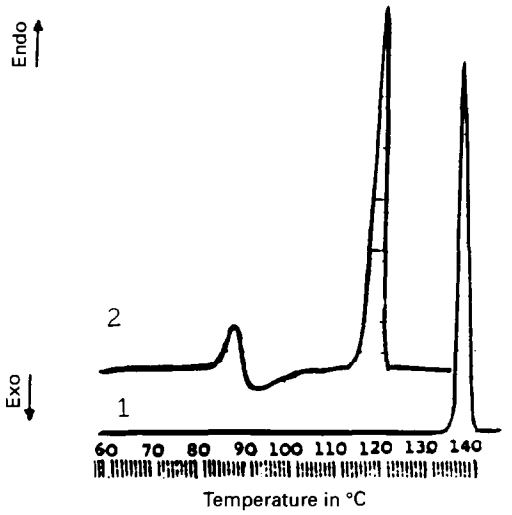


Fig. 25. Manufacture of metastable modifications in the DSC cell. Impure sample of β-hydroxypropyltheophylline. Curve 1, first DSC scan; curve 2, second run after quenching from the melt.

Fig. 26 demonstrates the use of cooling and reheating curves for a purine derivative. The DSC scan of the sample showed a small endothermic peak before melting. The cooling and reheating experience showed that the endothermic peak is reversible, a case of enantiotropy. This explained why, in all crystallisation experiments, it was not possible to isolate at room temperature the second form obtained only at temperatures above this transition. The same procedure was used for

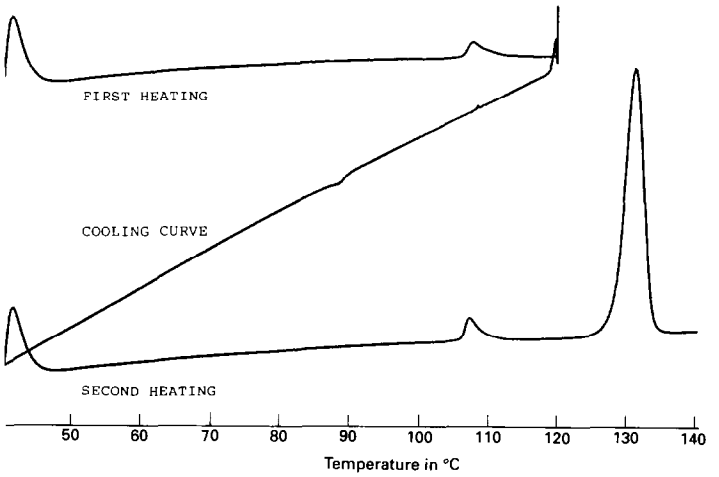


Fig. 26. Use of heating and cooling cycles from the study of a reversible endothermic transition of a purine derivative.

tolbutamide. The values of the heat of transition obtained by heating or by cooling were almost identical [300].

The polymorphic behaviour of propyphenazone shown in Fig. 22 could be studied because it was possible to find a reproducible way of obtaining the pure high melting form [4,268]. An isothermal treatment at 100°C, just before the melting of form I of samples of manufacturer 2 was undertaken. The pure forms could be used for equilibrium experiments with solvents, solubilities and DSC study of the phase transition. It is a case of enantiotropy which also confirms the melting enthalpy rule of Burger. The higher melting form was stable for several months at room temperature. Characteristic physical parameters could be measured and an X-ray diffraction quantitative method was elaborated [145]. It was also possible to obtain mixtures of both forms by rapid cooling from the melt.

Fig. 27 deals with a methyl-naphthalene derivative with two modifications. Each modification has its melting point. Because the melting enthalpy of the high melting

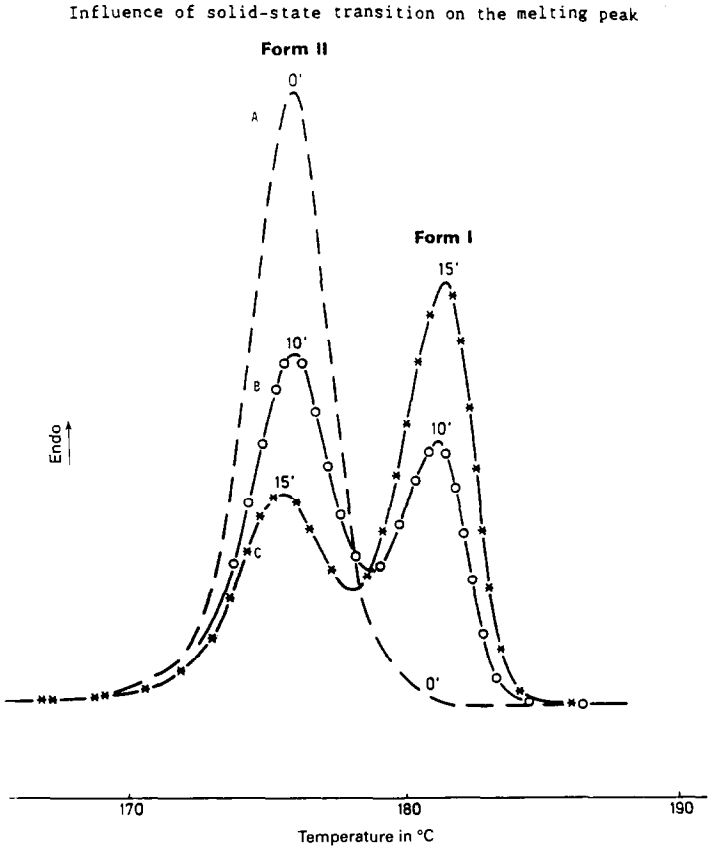


Fig. 27. Influence of isothermal pretreatment of a metastable modification of a methyl-naphthalene derivative. Curve A, DSC run of form II; curve B, DSC run of form II after pretreatment for 10 min at 150°C; curve C, DSC run of form II after pretreatment 15 min at 150°C.

form was higher, it should be a case of monotropy, but no transformation of the lower melting modification (called form II) was apparent on the DSC scans. The lowe melting form had a slightly higher solubility in water (0.78% at 25°C compared to 0.68% for form I). Mixtures of both forms were studied using equilibration of saturated solutions. Form I was obtained and therefore was the stable modification at room temperature. From these results, a transition in the solid state before melting of form I should be possible. Pretreatment at 150°C of the lower modification allows a complete transition in form I. Fig. 27 shows the DSC scans obtained with modification II after different pre-treatment times at 150°C.

Fig. 28 shows the case of an aminobenzoic acid ester with a solid–solid endothermic enantiotropic transition of modification B into modification A before melting of the form A. Some batches showed only the melting peak of form A. The melting point did not allow a differentiation of both forms. A tempering of form B after the first endothermic peak and cooling allowed form A to be obtained as demonstrated by additional X-ray diffractograms. The rate of transformation of this "metastable" form A was very slow. Analysis of samples which were mixtures of both forms revealed them to be very stable on storage.

Modern equipment includes robotics [269]. Therefore, such heating–cooling cycles are very efficient for the study of polymorphism. Thermal analysis methods are generally completed by spectroscopic techniques [91,260,267], or by thermo-

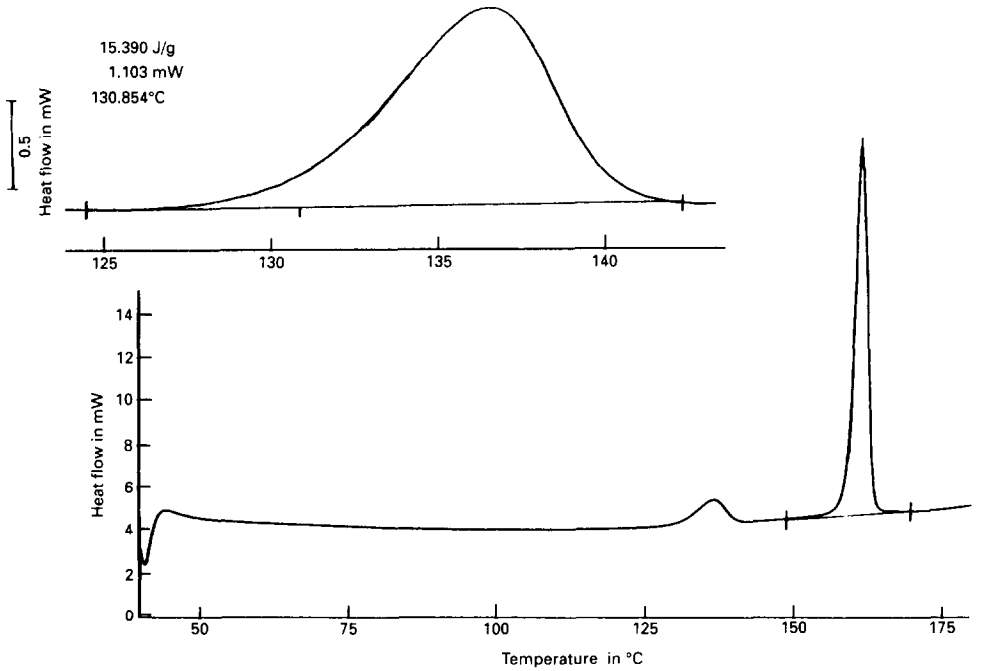


Fig. 28. Enantiotropic transition of an aminobenzoic acid derivative. The high melting form does not revert to the low melting form after cooling. The top trace is an enlargement of the lower trace.

microscopy [20]. Thermo-optical methods [270] include use of the microscope, video camera and photo monitor. A thermal-optical curve (TOA) is obtained.

7. Combined thermal and spectroscopic methods

Temperature resolved X-ray powder diffraction and temperature resolved FTIR combined the controlled heating of the sample with a spectroscopic measurement. Both techniques are ideal complements to thermal analysis for correct interpretation of DSC thermal events. Changes of structure during the heating of the sample, for which no DSC thermal event is detectable, can be clearly demonstrated.

The temperature resolved X-ray powder diffraction technique is increasingly being implemented in polymorphism studies [271]. Epple and Cammenga [272] used it for caffeine, Guyot-Hermann and Conflant for lactose [243], mannitol and paracetamol [170].

The Scintag X-ray power heating cell was used in order to study the solid–solid transition of the purine derivative, given in Fig. 26 [300]. The X-ray diffractogram was taken at 25°C, 80°C, 105°C, 115°C, 120°C, then the cell was cooled to 50°C and heated again up to 125°C. This experiment confirmed the temperature range of the transition and its reversibility. The diffractograms measured at 50°C and 125°C are given in Fig. 29.

Details describing the combination with FTIR [273] and especially FTIR microscopy during heating have also been published [156].

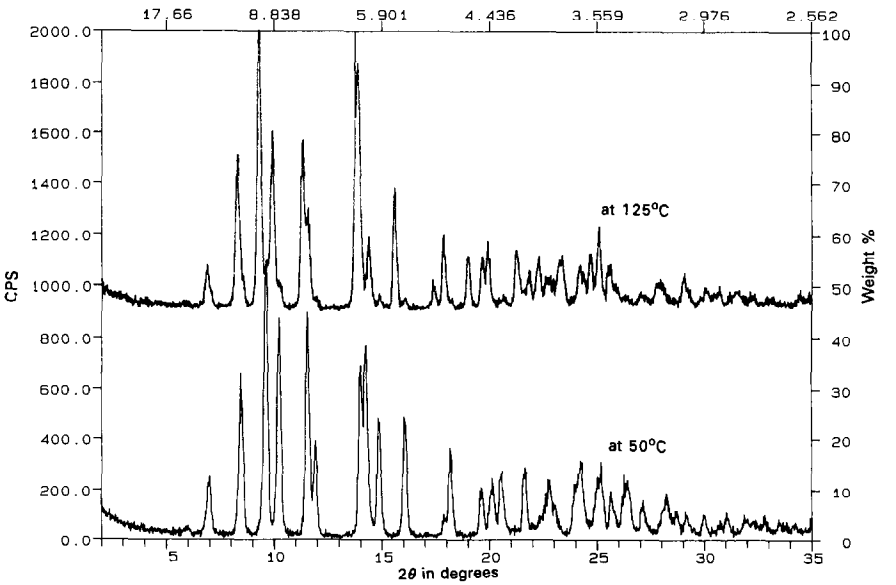


Fig. 29. Temperature resolved X-ray powder diffractogram corresponding to the DSC scan of Fig. 26.

8. Studies of fats and of dosage forms

8.1. Polymorphism of fats

All the derivatives of fatty matter present the phenomenon of polymorphism. Thermal analysis is widely used for characterisation and ageing controls of paraffins, fatty acids, alcohols, esters and, above all, glyceride derivatives (mono, di, tri) which are natural constituents [231–240,274–276].

Consequences for pharmacy

The problem of ageing of suppository masses has been known for a long time. Cocoa butter has at least six polymorphs. During storage, the transition to a stable form is indicated by an increase in the melting temperature of the mass of the fatty matter. Numerous authors have shown that this transformation for masses with a high melting point is accompanied by a loss in bioavailability of the dosage forms [7,11]. Fig. 30 shows two cases where it was decided to change the suppository base due to this ageing problem.

DSC analysis is particularly useful for the study of fats because the final melting can be measured accurately. The percentage of the solid mass, called the solid index, can be calculated and plotted as a function of temperature. The first example, given in Fig. 30(a,b), concerns suppositories manufactured by compression. The excipient, which was stored at room temperature, was reused for a second batch six months after the manufacture of the first batch. The DSC curves reflect the ageing of the mass and a difference in the dissolution rate is observed for the second batch at 36.5°C [233]. The second example (Fig. 30(c,d)) shows the influence of the stored temperature. A temperature increase of approximately 3°C for the point corresponding to 50% of the melting if the suppositories are stored at 25°C occurred, whereas there is practically no change for the suppositories stored at 5°C or 20°C.

DSC was very suitable for ageing studies of glycero-palmitostearate [13]. The DSC scans were used in order to know the melting range of this excipient throughout the storage conditions. The temperature of the manufacturing process and the ageing of the formulations done with this excipient may also be affected.

In the case of liquid oils or derivatives, the solid fat index obtained by DSC is currently used for monitoring crystallisation or separation processes or for blending [234,275–278].

8.2. Dosage forms

DSC is extremely valuable for analysing small samples and can be used to solve some problems in the dosage form. For example, crystal growth in a commercial cream of phenylbutazone was due to the formulation [29]. A new highly insoluble modification was induced by the liquid excipients of the galenical solution [279]. Therefore the new modification was prepared and was used for the optimisation of a new liquid formulation.

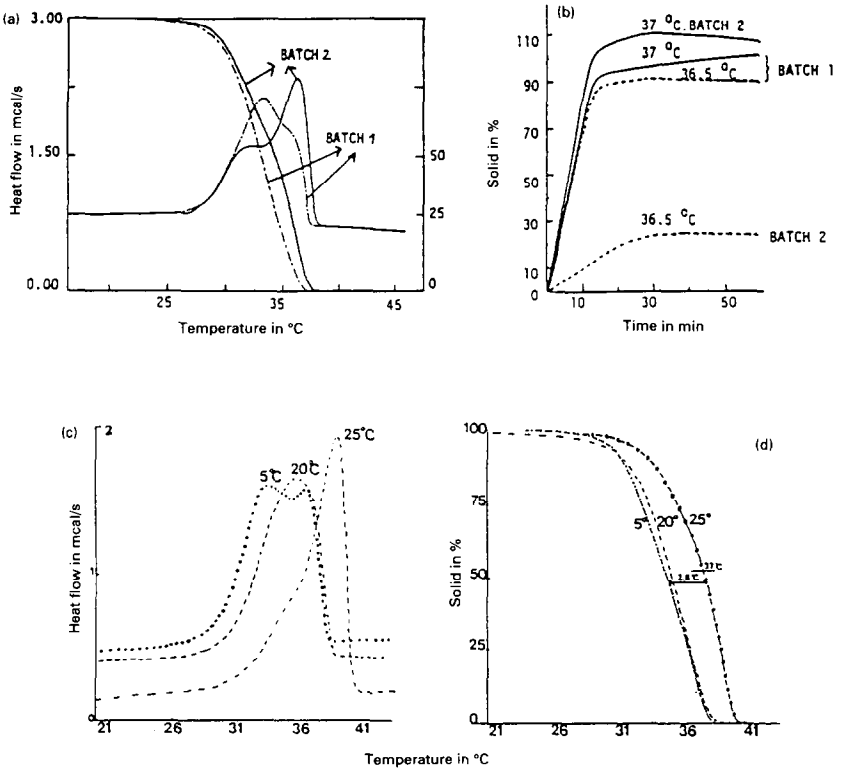


Fig. 30. Problems arising from suppository masses being waxes which exhibit polymorphism, $\alpha \leftrightarrow \beta' \rightarrow \beta$. Effect of batch reproducibility due to raw material is shown by (a) DSC curves of two batches of compressed suppositories manufactured with the same batch of Witespol H15 within 6 months and (b) corresponding dissolution rate curves. Ageing effect giving rise to problems in dissolution rate and availability is shown by (c) DSC curves and (d) solid fat index of compressed suppositories of paracetamol after 18 months storage; heating rate 2.5 K min^{-1}.

For the example given in Fig. 31, DSC was a better technique than X-ray diffraction. The dosage form contained a high amount of lactose. As there was no interference between lactose and the drug substance, the identification of each modification in the dosage form was possible.

DSC has been used for the study of a granulate. It could be demonstrated that no transition occurred during the granulation process [269]. In the case of phenobarbital, DSC demonstrated the formation of the hydrated form of phenobarbitone [279].

Solid dispersions may be manufactured by crystallisation from solutions or from the melt. DSC is very valuable for studying the phase diagrams and for demonstrating the appearance of metastable forms from the melt (Fig. 32 [300]).

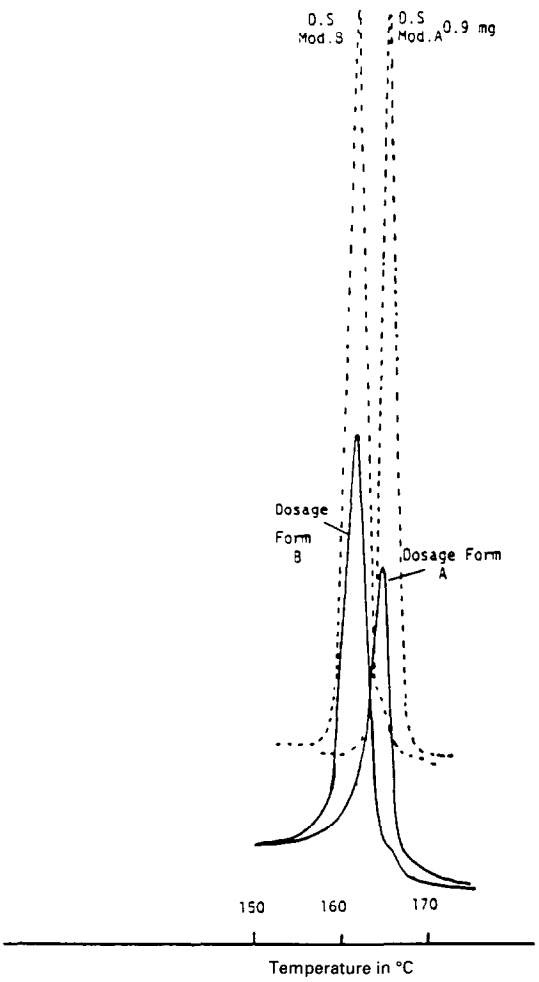


Fig. 31. Identification of two modifications of a drug substance in a capsule formulation. DSC scans were obtained after 5 min isothermal treatment at 140°C in order to eliminate the water peak of lactose.

9. Quantitative aspects

9.1. Polymorphism/pseudo-polymorphism

DSC and TGA are unique techniques for the study of polymorphism. Combined with equilibrium studies between drug and solvent in order to produce stable polymorphs or pseudo-polymorphs, these techniques allow quick interpretation of thermodynamic and kinetic transformations, making possible a rational choice of crystalline modifications at the beginning of the development. However, due to

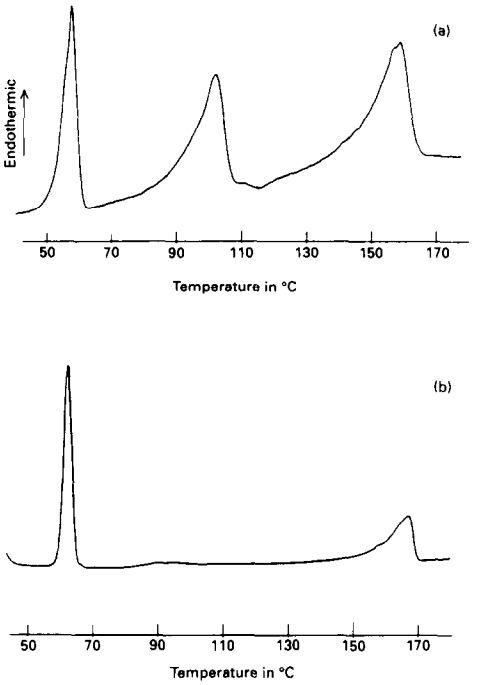


Fig. 32. Effect of manufacturing process on polymorphism in solid dispersions of a 70% drug substance in PEG 6000; (a) fused mixture showing different polymorphic forms detected by DSC (heating rate 10°C min^{-1}); (b) mechanical mixture showing eutectic behaviour detected by DSC (heating rate 20°C min^{-1}).

transitions during heating, quantitation is difficult and not recommended, apart from some well defined cases.

Generally IR, solid NMR and X-ray diffraction are preferred for quantitative analysis [4,145]. However for solvates and hydrates, DSC and TG analysis can be very sensitive in detecting traces of pseudo-polymorphs in the sample. TG, which determines the loss in mass, allows the quantitation of hydrates or solvates. It is, for example, possible to perform such analysis by using the dehydration peak of lactose-monohydrate which is very reproducible [18,269].

In cases of enantiotropy, the endothermic transition peak may be used for the determination of the low melting form. If the high melting form does not revert to the lower melting form on cooling, analysis of mixtures of both forms may be done by DSC. Such a calculation is possible for the aminobenzoic acid ester given in Fig. 28. Batches containing pure forms of both modifications A and B and batches containing mixtures were analysed by DSC and X-ray diffraction. No transformation occurs during storage after several years even at 30°C. Therefore the quantitation of the low melting form B would be possible by using the endothermic

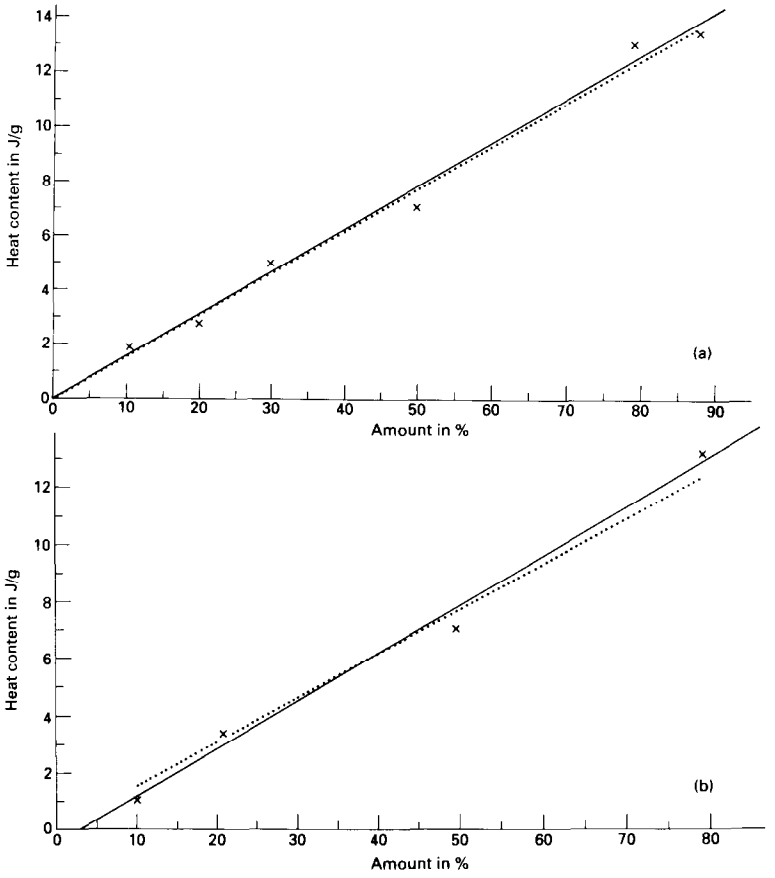


Fig. 33. Quantitation of mixtures of a polymorphs of an aminobenzoic acid derivative using the endothermic transition: $\Delta H_t = 15.6$ J g^{-1} ($n = 10$, $s = 6\%$), theoretical curve, · · · ; experimental curve, ——. (a) Mixture weighed in the DSC pan, $r = 0.9954$. (b) Mixture ground in a mortar before DSC analysis of an aliquot $r = 0.9948$.

transition peak. Some mixtures of known composition have been analysed by DSC [300]. Fig. 33 shows the plots of the heat measured versus the amount of form B. Fig. 33(a) corresponds to mixtures weighed in the DSC pan and Fig. 33(b) to mixtures ground in a mortar before the DSC analysis of an aliquot. The linear relations for both conditions are good. The results fit better to the theory when mixing was accomplished in the pan, because the second method may introduce problems of inhomogeneity.

9.2. Determination of crystallinity by DSC

When the amorphous state is suitable, or when it is desirable to study the loss of crystallinity during processing, it is mandatory to have a quantitative method to

determine crystallinity. The concept "crystallinity" depends on the method used. Apart from X-ray diffraction, the methods most used are DSC or microcalorimetry.

The conditions for maintaining the glassy state depend on the glass transition which is ideally determined by DSC. The glass point is an important feature of crystallisation. Amorphous substances are hygroscopic; therefore, the glass transition is lowered. Once the crystallisation begins, the amount of water is free for the amorphous part. The glass point is lowered and an acceleration of the crystallisation process occurs.

When the crystallisation in the crystalline form followed by the melting is measured by DSC, the crystallinity can be calculated considering only the difference between the crystallisation and the melting heats (e.g. sucrose [250]), or the amorphous part can be deduced from the exothermic crystallisation peak (e.g. lactose [280]).

When no crystallisation of the amorphous part takes place, the crystallinity can be calculated from measurement of the melting heat of the sample compared to a 100% crystalline reference of the same drug.

10. Study of transition kinetics

Knowledge of the transition temperature or of the critical relative humidity level is mandatory for galenical processing. Some transitions such as in tolbutamide or fats, occur at temperatures which are in the climatic range. For example calcium hydrogen phosphate dihydrate (dibasic calcium phosphate) loses water at temperatures above 36°C and the liberated water accelerates the further loss of water of crystallisation [224,225]. Under pressure this excipient also loses water as was demonstrated by DSC and TG [281].

The study of absorption and desorption isotherms of drug substances is also a part of studies on polymorphism. TG can be used if the mass is recorded under defined moisture amounts. DSC and TG curves allow the best determination of different hydrated forms and the knowledge of critical humidity levels. For example, Paronen et al. [85] demonstrated that cyclophosphamide hydrate is stable at $RH > 70\%$ and that otherwise the anhydrous form occurs. Medetomidine hydrochloride is anhydrous only for $RH < 30\%$ [282].

The purpose of any kinetic study is to obtain information concerning the reaction mechanism through comparison of a series of measured fractions converted versus time. Most mechanisms in the solid state are via a nucleation period, a growth zone and an unreacted core. For phase transitions of polymorphs and pseudo-polymorphs, only heterogenous kinetics apply (at least two modifications or two phases and a gas). In heterogenous kinetics a great number of factors should be considered, e.g. temperature gradient in the sample, particle size, activation, nucleus or diffusion. The reaction rate $d\alpha/dt$ is a function of the temperature T and a function $f(\alpha)$ according to

$$\frac{d\alpha}{dt} = k(T)f(\alpha) \tag{7}$$

where α is the extent of reaction (0 to 1).

$$\int \frac{d\alpha}{f(\alpha)} = g(\alpha) = k(T)t \tag{8}$$

where $g(\alpha)$ and $f(\alpha)$ are mathematical functions of α.

The value of k at different temperatures is assumed to be governed by the Arrhenius equation

$$k = A \exp(-E/RT) \tag{9}$$

where A is the pre-exponential factor and E is the activation energy.

$f(\alpha)$ and $g(\alpha)$ have been classified as a function of the type of transition. Values of $f(\alpha)$ and $g(\alpha)$ corresponding to different types of reaction rates are given in Table 6 [283].

Six types of reaction have been classified [27], solid–liquid transition, reaction with nucleus, nucleus at the surface, nucleus in three dimensions (Avrami–Erofeev), reactions of contact and diffusion controlled reactions.

The values $d\alpha/dt$ are obtained from DSC and TG measurements according to Eqs. (10) and (11). In DSC

$$\frac{d\alpha}{dt} = \frac{dH}{dt}\frac{1}{\Delta H_t} \tag{10}$$

Table 6
Mathematical models of reaction mechanisms from Ref. [283]

		$g(\alpha) = kt$	$f(\alpha) = 1/k)(d\alpha/dt)$
(1) Acceleratory α–time curves			
P1	Power law	$\alpha^{1/n}$	$n(\alpha)^{(n-1)/n}$
E	Exponential law	$\ln \alpha$	α
(2) Sigmoidal α–time curves			
A2	Avrami–Erofeev	$[-\ln(1-\alpha)]^{1/2}$	$2(1-\alpha)(-\ln(1-\alpha))^{1/2}$
A3	Avrami–Erofeev	$[-\ln(1-\alpha)]^{1/3}$	$3(1-\alpha)(-\ln(1-\alpha))^{2/3}$
A4	Avrami–Erofeev	$[-\ln(1-\alpha)]^{1/4}$	$4(1-\alpha)(-\ln(1-\alpha))^{3/4}$
B1	Prout–Tompkins	$\ln[\alpha/(1-\alpha)] + c$	$\alpha(1-\alpha)$
(3) Deceleratory α–time curves			
(3.1) based on geometrical models			
R2	Contracting area	$1-(1-\alpha)^{1/2}$	$2(1-\alpha)^{1/2}$
R3	Contracting volume	$1-(1-\alpha)^{1/3}$	$3(1-\alpha)^{2/3}$
(3.2) based on diffusion mechanisms			
D1	One dimensional	α^2	$1/2\alpha$
D2	Two dimensional	$(1-\alpha)\ln(1-\alpha)+\alpha$	$(-\ln(-(1-\alpha))^{-1}$
D3	Three dimensional	$[1-(1-\alpha)^{1/3}]^2$	$3/2(1-\alpha)^{2/3}(1-(1-\alpha)^{1/3})^{-1}$
D4	Ginstling–Brounshtein	$(1-2\alpha/3)-(1-\alpha)^{2/3}$	$3/2((1-\alpha)^{-1/3}-1)^{-1}$
(3.3) based on 'order' of reaction			
F1	First order	$-\ln(1-\alpha)$	$1-\alpha$
F2	Second order	$1/(1-\alpha)$	$(1-\alpha)^2$
F3	Third order	$[1/(1-\alpha)]^2$	$0.5(1-\alpha)^3$

where dH/dt is the DSC signal at a given time t and ΔH_t is the integral of the signal dH/dt of the transition (heat of transition). In TG

$$\frac{d\alpha}{dt} = \frac{dm}{dt}\frac{1}{\Delta m} \tag{11}$$

where dm is the TG signal at the time t and Δm is the loss of solvent for solvates.

10.1. Isothermal measurements

Generally, the value α at $t_{0.5}$ is determined at different temperatures and the curve α versus $t/t_{0.5}$ is plotted. The calculations are done with the different models in Table 6 and the best model is applied. Hemminger and Cammenga [27] used this method for the study of the dehydration of caffeine 0.8 hydrate with thermogravimetry. Thermomicroscopy allowed them to attribute this to a three-dimensional surface reaction of the type R3. York and Agbada [284] applied the Avrami–Erofeev model to the dehydration of theophylline monohydrate and obtained activation energy values ranging from 70 to 90 kJ mol^{-1}. Suzuki et al. [285] preferred the Avrami–Erofeev model and found a value of 120 kJ mol^{-1}.

10.2. Non-isothermal measurements

The technique requires less measurements and is attractive because DSC and TG are dynamic methods. A great number of methods have been described. The best known direct method is the method of Borchard and Daniels which requires a multiple regression calculation. The Doyle method is an integral method.

Kissinger [286] applied this method for the peak maximum of the reaction. The ASTM E698 method applies the Kissinger equation

$$d[\ln(\theta)/T_{max}^2]/d(1/T_{max}) = -E/R \tag{12}$$

where θ is the heating rate, T_{max} is the absolute temperature at the peak maximum, E is the activation energy and R is the gas constant.

The Ozawa equation [287] also uses the peak maximum.

$$E = -2.19R\frac{d(\log\theta)}{d(1/T_{max})} \tag{13}$$

Van Dorren and Müller [288] applied the methods of Kissinger and Ozawa for the dehydration peak of three organic hydrates and the transition of potassium nitrate and hexamethylbenzene. They found a great influence of the particle size. These calculations have also been used for phenobarbitone monohydrate and hemi-hydrate, for the four modifications of frusemide, for the monohydrate of cephalexin [281], for phenylbutazone [289], for calcium gluceptate [296] or for oxazepam [168]. Sasaki et al. [217] applied the Ozawa method for the dehydration of trazodone tetrahydrate and found the activation energy of 37 kcal mol^{-1}. The dehydration began at RH < 51%.

Other methods have been applied. Byrn [6] described many solid state kinetics of pharmaceutical compounds. House and Ralston [290] applied 17 rate laws for the kinetics of dehydration of ammonium oxalate monohydrate. They recommended the use of both isothermal and non-isothermal techniques. A reasonable number of runs should be made so that sample-to-sample variations can be minimised. A high quality of data and sophisticated comprehensive procedures should be used. A software enabling kinetic analysis under non-isothermal or isothermal conditions of DSC and TG has been recently described [291].

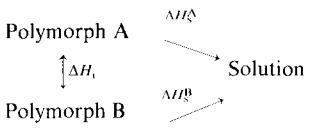
Publications on kinetics of polymorphic transitions mostly describe experiments performed using spectroscopic methods and isothermal conditions.

11. Microcalorimetric techniques

11.1. Solution calorimetry

Solution calorimetry allows us to investigate processes which involve enthalpy changes. Adiabatic microcalorimeters and isoperibol calorimeters used in batch modes or flow modes allow the precise determination of the heat of solution. Mixing the reactants is accomplished by breaking a bulb allowing reactants to mix or in special chambers where the reactants are mixed together.

If a compound exists in two or more different crystalline or amorphous configurations with different lattice energies, the heating of solution in any given solvent will differ. The difference in the heats of solution will be equal to the difference in lattice energy of the solids provided that the solid compounds are chemically identical.



Scheme 1.

The difference in solution enthalpy between both forms is equal to the heat of transition ΔH_t where

$$\Delta H_t = \Delta H_s^A - \Delta H_s^B \tag{14}$$

This relationship is valid for solvents, which allows a rapid dissolution in the calorimeter. Whereas ΔH_s^A and ΔH_s^B depend on the solvent (if no association or complexation takes place), the difference between them is independent of the solvent. The heat of transition ΔH_t should also equal the difference of the melting enthalpies of A and B which may be determined by DSC (Eq. (2)). The solid–solid transition energy ΔH_t may also be measured by DSC. The same principles apply for solvates and hydrates. Because the heat of solution is of low energy, modern accurate microcalorimeters deliver accurate determinations. In the past, most published values for heat of solution have been measured via solubility measure-

ments (or dissolution rate measurements). For each form, for dilute solutions, the van't Hoff equation is given in Eq. (3). The slope of the plot $\log C = f(1/T)$ allows the determination of ΔH_s. Solubilities have to be measured very quickly (or at different time intervals). In the case of transition within the solvent, erroneous values can be obtained for metastable forms. Accuracy of the heat of solution obtained by this method comes into question, especially for monotropic systems.

Pikal et al. [172] first used solution calorimetry in order to determine the degree of crystallinity. Table 7 summarizes some data obtained by solution calorimetry. For stearic acid [257], values for ΔH_t obtained by solution calorimetry in methanol or by solubility measurements in methanol were similar to DSC values. For auranofin [292], a good correlation between solution calorimetry and DSC was obtained. For carbamazepine the value of ΔH_t obtained by solution calorimetry in methanol is within 10% of the value measured in DSC. Furthermore, Behme and Brooke [64] determined the heat of transition via solubility plots in 2-propanol. The values of the heat of solution are different from the calorimetric values obtained in methanol. However the same heat of transition is obtained. Wu et al. [301] found the same values for the heat of transition of the polymorphs of losartan by measuring the heats of solutions in water and in *N*,*N*-dimethylformamide. They preferred this method to DSC because the heat of transition measured by DSC was not reproducible.

Guillory [293] applied the method to two polymorphs of sulphamethoxazole and the semihydrate. The calculation of relative solubility of polymorph I (Cn) to solubility of the semihydrate (C_H) agrees well with the measured value, where T_t is the transition temperature observed in DSC.

$$\ln \frac{Cn}{C_H} = -\frac{\Delta H}{R}\left[\frac{1}{T} - \frac{1}{T_t}\right] \tag{15}$$

For chloramphenicol palmitate, Winike et al. [295] obtained quite different data when comparing differences of melting enthalpies and of heats of solution. They suggest that heat of wetting might play a role. For sorbitol, Cammenga and Steppuln [294] preferred the calorimetric measurement of heat of solution to the DSC measurements because melting enthalpies may be difficult or impossible to measure in the DSC (degradation, melting-crystallisation, desolvation). These examples show that the measurement of the heat of solution obtained by calorimetry is a good way to determine transition enthalpies.

Pikal et al. [172] proposed the use of solution calorimetry in order to quantify amounts of amorphous lactam antibiotics.

$$\text{Crystallisation} = 100 \times \frac{\Delta H_s - \Delta H_a}{\Delta H_c - \Delta H_a} \tag{16}$$

where ΔH_s, ΔH_a and ΔH_c are the heat of solution of the samples, of the 100% amorphous form a and of the 100% crystalline form c. Suryanarayanan and Mitchell [296] used the technique for calcium gluceptate and compared the values with X-ray diffraction and with density measurements. The values obtained using different methods did not correspond well. For example, for one sample they found

Table 7
Comparison of DSC and solution calorimetry or the determination of heat of transition of polymorphic forms

Sulphathiazole [52]	ΔH_I/ (kcal mol^{-1})	ΔH_{II}/ (kcal mol^{-1})	$\Delta H_I - \Delta H_{II}$/ (kcal mol^{-1})	
Acetone	2.85	1.23	1.62	
Dimethylformamide	−1.11	−2.74	1.63	
Indomethacin [52]	ΔH_β/ (kcal mol^{-1})	ΔH_α/ (kcal mol^{-1})	$\Delta H_\beta - \Delta H\alpha$/ (kcal mol^{-1})	
Methanol	6.99	6.72	0.27	
Acetone	4.83	4.63	0.20	
Auranofin [292]	ΔH_A/ (kcal mol^{-1})	ΔH_B/ (kcal mol^{-1})	$\Delta H_A - \Delta H_B$/ (kcal mol^{-1})	ΔH transition/ (kcal mol^{-1}) DSC
95% Ethanol	12.42	9.52	2.90	
Dimethylformamide	5.57	2.72	2.85	
$\Delta H_{fA} - \Delta H_{fB}$ (DSC)			–	3.20
Bendroflumethiazide [52]	ΔH_I/ (kcal mol^{-1})	ΔH_{II}/ (kcal mol^{-1})	$\Delta H_I \quad \Delta H_{II}$/ (kcal mol^{-1})	
Acetone	−3.24	−2.83	0.41	
Carbamazepine [64]	ΔH_{III}/ (kJ mol^{-1})	ΔH_I/ (kJ mol^{-1})	$\Delta H_{III} - \Delta H_I$/ (kJ mol^{-1})	ΔH transition/ (kJ mol^{-1}) DSC
Methanol	17.1	14.1	3.0	–
DSC solid transition	–	–	–	3.3
Via solubility plots in 2-propanol	31.5	28.0	3.5	
Enalapril maleate [100]	ΔH_{II}/ (kcal mol^{-1})	ΔH_I/ (kcal mol^{-1})	$\Delta H_{II} - \Delta H_I$/ (kcal mol^{-1})	
Methanol	9.19	8.68	0.51	
Acetone	14.91	14.22	0.69	

Sulphamethoxazole [293]	$\Delta H_{\text{semi-hydrate}}$/ (kcal mol^{-1})	ΔH_{I}/ (kcal mol^{-1})	ΔH_{II}/ (kcal mol^{-1})	$\Delta H_{\text{semi-hydrate}} - \Delta H_{\text{I}}$/ (kcal mol^{-1})	$\Delta H_{\text{semi-hydrate}} - \Delta H_{\text{II}}$/ (kcal mol^{-1})	$\Delta H_{\text{I}} - \Delta H_{\text{II}}$/ (kcal mol^{-1})
DMF/water	6.56	5.77	5.44	0.79	1.12	0.34
Sorbitol [294]	ΔH_{I}/ (kJ mol^{-1})	$\Delta H_{\text{hydrate}}$/ (kJ mol^{-1})	ΦH_{SM}/ (kJ mol^{-1})	$\Delta H_{\text{hydrate}}$ to SM/ (kJ mol^{-1})	$\Delta H_{\text{hydrate}}$ to Γ/ (kJ mol^{-1})	ΔH_{Γ} to SM/ (kJ mol^{-1})
Solvent	17.4	26.3	15.0	9.9	11.3	2.4
DSC ΔH_{Γ} difference				−0.7	9.7	10.2
Chloramphenicol palmitate [295]	ΔH_{A}/ (kJ mol^{-1})	ΔH_{B}/ (kJ mol^{-1})	$\Delta H_{\text{A}} - \Delta H_{\text{B}}$/ (kJ mol^{-1})	ΔH transition (kJ mol^{-1}) DSC		
95% ethanol	63.2	55.7	7.5			
$\Delta H_{\text{fA}} - \Delta H_{\text{fB}}$				18.8		
Caffeine [27]	$\Delta H_{\text{hydrate}}$/ (kJ mol^{-1})	ΔH_{β}/ (kJ mol^{-1})	$\Delta H_{\text{hydrate}}$ (kJ mol^{-1})	$-\Delta H_{\beta}/\Delta H_{\text{I}}$/ (kJ mol^{-1})		
Water (25°C)	23.4	16.3	7.1			
DSC				6.8		
Stearic acid [257]	ΔH_{B}/ (kJ mol^{-1})	ΔH_{C}/ (kJ mol^{-1})	ΔH transition/ (kJ mol^{-1})			
Methanol calorimetry	81.3	75.4	5.9			
Methanol solubility	88.9	84.4	4.5			
Decane calorimetry	70	64	6			
Decane solubilities	69.0	64.4	4.6			
DSC		–	5.7–6			
Losartan [301]	ΔH_{I}/ (kcal mol^{-1})	ΔH_{II}/ (kcal mol^{-1})	$\Delta H_{\text{I}} - \Delta H_{\text{II}}$/ (kcal mol^{-1})	ΔH transition/ (kcal mol^{-1}) DSC		
Water	2.31	0.59	1.72			
Dimethylformamide	−2.60	−4.36	1.76			
DSC				0–1.05		

Table 8
Quantitative analysis of binary mixtures by solution calorimetry [293]

Theoretical/%	% I (+ semi-hydrate)	% II (+I)	% II (+ semi-hydrate)
25	27	25	25
50	49	51	49
74	74	74	72

values of 72.4% by X-ray, 61.8% by calorimetry and 68.4% by density measurement. For another sample the values were 32.2% and 48.4% respectively.

Guillory [293] found a good correlation for quantitation of binary mixtures of polymorphs I and II of sulphamethoxazole (Table 8).

11.2. Quantitation of amorphous part by measurement of the heat of crystallisation

Byström [297] developed a technique in order to determine the crystallinity of drug substances. Considering that micronisation introduces amorphous regions not measurable by X-ray diffraction, the method should be an analytical tool for analysing batch-to-batch quality.

The principle of the measurement lies in the transformation of the amorphous state to the crystalline one at high humidity levels. The amorphous substance adsorbs water and the glass transition is lowered, permitting the acceleration of the crystallisation. The energy evolved is measured as a function of time by isothermal microcalorimetry.

Such a measurement was done for a drug substance with the Setaram micro DSC. In the upper part of the cell a solution with saturated salt allowed the monitoring of the moisture level. The amorphous substance was obtained by quick evaporation (rotavapor) of a solution. The X-ray diffraction pattern showed it to be amorphous. The crystallinity of the sample after the microcalorimetric experiment was confirmed by X-ray diffraction. At 25°C, values for the energy of crystallisation ranged from 30 to 34 J g^{-1} for a sample mass of 40–50 mg [298].

12. Conclusions

Thermal analysis and calorimetric methods offer great advantages for the study of polymorphism and pseudo-polymorphism, which is an important part of the preformulation studies, beginning with the choice of the salt form. Only a few milligrams of sample per experiment are necessary. The distinction between polymorphism and pseudo-polymorphism is easy and the number of forms in mixtures can be deduced from DSC and TG curves. A simultaneous indication of the purity is given by DSC purity calculations performed on the same scan. Analysis of dosage forms is possible. Modifications can be produced in the instrument and subse-

quently analysed. Because thermodynamic relationships have to be known before the choice of the crystalline form is made, thermal analysis is the best method to be used, in combination with equilibrations and crystallisations, mesurements of solubility and hygroscopicity. However transitions of small energies or polymorphs with the same melting point are often not detected. For complex cases involving several polymorphs and pseudo-polymorphs (13 for phenobarbitone), other methods should be run in parallel. Due to the influence of particle size and impurities within the sample, DSC is of questionable use for routine quantitative application. Microcalorimetry techniques, which are increasingly used in the field of pharmacy [299], are useful complements of thermal analysis methods.

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