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Thermal analysis of spray dried products

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Abstract

The ability to alter and control such properties as particle shape, particle size and size distribution, bulk density, porosity, moisture content, flowability, stability, dispersability and friability has led to the increasing use over the last fifty years, of spray drying methods in the manufacture of pharmaceutical dosage forms. However, in addition to the above changes, alterations may also occur in the energy of the spray dried solid components ranging from the disordering of the crystal lattice, the formation of polymorphic and/or pseudopolymorphic forms, the elimination of crystallinity to complex formation. These changes can have far reaching effects on the biopharmaceutical properties and stability of the dosage forms. In this paper reports of such changes occurring in pharmaceutical systems are reviewed and in particular the use of thermal analytical methods to both qualitatively and quantitatively evaluate the occurrence of these solid state modifications.

Keywords: Drug; DSC; DTA; Polymorphism; PVP; Spray drying; Stability; TA

1. Introduction

Spray dried materials have been used in the manufacture of solid dosage forms since the 1940s [1,2]. Solid dosage forms are composites containing drug(s) and appropriate excipients. The physicochemical properties of both the drug and the excipients may be altered, to a greater or lesser extent, by the processes used in their preparation and/or in the fabrication of the dosage form. The properties which may be affected range from melting point, solubility and dissolution rate to crystal habit, cohesiveness and compressibility [3]. In essence processing may alter both the physical characteristics (e.g. micromeritic) and chemical characteristics of the

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material(s). The latter are reflected in enthalpy as well as entropy changes. Such alterations in the inherent thermodynamic properties of the drug and/or excipients, particularly in so far as they affect solubility, dissolution rate and drug release from the dosage form, can influence the bioavailability and ultimately the efficacy of the product. The process of spray drying is widely used both in food and pharmaceutical manufacturing processes [4]. Originally its use was advocated as a rapid method for drying drugs from slurries which showed unacceptable levels of degradation when dried in the slower conventional drying ovens. Drying times are of the order of 5–100 s. However the unique physical properties of spray dried materials, particularly as they related to flow characteristics led to an extension of the method to excipients and drug excipient mixtures with a view to providing direct compression composites for use in the tableting process [2,4,5]. Primary particles can range from 2–500 μm depending on the drier configuration and conditions employed. Likewise the physical characteristics of particles of spray dried materials may consist of intact spheres, spheres with buds, ruptured hollow spheres, or sphere fragments [4]. More subtle changes, ignored in many of the early publications, may however occur in the energy of the solid components present and these are often most readily detected by thermal methods such as DTA, DSC and solution calorimetry.

The objective of this paper is to examine the changes in thermal properties of pharmaceuticals which may result as a consequence of spray drying.

2. The process

Spray driers convert a liquid, solution or suspension, into a powder in a one step process. Spray driers consist of the following components: the feed delivery system, an atomizer, a heated air supply, drying chamber(s), solid–gas separators and product collection systems [4]. The rate of feed delivered to the atomizer is adjusted to ensure that each spray droplet is completely dried before it comes in contact with the walls of the drying chamber. Appropriate adjustment of the drying air temperature and flow rate is also essential. The physical properties of the product produced are also dependent on the type of atomizer used; these include pneumatic atomizer, pressure nozzle and spinning disk configurations. Drying chambers may be designed to provide concurrent and or counter current mixing of the drying air with feed droplets. Separation of the solid product from the gas is usually accomplished by means of a cyclone separator. Product may be recovered not just from the cyclone separator but also from the drying chamber and the filter bag collectors. The final dried product is often a mixture of the chamber and cyclone products. However in some cases these may have different properties. The chamber product will have been subjected to longer heat exposure in a less dry environment [6]. For a more comprehensive discussion of the process the reader is referred to texts of Masters [4,7].

The product produced on spray drying may be a single compound, i.e. excipient or drug. Alternatively the product may be multicomponent containing drug(s) and

excipient(s). In the former cases the thermal changes observed may result from the formation on drying of a more disordered form of a normally crystalline drug. The crystal lattice is generally considered to be a highly ordered structure repeating itself in three dimensions. In practice crystal lattice imperfections such as point defects (e.g. vacancies, impurity defects), line defects (e.g. edge and screw dislocations) and plane defects (e.g. grain boundaries and crystal surfaces) are present. Rapid drying processes such as spray drying are likely to increase the level of such defects and these in turn will be reflected in the thermal properties of the material. More striking changes which may be observed include polymorphic changes, solvate formation and in some cases the production of drug in an amorphous or glassy form. When multicomponent solutions or slurries are spray dried then the above changes are possible for each of the solid constituents in the final dried product. In addition the possibility of solid solution and complex formation are also likely. These types of changes may not be evident on visual examination. Thermal analytical methods can be used to identify and elucidate the nature of changes observed, often in conjunction with microscopy, X-ray diffraction methods and IR spectroscopy.

3. Thermal changes in single component spray dried products

3.1. Quantifying solid state disorder

Grant and York [3] introduced the concept of entropy of processing as a means of comparing the levels of solid state disorder of pharmaceutical materials. These authors defined the entropy of processing or entropy of crystal imperfection (ΔS^{p}) as the difference between the entropy of the solid sample under investigation and the entropy of the same amount of a reference sample. The latter may be a pharmacopoeial reference standard. Consequently

$$\Delta S^{p}_{solid} = -\Delta S^{f}_{solid} + \Delta S^{f}_{D} \quad (1)$$

where ΔS^{p}_{solid} is the entropy of processing of the solid under study, ΔS^{f}_{solid} is the entropy of fusion of the sample and ΔS^{f}_{D} is the entropy of fusion of the reference substance D.

These entropies of fusion may readily be obtained by DSC or DTA using the relationship

$$\Delta S^{f} = \Delta H^{f}/T_{m} \quad (2)$$

where ΔS^{f} is the entropy of fusion at the melting point T_{m}. Similarly ΔS^{p} may be determined from solution calorimetry.

Arbitrarily choosing as reference sample a highly crystalline sample of the pure drug D these authors analysed a range of published data and estimated entropies of processing [3]. Among the data evaluated were solution calorimetry results which had been determined using spray dired and freeze dried antibiotics [8]. These are tabulated in Table 1 in terms of the enthalpy analogue ($\Delta H^{p}_{solid}/T$). Values for the

Table 1
Values of the entropy analogue ($\Delta H^{p}_{solid}/T$ in J K^{-1} mol^{-1}) for β-lactam antibiotics following spray drying or freeze drying (from Ref. [8]).

Drug	Spray dried	Freeze dried
Cefazolin sodium	173	185
Cefamandole nafate	75	89
Cefamandole sodium	47	78
Cephalothin sodium (1)	38.9	78.2
Cephalothin sodium (2)	1.1	–

spray dried antibiotics ranged from 173 to 1.1 (J K^{-1} mol^{-1}), while higher values were obtained in all cases when freeze drying was the drying process employed (185–78) (J K^{-1} mol^{-1}). It is evident from the results that the method could quantify differences between samples prepared by the two drying methods and also different spray dried samples of the same material (cephalothin sodium).

3.2. Polymorphic changes

The spray drying of drugs such as phenylbutazone from solution can result in a range of polymorphs [9,10]. Three different crystalline forms (α,β,ε) could be prepared from methylene chloride solution by varying the drying temperatures of the sprayed droplets in the range of 20–30°C. Form ε was confirmed as a novel form which could not be prepared by conventional recrystallization methods. DTA thermograms were presented distinguishing the phases present.

Previously we reported that spray drying of a solution of phenobarbitone from ethanol resulted in a product having the characteristics of form III when examined by powder X-ray diffraction, IR spectroscopy and DSC [11]. The commercially available form is generally form II [12,13]. The DSC pattern of phenobarbitone form III has two endotherms (Fig. 1). The magnitudes of these peaks were found to be dependent on the spray drying conditions employed. The results obtained on changing the spray flow setting in the range 200–750 nl h^{-1} are summarized in Table 2. A systematic decrease in the magnitude of the low temperature endotherm is evident. However as no significant change in X-ray diffraction pattern was observed, the possibility that a change either in crystal form or the formation of a mixture of two polymorphs was excluded. Light and electron microscopy also failed to reveal differences between the samples. Phenobarbitone phase transition rates have previously been reported to be dependent on the method of sample preparation [12]. Lattice disorder induced by the method of sample preparation can also alter heats of fusion [14]. Either of these effects may explain the quantitative differences between the ΔH^{f} changes observed.

Changing the concentration of dissolved drug in the mother liquor (i.e. changing the degree of saturation) also led to systematic changes in the DSC profiles. As the feed concentration of phenobarbitone was increased from 1 to 33% the size of the

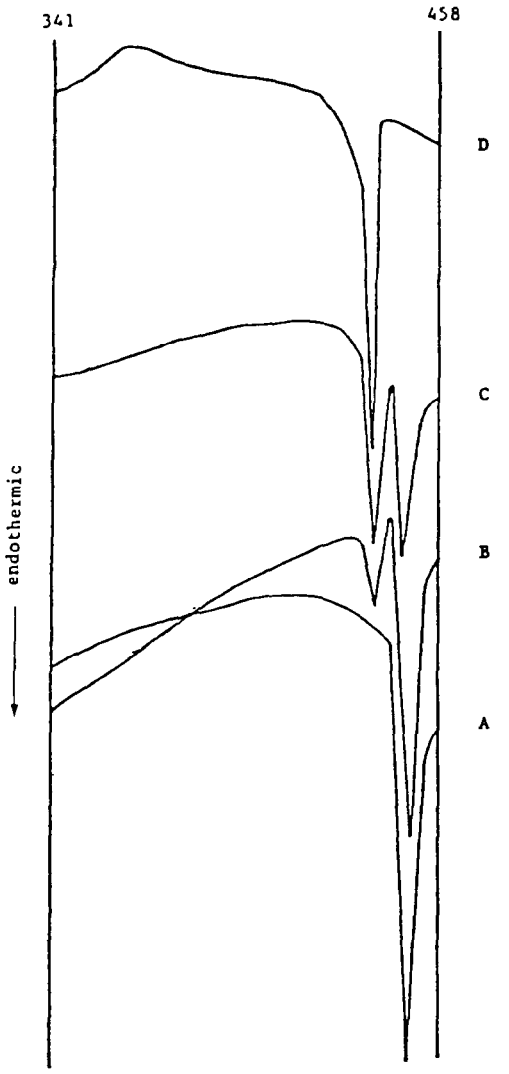

Fig. 1. DSC thermograms of phenobarbitone samples in kelvin: curve A, non spray dried; curve B, spray dried at spray flow rate of 750 nl h^{-1}; curve C, spray dried at a spray flow rate of 200 nl h^{-1}; curve D, spray dried from 10% PVP solution.

low temperature endotherm increased (Table 3). Changing the spray solvent from ethanol to ethanol–water mixtures and even to pure water did not result in the production of a different polymorph of drug despite the known existence of a hydrate [12]. Furthermore altering the inlet temperature in the range of 150–80°C and the outlet temperature in the range 95–60°C also resulted in form III [11].

Likewise spray drying conditions can also alter the polymorphic forms present in the excipient spray dried lactose [15]. The proportions of the various phases, both

Table 2
Effect of spray flow rate (nl h^{-1}) on the magnitude of the endothermic peaks (cal g^{-1}) of spray dried phenobarbitone

Flow rate	$\Delta H_{f(1)}$	$\Delta H_{f(2)}$	$\sum \Delta H_f$
Not spray dried			
–	–	22.33	22.33
Spray dried			
200	10.27	15.43	25.70
300	8.87	16.36	25.22
650	5.17	19.77	24.93
750	2.23	19.70	21.93

The conversion factor from calories to joules is 4.184.

Table 3
Effect of the phenobarbitone concentration in the feed liquor on the magnitude of the endotherms (cal g^{-1}) obtained on spray drying

Drug/%	$\Delta H_{f(1)}$	$\Delta H_{f(2)}$	$\sum \Delta H_f$
1	5.42	28.37	23.78
5	5.21	20.38	25.59
10	7.79	18.79	26.58
33.3	9.37	17.98	27.35

The conversion factor from calories to joules is 4.184.

crystalline and amorphous, appear to be important in determining the compression properties of the material [15]. As lactose is the subject of a separate article in this issue it will not be discussed further.

Spray drying of griseofulvin from chloroform based solvents can result in formation of a solvate, i.e. pseudopolymorph, as evidenced by the characteristic solvent related endotherm at 120°C. We have detected formation of the solvated drug form in the spray drying chamber with the solvate related peak absent from samples recovered from the cyclone separator and collecting vessel [16]. These findings stress the importance of exercising caution before mixing product output collected at the level of the spray chamber with that in the collecting vessels.

3.3. Amorphous drug phases

Frequently spray drying results in the formation of a glassy or amorphous drug phase. Spherical amorphous drug microparticles of digitoxin [17], 9.3″ diacetyl-midecamycin [18] and of a range of thiazide diurectics [19] have been produced by spray drying. These phases are readily identified by X-ray diffraction. In many cases their DSC scans will show two peaks; a lower temperature exotherm, reflecting conversion to the crystalline phase, followed by the melting endotherm. A small

endothermic transition may also be evident pior to the exotherm reflecting the glass transition. The higher thermodynamic activity of amorphous drug phases relative to the more common crystalline form has particular pharmaceutical significance in that the resulting increased solubility can result in improved biological activity, e.g. insulin, novobioin [20]. The solubility of spray dried 9.3″ diacetylmidecamycin was increased 20 fold [18] and that of polythiazide 9.8 fold [19] over that of the crystalline form. Furthermore the physicochemical properties of the amorphous form of a given drug phase produced by spray drying may be dependent on the spray drying conditions (see Table 1 above). Matsuda et al. [21] characterized two amorphous forms of frusemide prepared under different spray drying conditions. The glass transition temperature of amorphous form A was 44.2°C, while that of form B was 54.4°C. The activation energies for the glass transition and crystallization processes were also calculated from the DSC data.

Likewise different types of amorphous solids were prepared by spray drying dichloromethane solutions of 4″-0-(4-methoxyphenyl)acetyltylosin (MAT). Various spray inlet temperatures were used, i.e. 50, 70, 95, 102, 120, 145 and 160°C. No differences in the IR spectra of these samples were discernible. Distinct differences were observed however for the recrystallization temperature T_c and the heat of recrystallization $|\Delta H_c|$. When the inlet temperature was lower than the T_g, both T_c and $|\Delta H_c|$ were low. At inlet temperatures intermediate between T_g and T_c, markedly higher values were observed for T_c and $|\Delta H_c|$. At the temperatures above T_c, these values were observed to decrease rapidly. The results suggested that for inlet temperatures below T_g or above T_c, there might be some kind of micro-ordered structure in a three-dimensional array of MAT molecules during the process of drying. At inlet temperatures between T_g and T_c, however, the drug should be able to form a stable glassy state which has a greater degree of disorder in its molecular arrangement [22].

4. Thermal changes in two component spray dried products

Although multicomponent slurries of pharmaceutical interest have been prepared since the early 1960s [4,6,7] little has been published relating to their thermal properties. Kawashima et al. [23] on the basis X-ray diffraction data on spray dried agglomerates containing salicylic acid, sodium salicylate and a range of binders suggested conversion of the drug to an amorphous or disordered-crystalline form due to rapid drying of the slurry droplets. Subsequently this group reported that the spray drying of sulphamethoxazole with cellulose acetate phthalate resulted in the form II polymorph. In the absence of cellulose acetate phthalate the X-ray pattern was that of form I, the X-ray peaks also exhibiting lower intensities [24]. In subsequent work talc was also found to contribute to polymorphism of sulphamethoxazole and the DSC behaviour of a range of systems was reported [25]. These results indicated that the presence of a second solute in the spray solution may significantly alter the solid state properties of the drug being spray dried.

4.1. Spray dried polymer–drug systems

As polymeric materials are widely used in the formulation of pharmaceutical products we investigated the influence of the inclusion of polyvinylpyrrolidone (PVP) on the physicochemical properties of a number of drugs [11,26,27]. Hydroflumethiazide was spray dried with polyvinlypyrrolidone (PVP) to produce products containing 0–30% PVP. These systems were amorphous and differed from previously prepared coprecipitates of similar composition. DSC data suggested that at low PVP weight fractions both amorphous drug and an amorphous drug–PVP complex may be present in spray dried systems. The apparent aqueous solubility of hydroflumethiazide in spray dried products increased with increasing PVP content reaching a plateau value approximately four times that of the pure crystalline drug. The estimated free energy and entropy of the spray dried drug were greater than that of crystalline drug and also increased with increasing PVP content. Dissolution studies with compressed discs supported the apparent solubility data. The results suggest that amorphous phases having different orders of organization are formed in spray dried systems with increasing PVP content [26]. Subsequently Vachon and Grant [28] proposed that the concomitant energizing and disordering which occurs as a result of pharmaceutical processing operations, such as spray drying, may reflect enthalpy–entropy compensation. From the hydroflumethizide–PVP spray dried solubility data discussed above [26] they estimated a compensation temperature of only 27 K indicating a considerable compensating effect [28].

Spray drying of phenobarbitone does not, in contrast to hydroflumethizide, result in an amorphous phase of drug, but rather phase III [11]. The effect of increasing the proportion of PVP to drug in the mother liquor on the thermal behaviour of the resulting spray dried products is summarized in Table 4. Both the drug related endotherms decreased in magnitude and eventually disappeared on increasing the PVP content. A small exotherm was evident in the 10% PVP sample reflecting recrystallization of amorphous phenobarbitone during heating. At higher PVP contents, as was the case with hydroflumethizide, recrystallization of drug during heating was completely retarded.

As little as 5% PVP was sufficient to eliminate the crystallization exotherm in amorphous indomethacin–PVP products [27].

Table 4
Effect of PVP concentration on the magnitude of the thermal events (cal g^{-1}) observed on spray drying phenobarbitione–PVP systems

PVP/%	ΔH_{exo}	$\Delta H_{(1)end}$	$\Delta H_{(2)end}$
0	–	–	22.33
1	–	4.39	14.39
5	–	3.17	12.39
10	1.86	2.14	5.68
20		–	1.80

The conversion factor from calories to joules is 4.184.

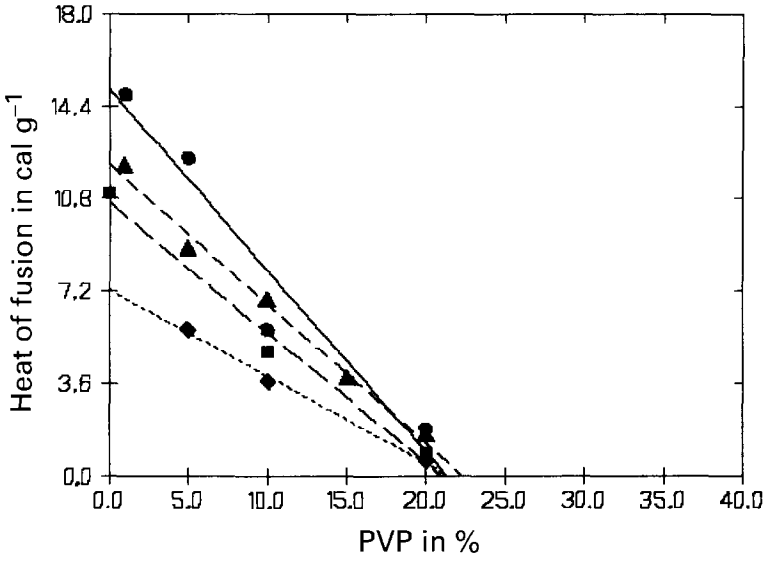

Fig. 2. Relationship between the heat of fusion (ΔH_f) and PVP content of spray dried PVP–drug systems. Key: ●, phenobarbitone; ▲, hydroflumethizide; ■, cholesterol; ◆, dipyridamol.

This decrease and eventual elimination of the enthalpy of fusion (ΔH_f) of drugs on spray drying with increasing concentrations of PVP has also been observed with cholesterol and dipyridamol. The relationships between drug concentration and ΔH_f for the four compounds are plotted in Fig. 2. Reasonably good linear relationships are evident in each case. The intercepts on the x axis occur in the PVP concentration range 20–25% reflecting the minimum amount of PVP required to inhibit crystal nucleation and promote stabilization. The decline in ΔH_f with increasing PVP content probably also reflects effects such as molecular dispersion, complexation and/or solubility of the drug in the polymer. However the PVP concentration required to eliminate the crystallinity of cholesterol on spray drying is much lower than that previously reported (87%) for systems prepared by the solvent method [29]. Differences in the thermal properties of spray dried and coprecipitate griseofulvin–PVP systems have also been documented. The coprecipitate systems all contained drug in the lower energy crystalline chloroform solvate while the spray dried systems were amorphous [30].

4.2. Disruptive index

Changes in crystal properties, such as habit, density, energy, entropy are mediated by changes in the concentration or density of crystal defects and these may be induced by "impurities" present during crystallization. The disruptive influence of an additive or impurity may be quantified by the entropy, and York and Grant [3,31] introduced the dimensionless entropy increment ratio; the disruption index

(d.i.) for quantifying the influence of a guest on the difference in entropy between the more or less crystalline host and the liquid host, i.e.

$$\text{d.i.} = -\delta(\Delta S^{\text{f}})/\delta(\Delta S^{\text{m}}_{\text{ideal}}) \tag{3}$$

or

$$\text{d.i.} = -\delta(\Delta S^{\text{s}})/\delta(\Delta S^{\text{m}}_{\text{ideal}}) \tag{4}$$

where ΔS^{f} is the entropy of fusion, ΔS^{s} is the entropy of solution and $\Delta S^{\text{m}}_{\text{ideal}}$ is the ideal entropy of mixing. Values of d.i. were grouped as follows [32]:

(i) d.i. < 0, where the presence of the guest molecules creates less disorder (entropy) in the host's crystal lattice than in the liquid host (d.i. is negative). This type of behaviour has not yet been observed.

(ii) d.i. $= 0$. In theses cases the solid state is as sensitive as the liquid state to the disordering effect of the guest. Examples include ideal solutions and regular solutions. Simple metallic systems approximate to this behaviour [31].

(iii) d.i. > 1. In these cases the presence of the guest molecules creates more disorder (entropy) in the host's crystal lattice than in the liquid host so that d.i. is positive. These d.i. values were placed in the following subgroups based on their orders of magnitude: (a) order of magnitude about 1, e.g. partial dehydration of cephaloridine monohydrate; (b) order of magnitude about 10 for several organic molecules as additives in organic crystals, such as acetaminophen, DDT, griseofulvin, and phenacetin; (c) order of magnitude about 10^2 for the polymeric additive, Pluronic F68, in crystals of phenylbutazone; (d) order of magnitude about 10^2 or 10^3 for fatty acid additives in crystals of adipic acid.

The effect of the presence of adipic acid in the spray solution on properties of spray dried griseofulvin was examined in the mole fraction range 0.021–0.11 (Fig. 3) [16]. The d.i. calculated from the heat of fusion data was 4.5, consistent with the value of 5.1 previously calculated for the griseofulvin–lecithin system [31]. For a more detailed discussion of the uses and limitations of the disruption index approach the reader should consult the original reports [3,31–33]. A more extensive study of the griseofulvin–adipic acid system is in progress.

5. Spray dried microspherical products

Spray drying is frequently used to produce a range of encapsulated products [2]. For example biodegradable microparticles are increasingly being explored as components for entrapping therapeutic agents in drug delivery systems. A frequent problem encountered using the conventional emulsion solvent evaporation method of microsphere preparation is crystallization of the drug in the aqueous phase. This problem was overcome in the case of progesterone loaded polylactide microspheres by using a spray drying method, hot air being the external phase [34]. Systems were characterized by DSC. A second polymorph of the drug developed on spray drying. The presence of PLA influenced the crystallization process of the drug. The α form was dominant when progesterone alone was spray dried, while the β form predom-

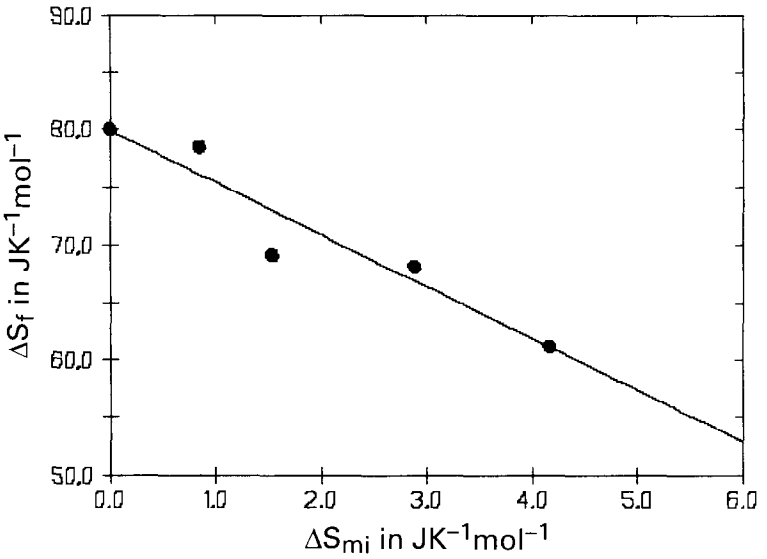

Fig. 3. Correlation between the entropy of fusion (ΔS_f) and the ideal molar entropy of mixing (ΔS_{mi}) for griseofulvin–adipic acid spray dried systems.

inated when the drug–polymer combination was dried. The proportion of the second polymorph increased on increasing the drying temperature. The drug was not detectable in the polymer at concentrations below 10%. The process parameters, e.g. temperature, air flow and spraying rate, also significantly affected the yield.

Recently we successfully prepared levamisole–lactide–co-glycolide biodegradable microspheres using a spray drying technique. DSC analysis indicated that spray dried levamisole base resulted in the formation of the conventional crystalline drug phase. The melting endotherm was however absent from the 20% drug loaded spray dried microparticles in contrast to corresponding physical mixtures of the drug and polymer; indicating that drug is present in a non-crystalline state in the microparticles [35].

Eldem et al. [36,37] prepared lipid micropellets using glycerides such as glycerol behenate and glycerol tristearin, by spray drying from chloroform–methylene chloride solvents, in the presence of lecithin and steroidal drugs such as estradiol 17β-cypionate and medroxyprogesterone acetate. All spray dried micropellets possessed an unstable polymorphic lipid structure. During ageing at elevated temperatures the unstable form of lipid transformed to a stable form and the products lost their almost spherical surface structure. The polymorphic transformation was monitored by DSC and the surface changes by SEM. Improved photostability of spray dried ubidecarenone microcapsules by incorporation of the fat soluble vitamins tocopherol, tocopherol acetate and phytonadione, has been reported [38]. On the basis of DTA data the authors concluded that the microcapsules were non-crystalline.

Recently thermal methods have been used to link the performance of latex polymers in spray drying to the material properties of the latex and ultimately to its

composition. The authors concluded that the glass transition temperature of the latex T_g and its relationship to the processing temperatures characteristic of the spray drying procedure had a major effect on the quality of the capsules formed and also on the yield [39].

6. Complex formation

Spray drying may also be used as a convenient method for producing pharmaceutical complexes and thermal methods have been used in their characterization [2].

Takenaka et al. [40] successfully prepared aminophylline by spray drying a solution of theophylline and ethylenediamine. The DSC data suggested that the strength of the bond between ethylenediamine and theophylline was affected by the drying temperature. Also investigated was the production of aminopyrine barbital complexes by spray drying from feeds incorporating excipients to minimize aminopyrine oxidation [41,42].

Cyclodextrin–drug systems have also been prepared by spray drying. Improved solubility and dissolution of β-cyclodextrin–diazepam stystems have been reported. DSC data indicated that at diazepam loadings below 50%, the drug was only present as a complex. At higher drug loadings free drug was also present [43]. Complexes of indomethacin with both β-cyclodextrin and hydroxypropyl-β-cyclodextrin were prepared by a range of methods including spray drying and their thermal characteristics evaluated by DSC and thermomicroscopy. The nature of the spray dried product was not considered to be well defined [44]. A range of amorphous spray dried drug–β-cyclodextrin complexes was also reported by Lin and Kao [45].

Complex formation was also detected [46] on spray drying theophylline–phenobarbital. Drying temperature affected the amount of molecular complex in the products. DSC was used to construct the phase diagram for the system and to determine the proportions of theophylline and phenobarbitone of the reference complex for identifying the spray dried products. A 2:1 theophylline–phenobarbitone complex was indicated. Higher ratios were obtained when spray dried products from the cyclone collector were analysed both in the presence and absence of colloidal silica, indicating that the spray dried product contained free theophylline and molecular complex. Inclusion of colloidal silica in the formulation decreased the theophylline–phenobarbitone ratio in the spray dried product from 3:1 to 2.27:1. Use of aqueous slurries containing ammonium hydroxide resulted in the molecular complex as product, while inclusion of increasing concentrations of methylcellulose led to an increase in the molecular ratio of theophylline to phenobarbitone as indicated by IR and X-ray analysis of the products [46].

7. Aerosol formulations

Spray drying methods are also being investigated for the production of dry powder aerosol formulations [2,47,48]. For example, spray dried disodium cromo-

glycate proved to be amorphous but the stability of this phase was sensitive to relative humidity, was highly hygroscopic and converted to the crystalline form. While to date these systems have only been studied by X-ray diffraction methods, the use of thermal methods such as DSC and TGA would be highly appropriate. As detailed in other sections of this review, thermal methods can identify and quantify the hygroscopic stability of amorphous states.

8. Summary

This review has shown that in addition to micromeritic changes, the process of spray drying may also result in alteration in the energy of the dried solids. These include disordering of the crystal lattice, formation of a polymorphic or pseudo-polymorphic phase, the elimination of crystallinity and in the case of multi-component systems complex formation. Thermal methods have proved particularly useful for identification and quantification of these events. This is particularly true for amorphous samples of materials, where X-ray diffraction and IR methods have failed to reveal differences.

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