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The thermal behavior of probenecid tablets. An example of the thermoanalytical complexity encountered in the pharmaceutical industry[1,2]

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Abstract

The complexities met in utilizing thermal analysis to describe the physico-chemical behavior of pharmaceutical compounds are demonstrated by discussing that of probenecid tablets. The DSC–TG characteristics (supported when necessary by X-ray diffraction measurements) of the active drug and major excipient components of the formulation are presented and discussed as an example of the information necessary to interpret the thermal behavior of the tabletted drug. Certain expected events are not observed with the tablets, and greater than expected weight losses are encountered. This complicates the interpretation of the thermal response, which is shown to be due to a variety of simultaneous and contiguous events. Loss of absorbed moisture and chemical dehydration, change in physical state, cold crystallization of amorphous material, sublimation, fusion and evaporation all contribute to the overall behavior.

Keywords: Cold crystallization; Dehydration; DSC; Moisture loss; Probenecid; TG; Thermal behavior; X-ray diffraction

1. Introduction

Apart from excipient behavior studies, the majority of published thermoanalytical investigations employed in the pharmaceutical industry pertain mainly to potential drug candidates and bulk active compounds. Studies of the behavior of formulated drugs in their final dosage form are limited. DSC and TG are the most widely used

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techniques, although the recently developed modulated DSC and high-resolution TG are being employed to study polymorphic and hydrated drug candidates [1]. Lvova et al. [2] have discussed the use of DSC in drug standardization and quality control. Wesolowski and co-workers [3,4] have discussed how DTA, DSC and TG have been applied to the investigation of various pharmaceutical products, and have emphasized the use of thermal decomposition studies. Several groups have employed the standard DSC and TG procedures, supported by X-ray powder diffraction measurements, to determine the physico-chemical nature and behavior of different forms; polymorphs [5,6], hydrated [5,6], and anhydrous [6] drugs. Analogous studies involving added excipients have also been made [7,8]. In addition, the effect of the physico-chemical behavior on the aqueous dissolution of the several materials monitored under well-defined hydrodynamic conditions have been discussed. Fernandez-Arevalo et al. [7] explored the effect of different excipients on the dissolution of a controlled-release tabletted drug.

The rate of dissolution of tabletted drugs in an aqueous medium is a key quality attribute of any pharmaceutical product and is well-accepted world wide. It must accord with a defined specification, conforming to the drug validation process. If the manufacturing process involves not only physical mixing but also a chemical reaction, the situation can become complicated. Governmental regulations controlling manufacturing operations require a detailed knowledge of the chemical nature of the active drug and the several excipients. Production engineering requires an understanding of the physico-chemical behavior of all components during manufacture. This is particularly important if wet granulation is employed, necessitating drying to a specified low level moisture content in the tabletted drug. It is important to elucidate fully the chemical and physical properties of the material as produced in its final dosage form, insofar as these attributes affect its dissolution behavior.

Thermoanalytical support is often requested to assist in providing such information and to define drying conditions. If the dosage form contains both free and bound water, there may be problems in interpreting the physico-chemical behavior of the drug undergoing thermal stress. This paper will describe such a process engineering supportive thermoanalytical investigation.

The probenecid tablet manufacturing process employs a neutralization reaction in a wet granulation stage, which converts a substantial portion of probenecid [9], a water-insoluble monobasic acid, into a water-soluble hydrated magnesium salt. The major excipient in the formulation is corn starch, which readily absorbs water. The formulation also contains small amounts of gelatin, a tablet binder, and calcium stearate, which acts as a lubricant in the tabletting operation. Drying will remove corn-starch-absorbed water but may dehydrate the active drug magnesium salt. The thermoanalytical and supporting X-ray diffraction investigation focused on answering three questions:

(1) What is the stoichiometry and physical state of the hydrated magnesium salt in the final tabletted form?

(2) How does the dehydration proceed, what is the physical state of the anhydrous salt, and what is the role of the corn starch during this thermally induced process?

(3) Can the final dosage form be dried without dehydrating the hydrated salt to any large extent?

2. Experimental

2.1. Materials

Drug components were studied as received. The thermal behavior of the minor excipients, gelatin and calcium stearate, was not investigated, since at the $< 1\%$ content level, their effects on the behavior of the dosage form were not expected to be discernible. Hydrated magnesium salt was prepared in the laboratory by stoichiometric neutralization of powdered probenecid and purified-grade light magnesium carbonate (hydrated basic carbonate) in the presence of excess water at ambient pressure and temperature over a 24-h period. The wet salt was vacuum-dried at ambient temperature for 5 d.

2.2. Thermoanalytical

All tests were performed using the Mettler TA3000 system. Open standard aluminum crucibles were utilized for both DSC and TG measurements. For selected TG experiments, alumina crucibles were used. Sample material, powder as provided, freshly crushed in the case of tablets, was employed and tamped into the crucibles. The tests were carried out entirely in an inert atmosphere, namely flowing nitrogen; 50 ml min^{-1} (DSC) and 100 ml min^{-1} (TG). DSC data are presented as normalized heat flow ($W g^{-1}$) and TG as a percentage of the initial sample mass. The data are presented objectively as calculated and displayed by the Mettler TA72 software, which uses the ICTA convention for heat flow DSC.

2.3. X-ray powder diffraction

X-ray powder diffraction patterns were recorded using a Siemens D5000 Diffractometer. Instrument parameters include: CuK_{α} radiation, scan-coupled sample rotation, 45 kV and 40 mA generator settings, 2 mm antiscatter slit, 1° divergence slit, 0.2 mm detector slit, 0.06° per step, 3-s step time. Acquisition range was 5–60° 2θ. A graphite monochromator was installed in front of the detector. Aluminum sample holders were used.

3. Results and discussion

Figs. 1 and 2 show for comparison the DSC and TG profiles, as functions of temperature at the 10°C min^{-1} heating rate, for the probenecid tablet, corn starch, probenecid, and the hydrated magnesium probenecid salt.

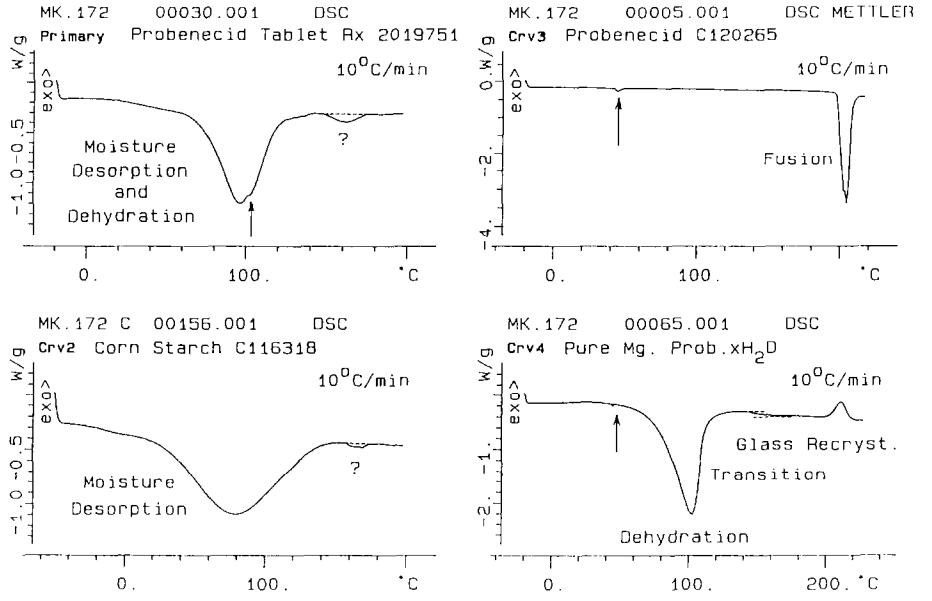

Fig. 1. Overview of the DSC characteristics at 10°C min^{-1} of the probenecid tablet final dosage form and its major components.

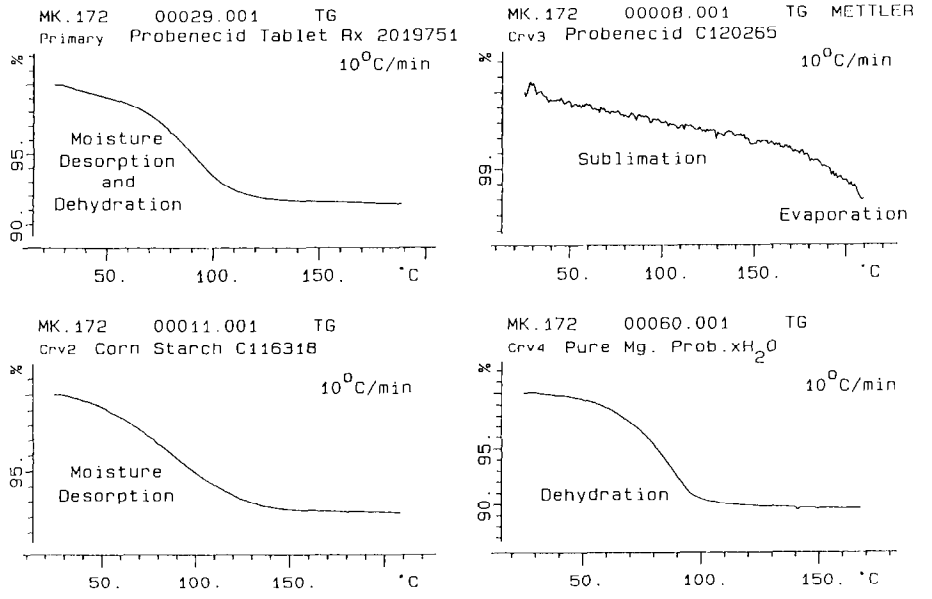

Fig. 2. Overview of the TG characteristics at 10°C min^{-1} of the probenecid tablet final dosage form and its major components.

The major endothermic mass loss processes are moisture desorption from the corn starch and, concurrently, the dehydration of the magnesium probenecid hydrated salt, proceeding mainly in the 0–100°C region. As shown by the corn starch DSC profile, Fig. 1, curve 2 (Crv2), moisture desorption commences well below 0°C. Fig. 2–Crv4 shows that while the salt dehydration is practically completed at 100°C, as confirmed by the sharp endotherm in Fig. 1–Crv4, the physical moisture desorption from the corn starch, Fig. 2–Crv2, continues up to ≈ 150°C, as confirmed by the broad endotherm, Fig. 1–Crv2. In the case of the probenecid tablet, note the conclusion of the endothermic dehydration before the completion of the drying of the corn starch constituent, indicated by the arrow in Fig. 1–Primary DSC profile. In the final stages of drying, corn starch exhibits a broad, low-intensity endotherm in the 140–180°C region, indicated by the question mark. Note that it is also observed with the probenecid tablet.

As shown in the TG profile, Fig. 2–Crv3, there is minimal loss, probably sublimative, from probenecid in the 25–150°C region, prior to the onset of evaporation following its fusion at ≈ 200°C. Probenecid undergoes a characteristic, low intensity endothermic process at ≈ 40°C, indicated by the arrow in Fig. 1–Crv3. This endotherm is also observed with the hydrated magnesium probenecid salt, shown in Fig. 1–Crv4. In the case of the probenecid tablet, its presence is obscured by the corn starch moisture desorption endotherm.

In the case of the magnesium probenecid salt, following its dehydration, the anhydrous salt exhibits a glass transition in the 140–160°C region followed by an exothermic transition, presumed to be a cold crystallization of the apparently amorphous material. This exothermic signal may obscure the endothermic signal characterizing the fusion of the small probenecid component in the tablet.

3.1. Corn starch behavior

Fig. 3 shows the DSC profiles for four sequential 10°C min^{-1} heating scans of corn starch from −50 to 200°C. Since dried corn starch will readily re-absorb moisture from the atmosphere, this sample was not removed from the DSC furnace between scans. At the conclusion of the final scan, the sample appeared visibly unchanged and showed a 10.88% weight loss. In run #1, an initial deviation from the baseline occurs at −27°C, followed by the onset of endothermic drying at +13°C, concluding at 150°C. As is seen, there is a slightly distorted minor endotherm in the 150–180°C region. On cooling rapidly and repeating the heating scan three times, the well-defined reproducible glass transition is observed in the 100–115°C region. A moisture desorption scan performed under the same conditions on a specimen of the corn starch sample, following six months closed-container storage under ambient conditions, yielded comparable data, namely, a 10.91% weight loss with a 219.1 J g^{-1} heat of drying. 1°C min^{-1} DSC scans from −20 to 200°C, shown in the upper part of Fig. 4, confirmed these values. TG data, generated at the same heating rate, shown in the lower part of Fig. 4, showed that (a) evaporative drying is under way as a sample is loaded into the thermobalance and (b) thermal degradation commences above 150°C.

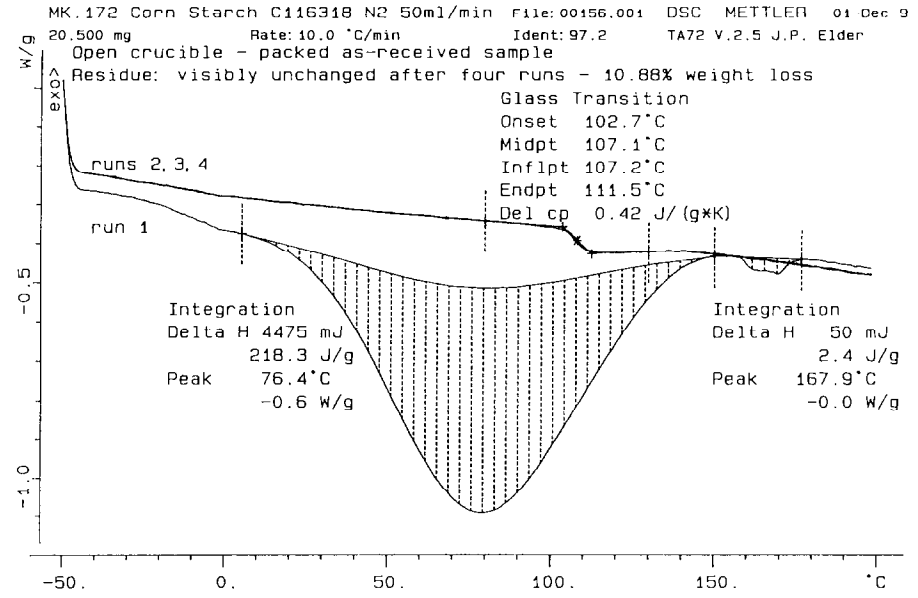

Fig. 3. DSC characteristics of the corn starch excipient in four sequential runs at 10°C min^{-1}.

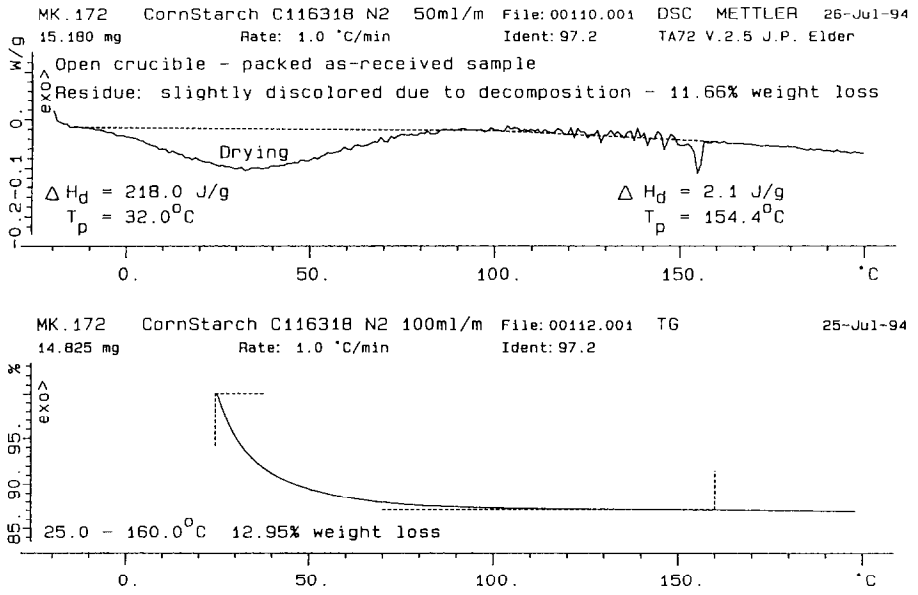

Fig. 4. Comparison of the DSC and TG profiles of the corn starch excipient at 1°C min^{-1}.

3.2. Probenecid behavior

Fig. 5 shows the 10°C min^{-1} heating and cooling DSC profiles of probenecid between −20 and 200°C. A low intensity (2 J g^{-1}) reversible solid state transition, with minimal hysteresis, is observed at 44°C. Dynamic TG measurements showed that sublimation commences prior to melting at 161°C. Fusion then proceeds in the 195–210°C region. 1°C min^{-1} DSC scans from 195 to 205°C, carried out in sealed crucibles to prevent sublimative loss during heat-up to the starting temperature, and evaporative loss during the 10 min scan, yielded a melting point, $T_f = 199.2$°C and a fusion enthalpy, $\Delta H_f = 33.04$ kJ mol^{-1}. Assuming the absence of impurities in solid solution, the purity level was assessed at 99.67 mol%. As is seen in Fig. 5, the melt exhibits marked supercooling, which was also observed when the melt was cooled at 1°C min^{-1} to room temperature.

3.3. Behavior of hydrated magnesium probenecid

The 10°C min^{-1} TG profile of the dry hydrated magnesium probenecid salt heated from 25 to 230°C, characterizing its dehydration, is shown in Fig. 6. The 10.88% weight loss indicates that the salt is a tetrahydrate (theoretical mass loss = 10.83%). During the course of this investigation, the mass loss on dehydration was confirmed by seven such TG and DSC measurements, yielding hydrate stoichiometries in the range 3.7 to 4.0. The 10°C min^{-1} DSC profile, monitored over the −20 to 225°C range, also shown in Fig. 6, details four main features.

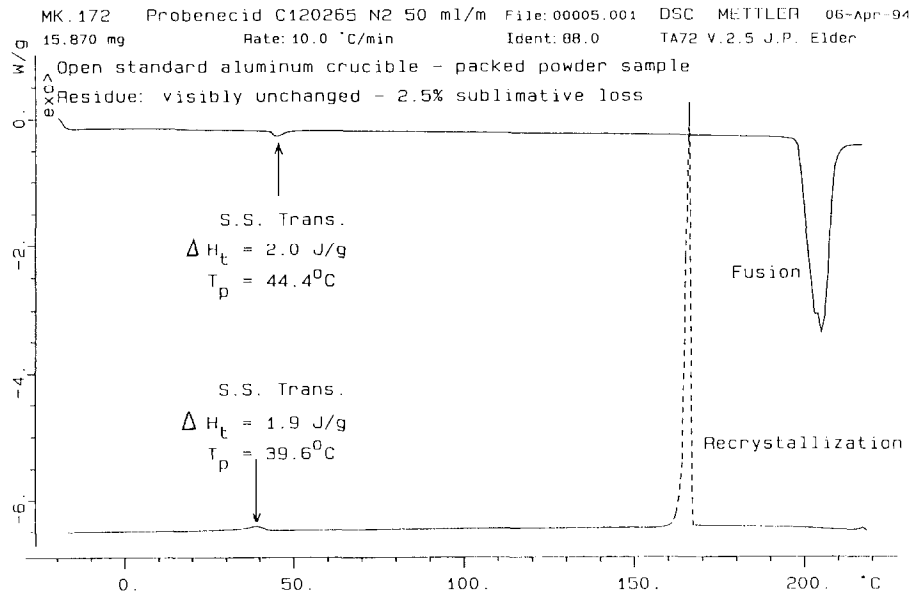

Fig. 5. Heating and cooling DSC profiles at 10°C min^{-1} of pure probenecid.

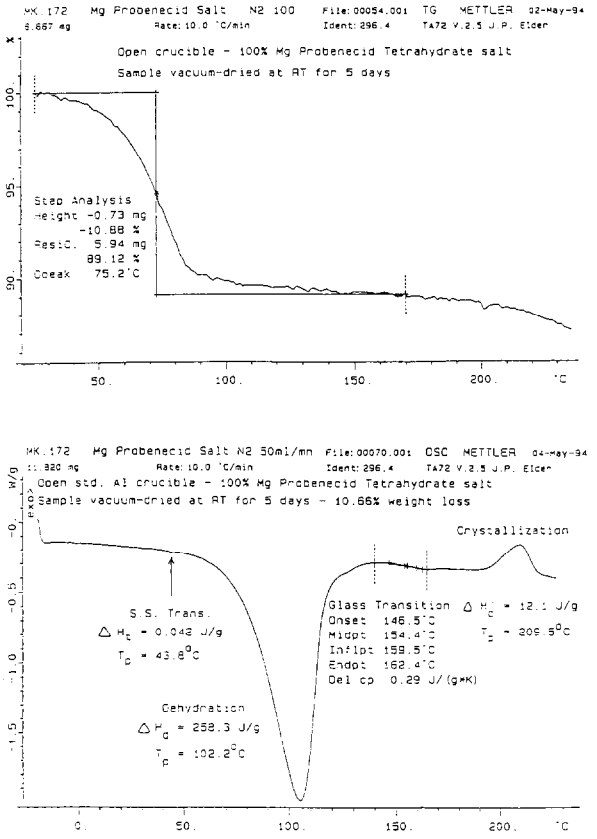

Fig. 6. TG and DSC profiles at 10°C min^{-1} of pure magnesium probenecid tetrahydrate.

(1) The low intensity (0.042 J g^{-1}) endothermic transition at 43.8°C, is characteristic of the probenecid moiety. The large decrease in the magnitude of the enthalpy relative to probenecid is attributed to the difference in the crystal lattice structures, as is discussed below.

(2) The 45–140°C dehydration endotherm with an enthalpic change, $\Delta H_d = 258.3$ J g^{-1}, $T_p = 102.2$°C. Similar measurements at the lower heating rate, 1°C min^{-1}, yielded comparable data, namely, an enthalpic change, $\Delta H_d = 256.9$ J g^{-1}, with a peak temperature, $T_p = 77.9$°C. Repeat measurements on the powdered hydrated salt exposed to ambient conditions for approximately 15 months yielded the following: at 10°C min^{-1}, $\Delta H_d = 258.2$ J g^{-1}, $T_p = 105.2$°C, while at 1°C min^{-1}, $\Delta H_d = 257.3$ J g^{-1}, $T_p = 78.0$°C. These data not only confirmed the original measurements, but also attested to the stability of the tetrahydrate.

(3) A glass transition region was observed between 140 and 170°C, indicative of the amorphous state of the freshly formed anhydrous salt.

(4) An exothermic transition was observed at 193.8°C onset temperature, with an enthalpic change, $\Delta H_c = 13.5$ J g^{-1} (value based upon the weight of the anhydrous

salt). This was conjectured to be a cold crystallization. Similar behavior has been observed with other pharmaceutical hydrates [10]. It appears, however, that at this heating rate the crystallization only proceeds to a limited extent. The apparently recrystallized solid, on quenching to room temperature, has a glassy appearance and, when crushed, only rehydrates to a limited degree in a water-saturated atmosphere. As shown in Fig. 6, there is no obvious manifestation of fusion of the partially crystallized anhydrous salt. By monitoring the behavior at 1°C min^{-1}, fusion is observed. Under these conditions, the onset of cold crystallization is 162°C, and the crystallization exotherm, $\Delta H_c = 7.4\,J\,g^{-1}$, $T_p = 166.4$°C, and fusion endotherm, $\Delta H_f = 7.3\,J\,g^{-1}$, $T_p = 183.6$°C, are clearly resolved. At the higher heating rate, it appears that fusion effects a distortion of the final stages of the crystallization exotherm, giving rise to an apparent baseline drift in the endothermic direction. Also, it is relevant to note that, above $\approx$ 230°C the anhydrous salt commences to degrade thermally. By lowering the upper integration limit from 230°C to 220°C, to obviate inclusion of most of the baseline drift in the integration, the crystallization enthalpy is reduced to a value more in line with that resulting from the analysis of the 1°C min^{-1} data.

Confirmation of the thermally induced physical changes of state were obtained by powder X-ray diffraction. Powder patterns over the 5–60° 2θ range for (a) probenecid, (b) magnesium probenecid tetrahydrate, and (c) the anhydrous magnesium salt, obtained by dehydrating the tetrahydrate at 120°C under vacuum overnight, are shown in Fig. 7a. As is seen, the tetrahydrate salt is indeed crystalline, and after dehydration it becomes completely amorphous. Studies of an analogous recrystalliz-

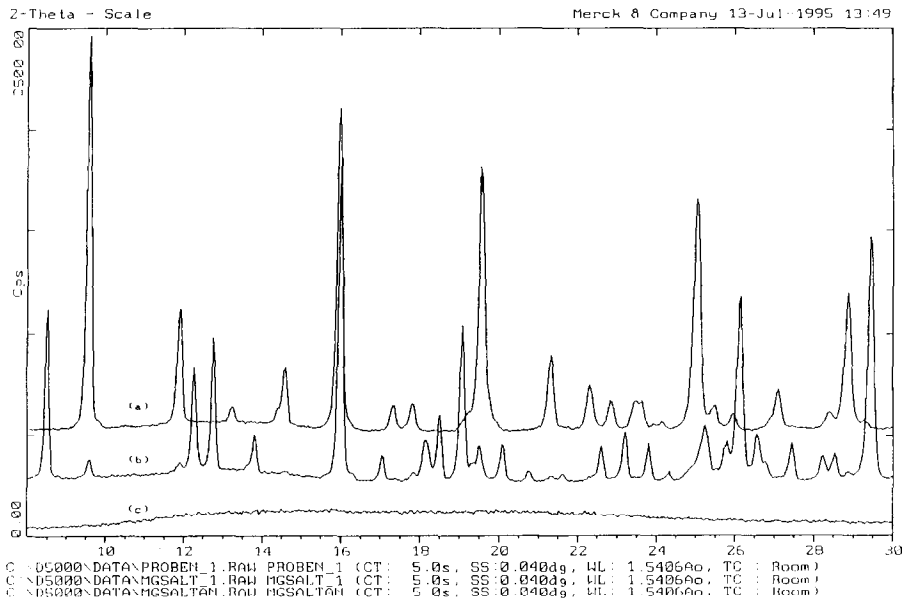

Fig. 7A. Comparison of the X-ray diffraction patterns of (a) probenecid, (b) magnesium probenecid tetrahydrate, and (c) anhydrous magnesium probenecid

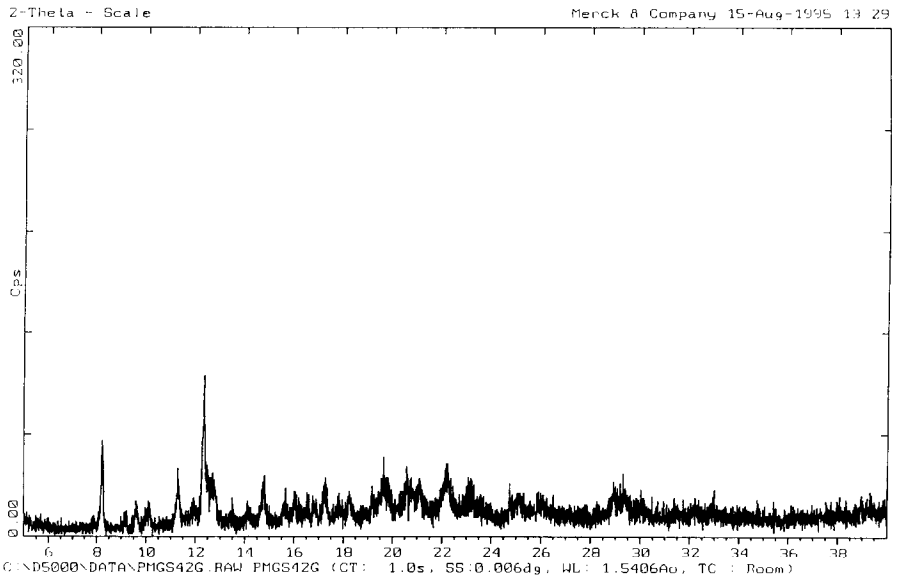

Fig. 7B. X-ray diffraction pattern of partially recrystallized anhydrous magnesium probenecid.

ation of an amorphous drug have shown the process to be kinetically controlled, conforming to a random nucleation mechanism [11]. Thermal scans in both pure oxygen and air showed that the amorphous anhydrous salt oxidizes exothermally in the same temperature region as the inert atmosphere recrystallization. Since it was not possible to maintain an inert environment during the high temperature X-ray diffraction analysis, a different approach was taken. A sufficient quantity of the anhydrous salt, necessary for X-ray analysis, was prepared by repetitive thermal treatment of the tetrahydrate salt under an inert atmosphere in the TG furnace. The samples were heated first from 25 to 160°C at 10°C min^{-1}. In the second stage, in an attempt to produce as much crystalline material as possible, the amorphous anhydrous salt was crystallized over a half-hour interval by heating from 160 to 190°C at 1°C min^{-1}. The powder diffraction pattern of the resultant anhydrous material at room temperature is shown in Fig. 7b. It clearly demonstrates that the amorphous anhydrous salt has partially crystallized. However, the amount produced was low, and the major proportion of the solid at this stage was amorphous. When the entire DSC behavior of the hydrated magnesium salt was monitored at 1°C min., the crystallization exotherm extended over the 171–185°C temperature region with an enthalpic change, $\Delta H_c = 13.0\ J\ g^{-1}$, in agreement with the value obtained at 10°C min^{-1}, shown in Fig. 6. Again, there was no indication of fusion in the partly crystalline solid after its formation. It should be emphasized that the X-ray patterns of the tetrahydrate and the recrystallized anhydrous salt are different and, furthermore, both differ from that of probenecid.

To gain further insight into the nature of the 'cold crystallized' residual solid, it was subjected to a series of step-wise 10°C min^{-1} heat treatments in the DSC furnace from −20°C to four upper limits: 135°C, 155°C, 210°C, and 280°C, followed by quenching to room temperature after each step. Weight losses, together with visible evidence of evaporation were only observed in the final two steps. Glass transition behavior was monitored between 20 and 80°C, an initial melt between 130 and 145°C, and on unresolved exothermic–endothermic doublet between 150 and 190°C. Thus, the presence of both amorphous and crystalline material in the 'cold crystallized' anhydrous salt was confirmed. The endo–exo–endo sequence between 130 and 190°C is attributed to the presence of two polymorphic forms of the crystalline anhydrous salt. This was confirmed by subjecting the magnesium probenecid tetrahydrate to two 10°C min^{-1} controlled heating–cooling cycles from −20 to 220°C without removal of the sample from the DSC furnace. Two endothermic fusion and exothermic recrystallization steps were clearly seen.

3.4. Behavior of probenecid tablets

The thermal measurements on corn starch and the magnesium probenecid tetrahydrate emphasized the necessity of using variable heating rates in studying the behavior of the probenecid tablets. Thus, complementing the 10°C min^{-1} data shown in curve 4 in Figs. 1 and 2, Fig. 8 shows analogous data monitored at 1°C min^{-1}. Although the endothermic drying of the corn starch component is only manifest as a low-level endothermic shift in the DSC baseline, and the glass transition behavior of the

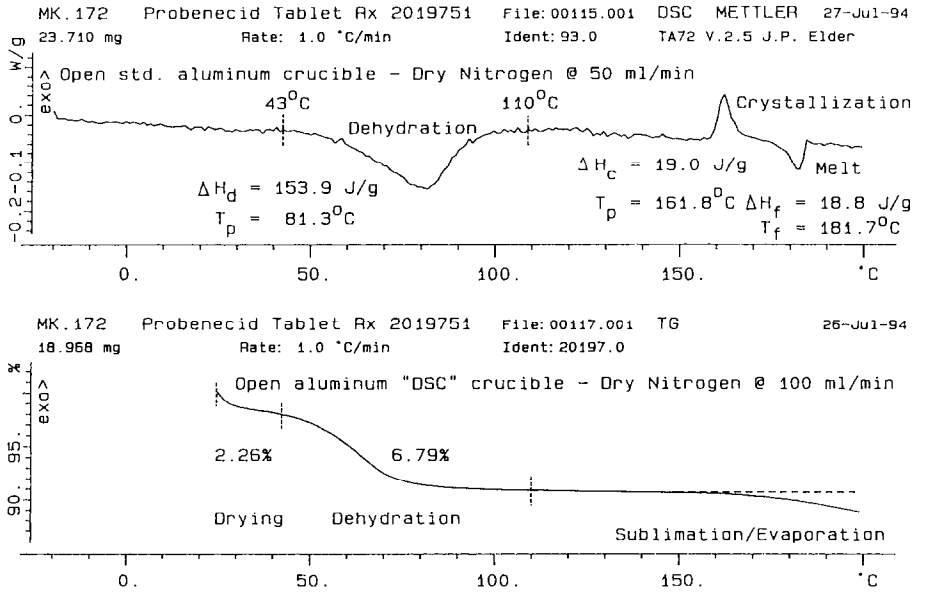

Fig. 8. Comparison of the DSC and TG profiles of probenecid tablet final dosage form at 1°C min^{-1}.

anhydrous magnesium probenecid is not discernible, the cold crystallization of the amorphous salt is clearly seen between 158 and 167°C, ≈ 10°C below the region monitored with the pure magnesium salt at the same heating rate. In the formulation environment, in contrast to the pure salt behavior, melting of the recrystallized salt is observed, confirmed by the equality of the concurrent exothermic and endothermic enthalpy changes.

The measured heat of dehydration, 153.9 J g^{-1}, is very close to the value calculated from the pure salt value, 256.9 J g^{-1} (vide supra) and the 60.58% content of the salt in the formulation, namely, 155.6 J g^{-1}. Similarly, the heat of crystallization in the formulation is calculated to be 11.6 J g^{-1}, close to the previously indicated value of 13.0 J g^{-1} for the salt alone.

One may evaluate the stoichiometry of the hydrated salt component from the dehydration mass loss, shown in the lower half of Fig. 8. The molecular mass of the anhydrous salt is 593. If "x" is the hydrate stoichiometry, then the fractional content of water of hydration is given by Eq. (1).

$$\frac{18x}{593+18x} = \frac{\%\ \text{Loss in probenecid tablet}}{\%\ \text{Mg. prob. in probenecid tablet}} \tag{1}$$

The separation of drying and onset of dehydration in the TG profile is the temperature at the minimum rate of weight loss (DTG profile not shown), namely 46°C. As such it is a low estimate, since analysis of the Fig. 4 TG data shows that, when measured separately at the 1°C min^{-1} heating rate, corn starch drying is 79% complete at 46°C. Nevertheless, using the mass loss data in the lower part of Fig. 8, one finds that for the 60.58% salt content in the formulation, the measured 6.79% mass loss between 46°C and 110°C yields $x = 4.16$. A repeat measurement on a sample from the same tablet lot after one year storage yielded a value $x = 4.24$. It should be noted that a 0.1% error in the measured mass loss only effects a ≈ 4% change in the computed stoichiometry. The very good agreement of these measured values attests to the effectiveness of the stoichiometrically designed neutralization.

Based upon the assessed 10.9% moisture content of the corn starch alone (cf. Fig. 3), the loss in the 20% content of this excipient in the probenecid tablet is 2.20%, in agreement with that indicated in the TG profile, shown in Fig. 8. As demonstrated, the onset of the dehydration of the magnesium probenecid tetrahydrate in the tabletted drug is not completely defined, even at the low heating rate employed. This question was addressed by using isothermal and dynamic TG scans of a freshly crushed tablet sample. A three-step sequential procedure was used; a 15-h isothermal hold at 25°C, followed by a 5°C min^{-1} heat to 40°C and a further 15-h hold at this temperature. Finally, the sample was heated at 1°C min^{-1} from 40 to 150°C. The weight loss profiles are shown in the three upper sections of Fig. 9. These data are compared with the results of a single stage 1°C min^{-1} heating scan of a fresh sample of this lot from 25 to 150°C, also shown in Fig. 9. As is clearly seen, the drying of the corn starch is complete at 25°C in about 4 h. Concomitant dehydration is under way at this time and continues monotonically for the remainder of stage 1. After raising the temperature at 5°C min^{-1} to 40°C and holding isothermally, dehydration continues in stage 2, initially at a greater rate than at 25°C but diminishing with time until completion in about 6 h. As

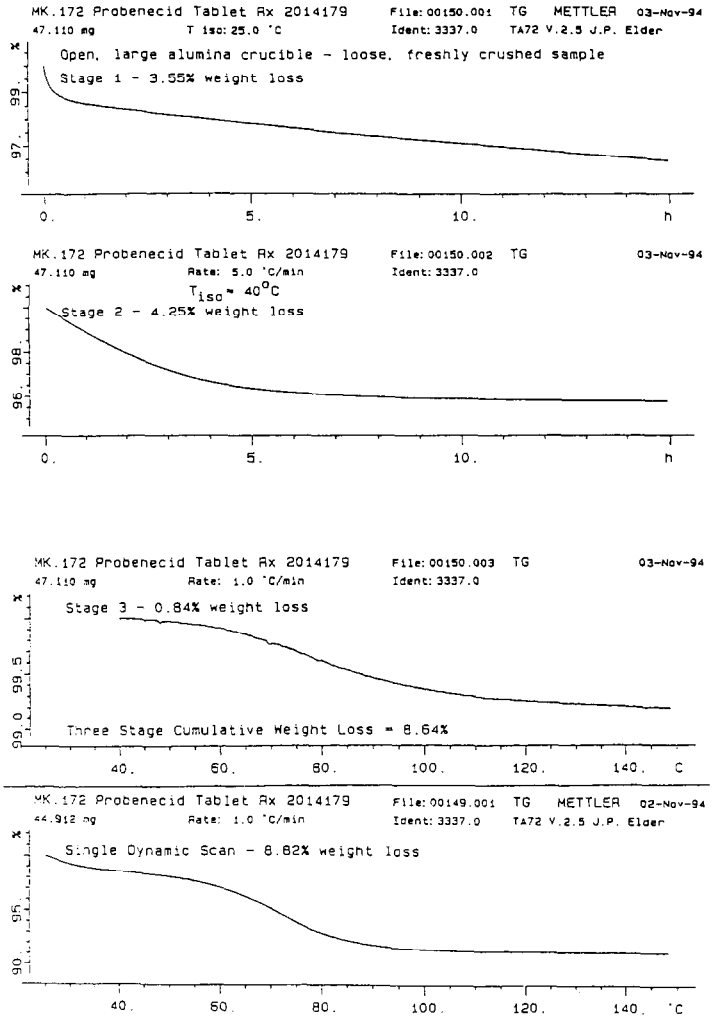

Fig. 9. Three-stage isothermal–dynamic and single stage dynamic TG profiles characterizing the drying and dehydration processes in the probenecid tablet final dosage form.

the dehydration continues, the solid matrix becomes increasingly amorphous. It is conjectured that residual released water is entrapped in this glassy material, and its removal necessitates heating to 150°C, as shown in stage 3. Finally, the single dynamic scan, at the same heating rate as employed in stage 3, on a freshly crushed sample confirms the quantitative three-stage cumulative weight loss. It is pertinent to note that isothermal TG measurements have shown that dehydration will proceed to completion in approximately two and a half days at 25°C. These measurements, although still unable to define dehydration onset clearly, do serve the vital purpose of optimizing drying conditions.

4. Conclusion

It has been shown that the magnesium probenecid produced in the wet granulation is a tetrahydrate, which has a different crystalline form from the parent probenecid. Dehydration of this salt proceeds in one step to the anhydrous state, which is completely amorphous, as shown by characteristic glass transition behavior and confirmed by the absence of an X-ray pattern.

Isothermal and dynamic TG measurements have been employed to optimize drying conditions, serving to emphasize the utility of the procedure for similar bound–free water situations in solid dosage forms.

The dehydration appears to proceed independently of the drying of the corn starch excipient. The anhydrous salt will crystallize from its amorphous state, even in the environment of dried amorphous corn starch. This exothermic crystallization obscures any indication of the fusion of the $\approx 20\%$ remaining probenecid in the formulated drug, which occurs independently in the same temperature region.

The confirmation of the effectiveness of the neutralization in the wet granulation by the establishment of the tetrahydrate stoichiometry in the tablets attests to effective corn starch drying with minimal salt dehydration during manufacture. Thus, the final dosage form is as formulated.

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