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# PHYSICOCHEMICAL PROPERTIES OF SPRAY DRIED DRUGS: PHENOBARBITONE AND HYDROFLUMETHIAZIDE

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## ABSTRACT

The potential of spray drying to produce high energy drug forms was investigated using phenobarbitone and hydroflumethiazide. Whereas commercial phenobarbitone is normally Form II, the product produced by spray drying had a large specific surface area ($17m^2/g$) and physical properties similar to Form III. The apparent solubility of this spray dried material was 25% greater than that of Form II. An amorphous product was obtained on spray drying phenobarbitone with 10% PVP. Spray dried hydroflumethiazide was amorphous and had an apparent solubility 1.61 times that of the crystalline form. Co-spray drying hydroflumethiazide with 10% PVP also produced an amorphous system. Differential scanning calorimetry suggested that the system contained both amorphous drug and an amorphous drug-PVP complex. The product had an apparent solubility 2.5 times that of the pure crystalline drug. Spray drying, either in the presence or absence of excipients, can result in the formation of high energy drug polymorphs or amorphous phases not normally obtained by conventional precipitation procedures.

## INTRODUCTION

Spray drying and spray dried products have been used in the production of pharmaceuticals for many years (1). The process has been used to dry heat sensitive drugs and to produce free flowing microparticles which may be used in the manufacture of conventional (2) and sustained action dosage forms (3). Microencapsulated products have also been prepared by spray drying techniques (4, 5, 6).

The application of spray drying to alter the biopharmaceutical properties of individual drugs has been less widely studied, given



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the influence drug solid state properties may have on bioavailability (7, 8). Specifically,drug particle size, degree of crystallinity and polymorphic form may frequently alter drug dissolution and hence bioavailability. The use of spray drying to achieve micronization and improved dissolution of a poorly water soluble quinazolinone compound has been documented (9). Sodium salicylate (10) and sulfamethoxazole (6,11) when spray dried with excipients resulted in alteration of the crystal form of the drug, either to a different polymorphic form or to an amorphous phase. Indeed spray dried lactose has been reported to be a mixture of three forms: the α-monohydrate, α-anhydrous and β-anhydrous (12). More recently a number of β-lactam antibiotics (13) were spray-dried in the absence of excipients and produced energy rich drug forms.

In this communication the authors investigate the potential of spray drying to enhance biopharmaceutically relevant properties of specific drugs. The preparation and properties of spray dried phenobarbitone and hydroflumethiazide are discussed. Phenobarbitone was chosen since it has been reported to exist in many crystalline modifications as well as a glass form (14, 15). In contrast, hydroflumethiazide has not been reported to exhibit true polymorphism but forms a solvate with ethanol (16) and a high energy amorphous phase in some polyvinylpyrrolidone (PVP) containing coprecipitates (20).

## MATERIALS AND METHODS

### Preparation of Spray Dried Samples

Materials to be spray dried were dissolved in a suitable alcoholic or aqueous-alcoholic solvent. The solution was dried using a Buchi Minispray 190 spray drier. Except where indicated otherwise, the inlet and outlet temperatures were in the ranges 130-140°C and 93-100°C respectively. Feed inputs in the range 0.5 - 1.0 L. $hr^{-1}$ were employed. Anhydrous phenobarbitone (Form II) was initially prepared from phenobarbitone sodium as previously described (17) and sieved to a fine powder (180 μm sieve). Hydroflumethiazide B.P. was used without further purification.

### X-ray Diffraction and Infra-red Analysis.

X-ray diffraction patterns were obtained on powder samples using nickel filtered copper radiation. Both the K Br disc and Nujol mull methods were used for infra-red analysis.

Differential Scanning Calorimetry (DSC)

Samples, 2 - 4 mg, were examined using a Perkin Elmer Model DSC 1B instrument at a scanning speed of $16^{o}$ $min^{-1}$.

Microscopy

Photomicrographs of spray dried particles were obtained using a Jeol J S M - T200 Scanning Electron Microscope. Samples were also examined with a hot stage microscope.

Surface Area Measurement

The specific surface area of powder samples was determined using a BET gas adsorption apparatus (Micromeritics Instrument Corporation, Atlanta, U.S.A. Model 220/42801 P/N). Sample weights in the range 0.4 to 1.5 G and $N_2$ were employed.

Solubility and Dissolution Rate

Solubilities were determined (a) from excess samples of drug equilibrated on a shaker bath at $37^{o}$C for 24 hrs and (b) in conical flasks stirred at 300 r.p.m. (18, 19) for 2 to 3 hours. Apparent solubilities of metastable systems were also determined in media containing 1% PVP (Plasdone C-15) in order to inhibit transformation of the metastable phase. When the inclusion of PVP failed to inhibit the transformation completely, further additions of the metastable form were made to the solution medium in order to establish the maximum apparent solubility of the unstable form.

Dissolution profiles were determined from compressed discs of drug mounted in paraffin wax as previously described (20). Both phenobarbitone (17) and hydroflumethiazide (20) were assayed by UV spectroscopy as previously described. A correction to the absorbence for phenobarbitone was necessary in systems containing PVP.

## RESULTS AND DISCUSSION

Phenobarbitone

Scanning electron micrographs of spray dried phenobarbitone are compared to the non spray dried material in Fig. I. Spray drying produced spherical particles of 3 μm in diameter which formed fairly uniformly sized particle aggregates of 8 μm in diameter. These powders exhibited a large specific surface of 16.9 $m^2 g^{-1}$ by the gas adsorption method.

X-ray diffraction (Fig. 2), DSC (Fig. 3) and infra-red data indicate a change in crystal form on spray drying, the form produced

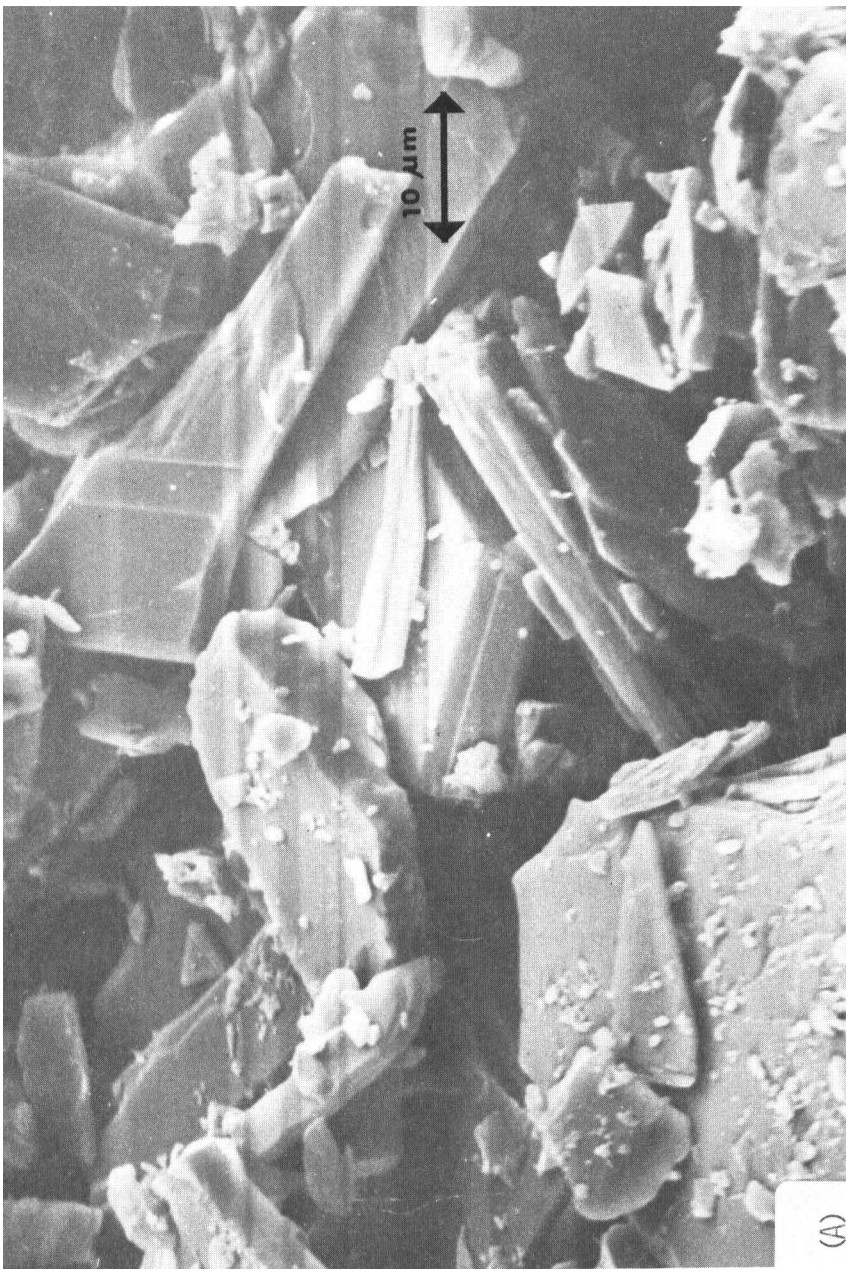


Fig. 1A. Electron photo-micrograph of phenobarbitone, non spray dried.

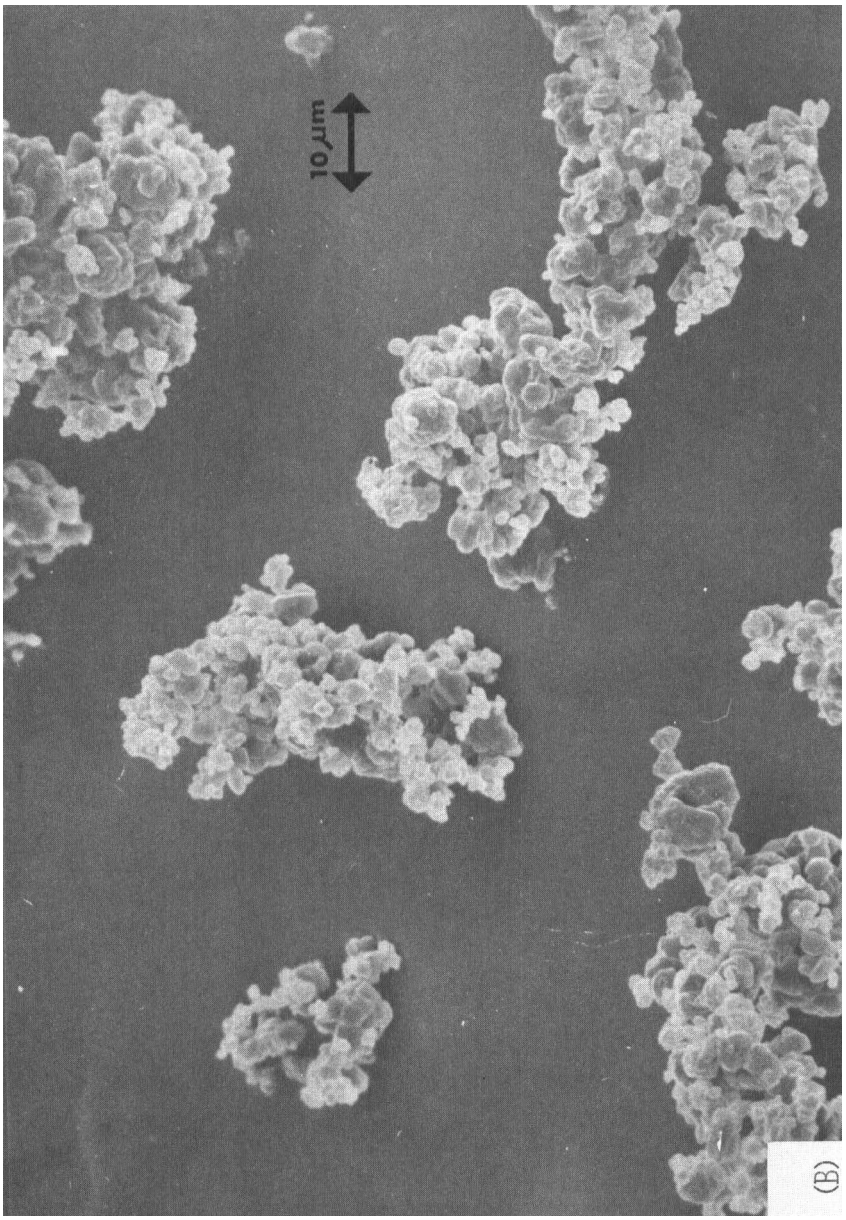


Fig. 1B. Electron photo-micrographs of phenobarbitone spray dried, sample A.

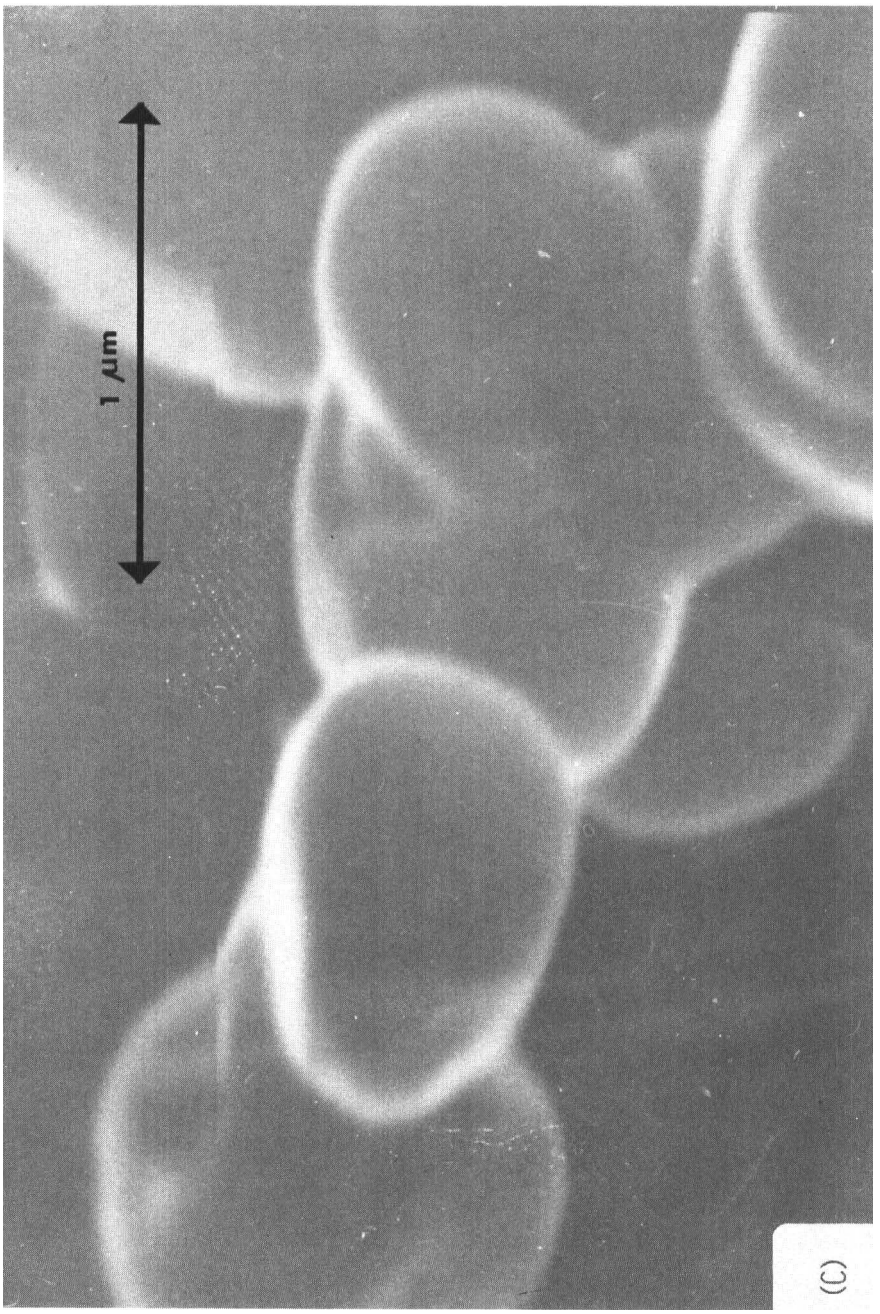


Fig. 1C. Electron photo-micrograph of phenobarbitone, spray dried.

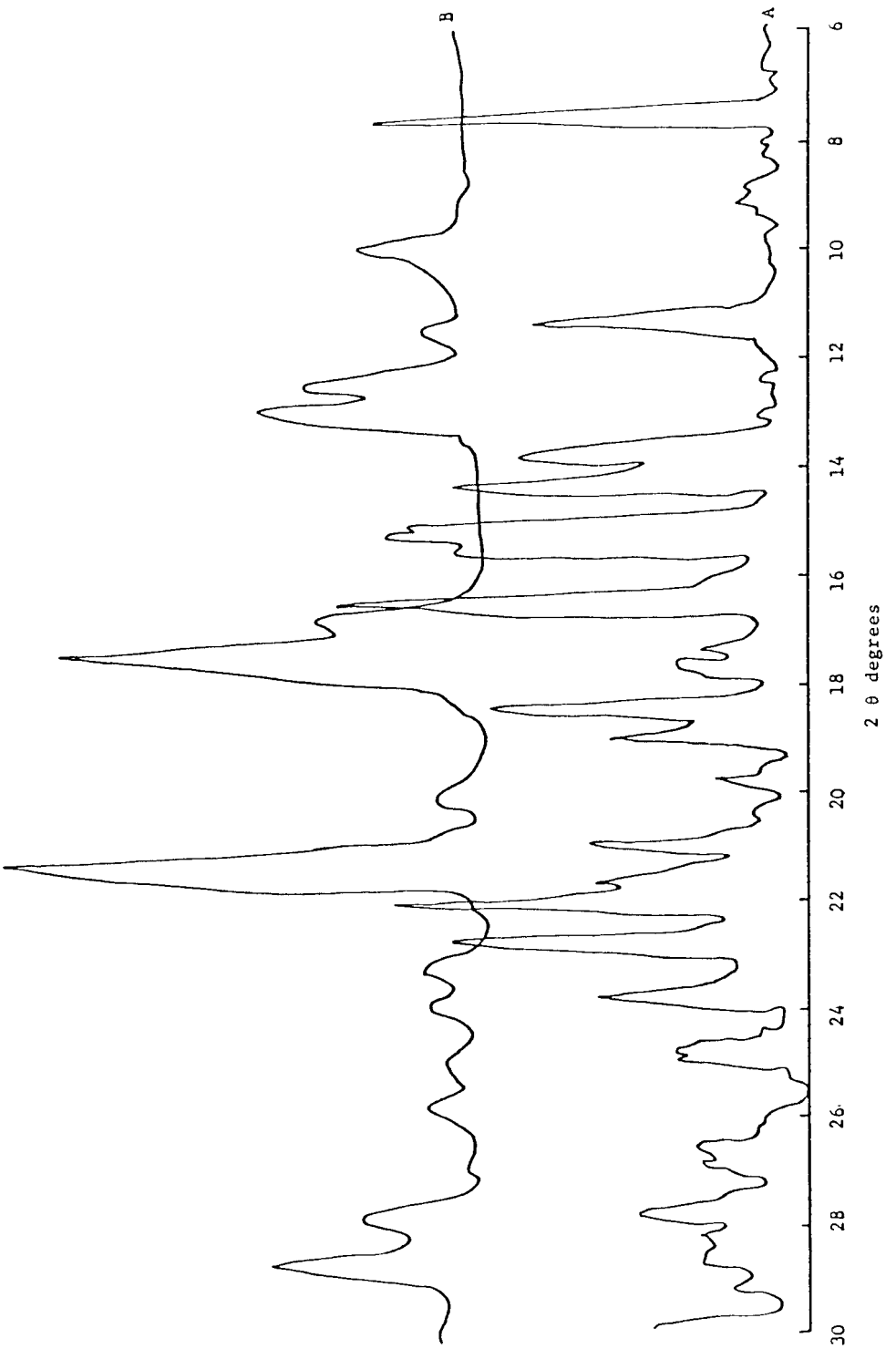


FIGURE 2

X-ray diffraction patterns for phenobarbitone samples - A, Non spray dried; B, Spray dried.

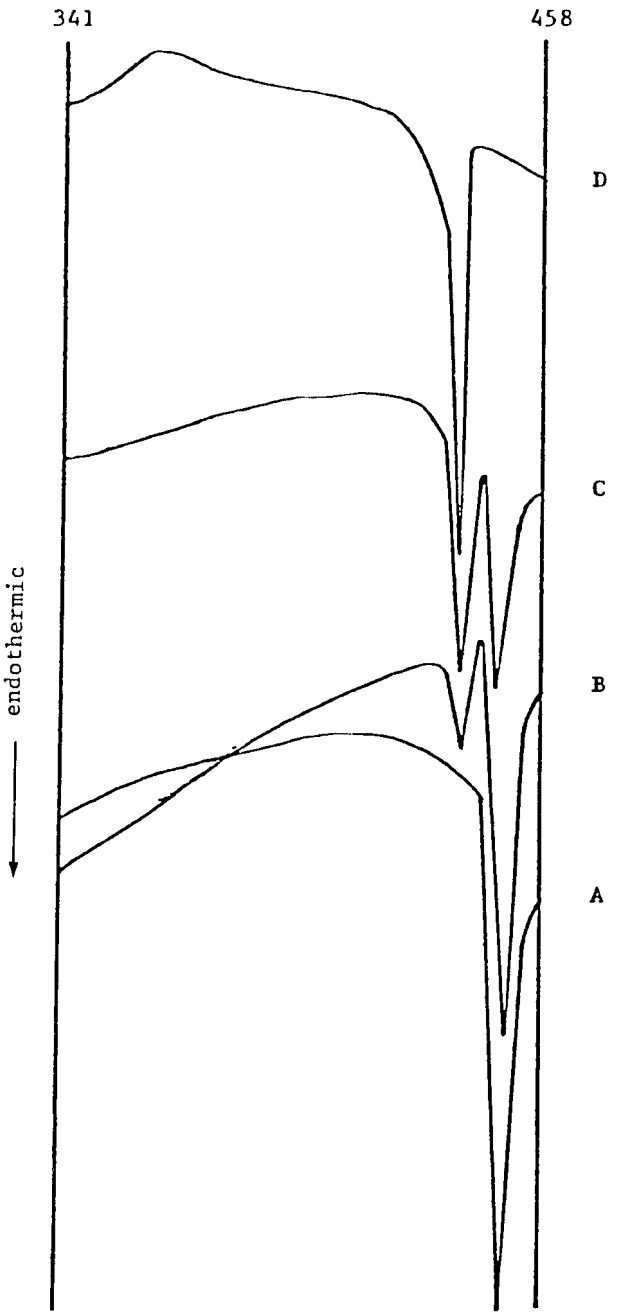


FIGURE 3

DSC thermograms of phenobarbitone samples ($^{o}K$)

A, non spray dried; B, spray dried at spray flow rate of 750 Nl.h$^{-1}$; C, spray dried at spray flow rate of 200 Nl.h$^{-1}$ D, spray dried from 10% PVP solution.

being similar in characteristics to Form III. Commercial phenobarbitone generally consists of Form II (21, 22) and it has been suggested (21) that Form III could not be obtained by precipitation.

Attempts were made to generate other forms by altering the spray drying conditions. Changing the solvent to water or ethanol-water mixtures still resulted in Form III. Similarly, changing the degree of solvent saturation, feed input rate or the temperature gradient (inlet range 150-80°C and outlet range 95-60°C respectively) did not alter the crystal form. Increasing the spray flow rate from 200 $Nl.h^{-1}$ to 750 $Nl.h^{-1}$ resulted in a systematic decrease in the size of the first DSC endotherm (Fig. 3). 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 forms can be excluded. Neither were significant changes evident from light or electron microscopy. Reily (21) has previously reported that phenobarbitone phase transition rates are dependent on the method of sample preparation, while lattice disorder induced by the method of preparation has been reported to reduce the heat of fusion of sulphathiazole (23). Either of these effects may explain the quantitative changes observed in the DSC thermograms with changing spray flow rate.

Solubility profiles at 37°C of spray dried and non spray dried phenobarbitone are shown in Fig 4. The spray dried drug had the higher initial solubility but converted to a more stable form. Solubilities were therefore determined in media containing 1% PVP, a polymer known to retard the crystal transformation of a number of compounds which occur in aqueous media (16, 24). The presence of PVP retarded the transformation of spray dried phenobarbitone and also seemed to slow the rate of equilibration of the non spray dried sample (Fig. 4). These results suggest that the spray dried form has a solubility at 37° which is 1.24 times that of Form II.

The dissolution profile obtained from compressed discs of constant surface area (in isotonic buffer pH 5.3 at 37°C containing 1% PVP) is compared to that of the non spray dried form in Fig. 5. Compression did not effect conversion of the spray dried material to Form II although some decrease in the area of the first DSC endotherm was evident on DSC scans of disc fragments. The difference

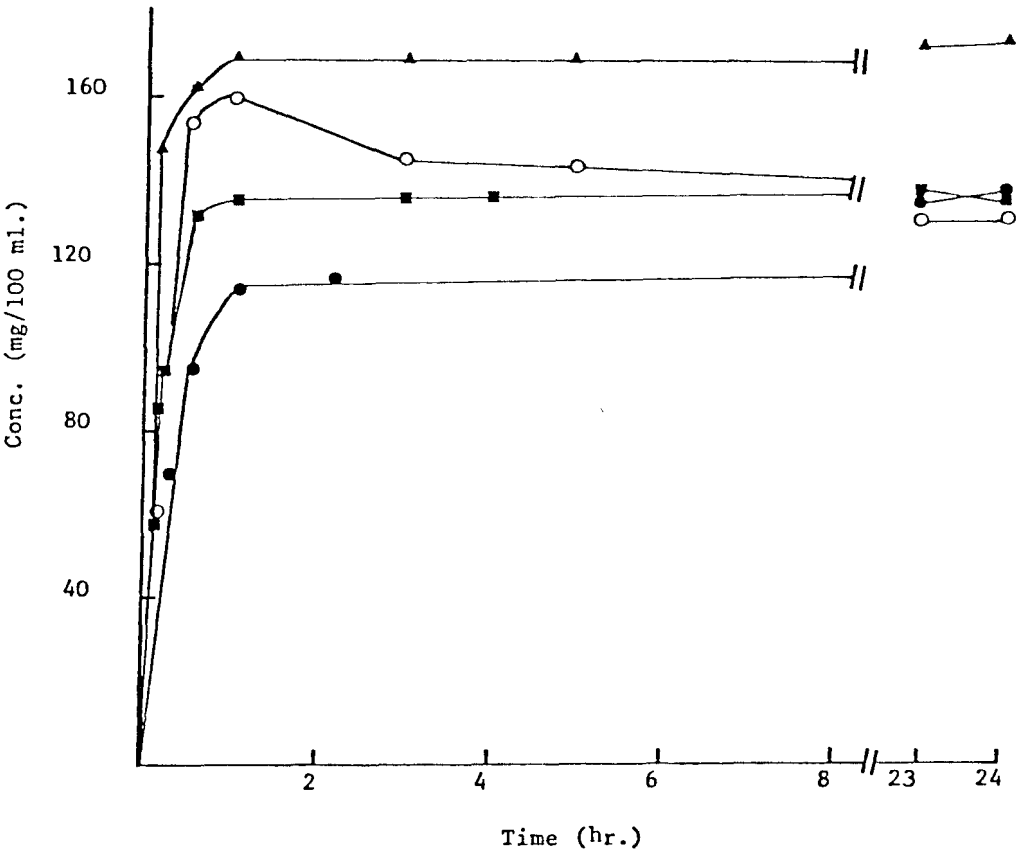


FIGURE 4

Solubility profiles of phenobarbitone samples at 37°.
(■) Non spray dried at pH 5.3; (○) spray dried at pH 5.3;
(●) Non spray dried in media containing 1% PVP;
(▲) Spray dried in media containing 1% PVP.

in dissolution profiles are consistent with the solubility data, the spray dried material having the higher dissolution rate. The inclusion of PVP in the dissolution medium, however, resulted in a lower dissolution rate for the non spray dried drug than previously observed in the absence of PVP (17). In the absence of PVP no difference in dissolution between the two forms was detected.

Previous reports have shown that phenobarbitone Form II is metastable in aqueous media (25, 26) converting to a hydrate (Form XIII).

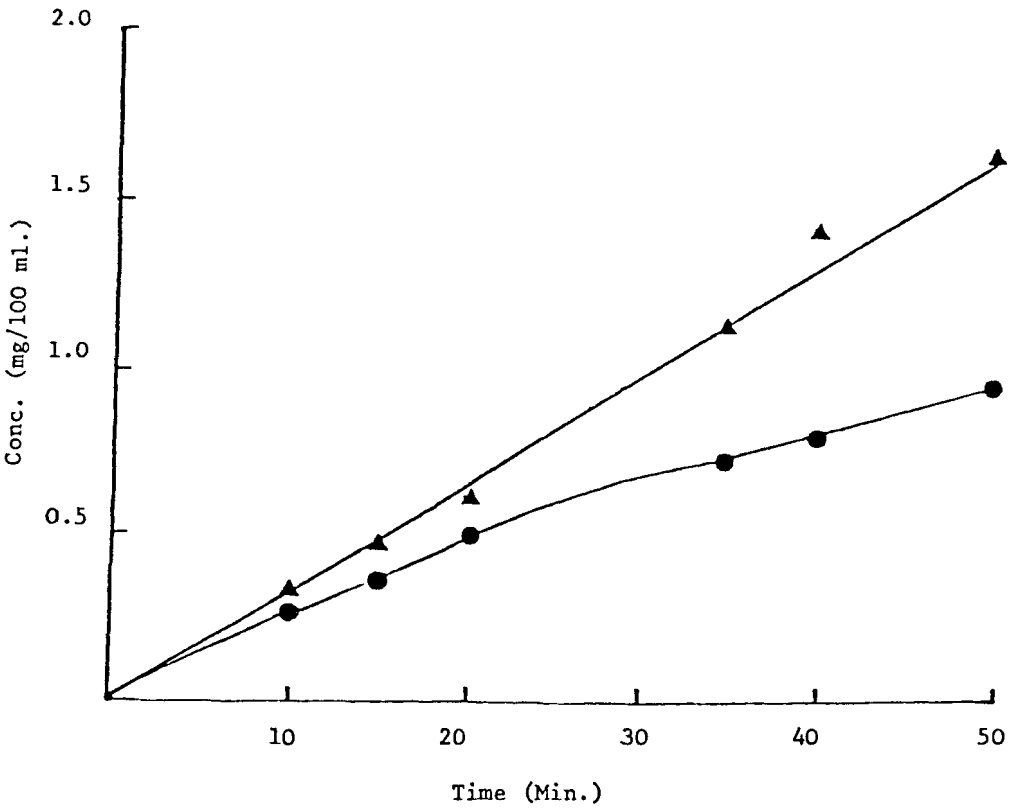


FIGURE 5

Dissolution profiles of phenobarbitone samples at 37° in isotonic phosphate buffer pH 5.3 containing 1% PVP. (●) Non spray dried; (▲) spray dried.

The transition temperature of these two forms is about 37°C and therefore evidence of this transition was not apparent from the solubility profiles in the current work.

Using a tape dissolution method, Clements and Stanski (22) examined the dissolution properties of a number of polymorphic forms of phenobarbitone. They observed that Form III dissolved 28% faster than Form II in purified water, a finding consistent with the difference detected in the current work.

The high energy form of phenobarbitone produced on spray drying seems quite stable as no change in physical properties occurred up to 9 months.

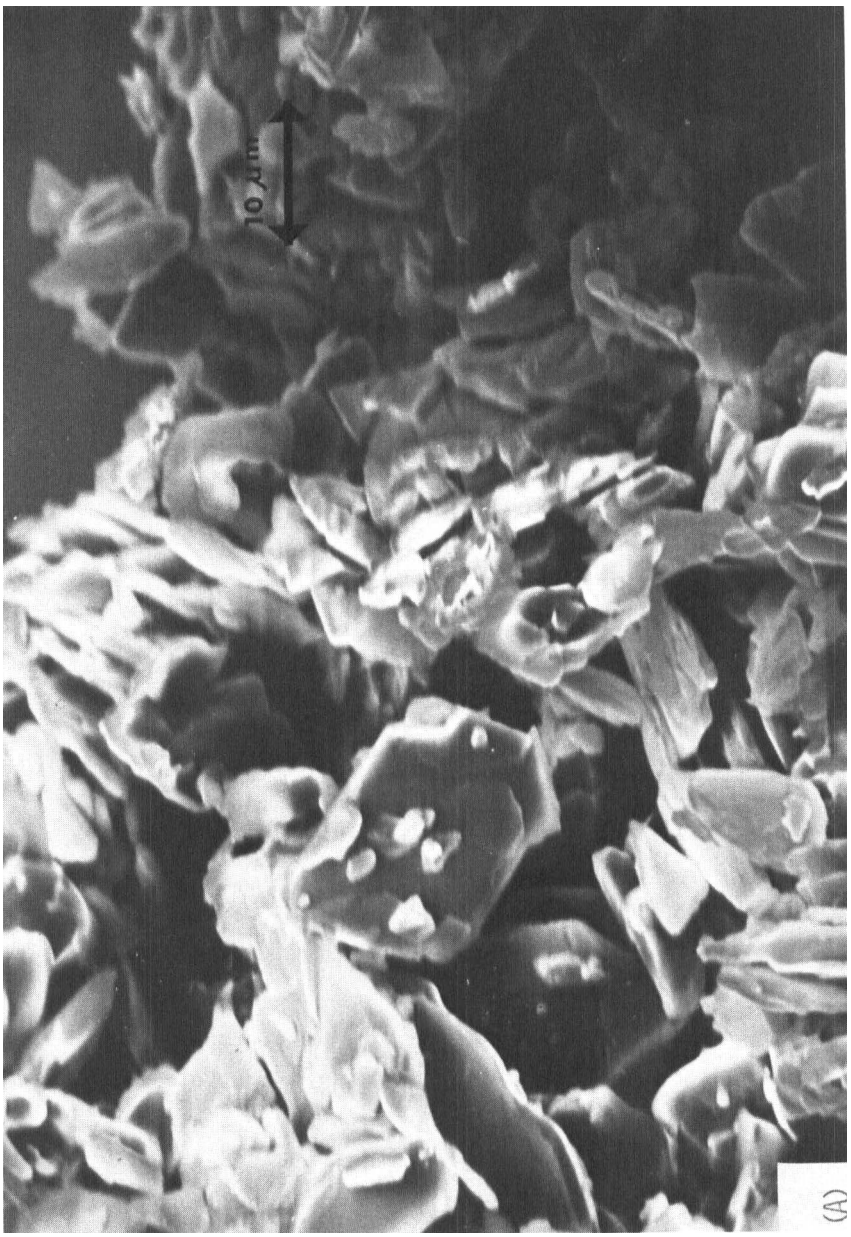


Fig. 6A. Electron photo-micrographs of hydroflumethiazide non spray dried.

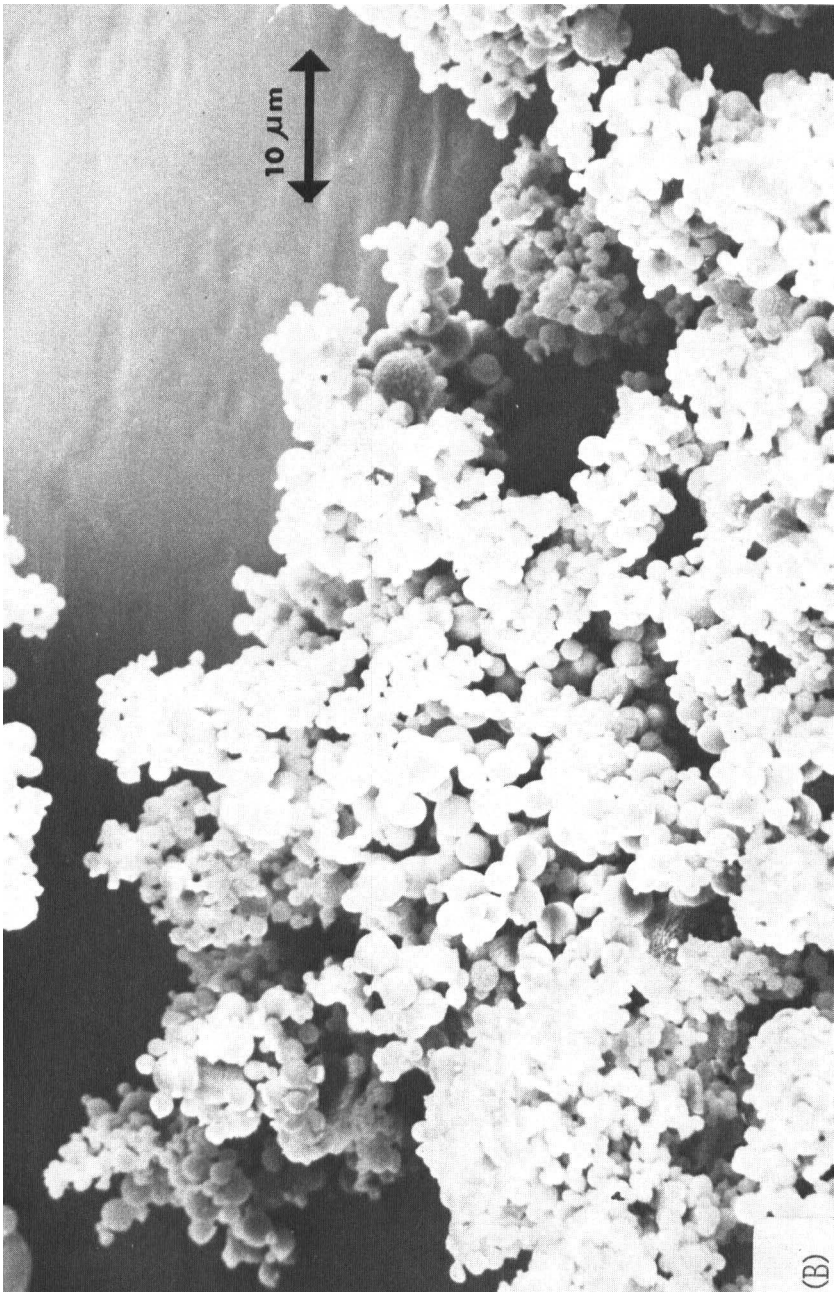


Fig. 6B. Electron photo-micrographs of hydroflumethiazide Spray dried.

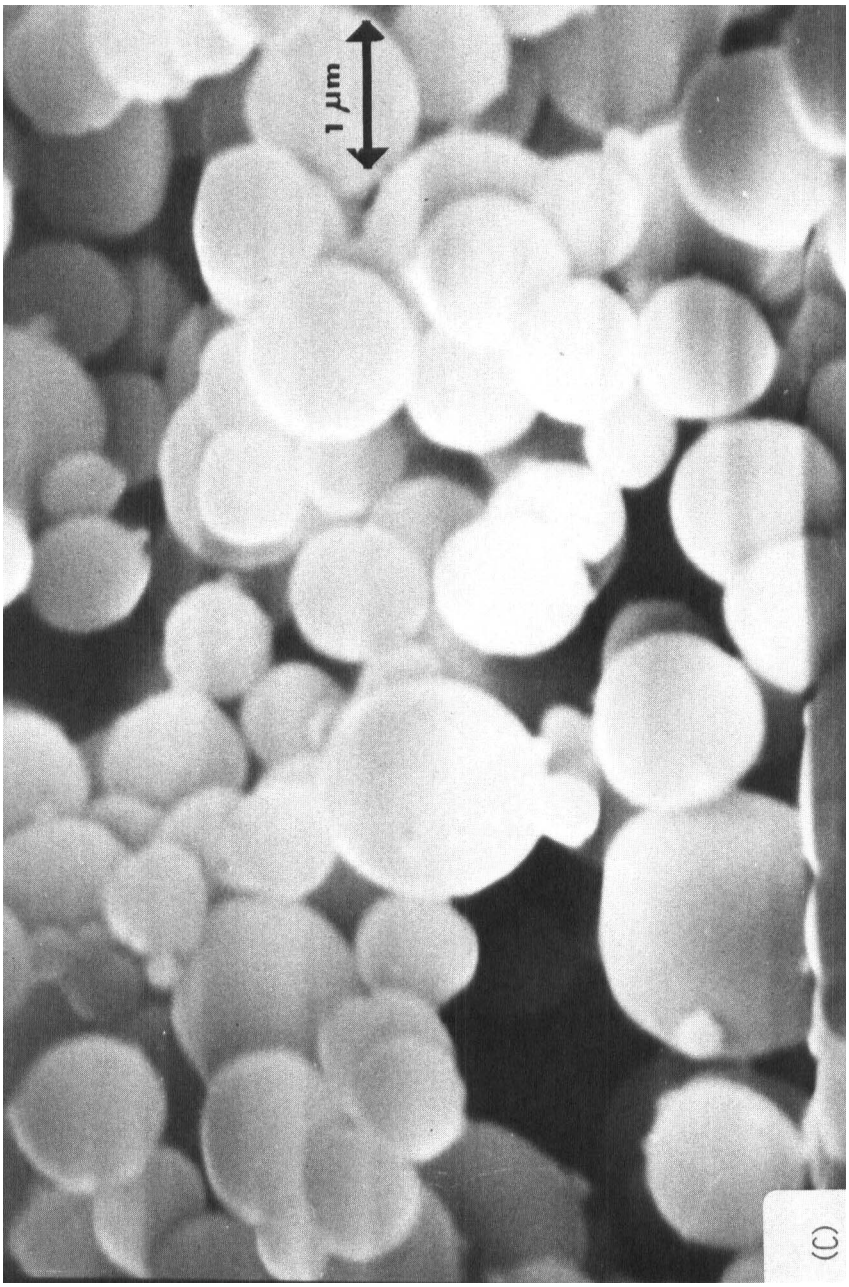


Fig. 6C. Electron photo-micrographs of hydroflumethiazide C spray dried.

Hydroflumethiazide

Scanning electron micrographs of spray dried hydroflumethiazide and non spray dried drug are shown in Fig. 6. The spray dried material consists of spherical particles of < 5μm approximately with a specific surface area of 14.7 $m^2 g^{-1}$. The X-ray diffraction patterns of the samples are compared in Fig. 7 and indicate that spray dried hydroflumethiazide is amorphous. The DSC thermogram of the spray dried drug differed from that of the normal crystalline form in the occurrence of an exothermic peak at 135°C (Fig. 8). Such exothermic-endothermic profiles are typical of amorphous or glassy forms (19,27). The amorphous phase of hydroflumethiazide was unstable at room temperature and converted to the more stable crystalline form in about 12 days. Thus spray drying of hydroflumethiazide from alcoholic media produces an amorphous drug form. In contrast, the rapid precipitation of hydroflumethiazide by conventional methods from ethanol, has been reported previously to produce an alcoholate (16).

The solubility profiles for spray dried hydroflumethiazide in 0.1 N HCl at 37°C in the presence and absence of 1% PVP are compared to the corresponding profiles for the crystalline drug in Fig. 9. In aqueous media, the amorphous phase is unstable converting rapidly to the crystalline phase in the absence of PVP. The apparent solubility of the unstable amorphous phase was estimated to be 1.61 times that of the crystalline form. Attempts to determine the intrinsic dissolution rate of this form were unsuccessful because of the brittle nature of the glassy discs produced on compression.

The existence of an amorphous phase of hydroflumethiazide was previously(20) suggested from studies of the properties of hydroflumethiazide-PVP coprecipitates. This phase was present in coprecipitates containing greater than 35% PVP (20) and dissolution experiments suggested that it had a solubility 4-5 times that of the crystalline drug. A similar difference in apparent solubility between an amorphous drug phase present in a PVP coprecipitate and that in a pure drug melt has also been reported for sulphathiazole (28).

Spray Drying with PVP

Since the spray drying of drugs in the presence of excipients has been reported to alter the solid state properties of drugs,

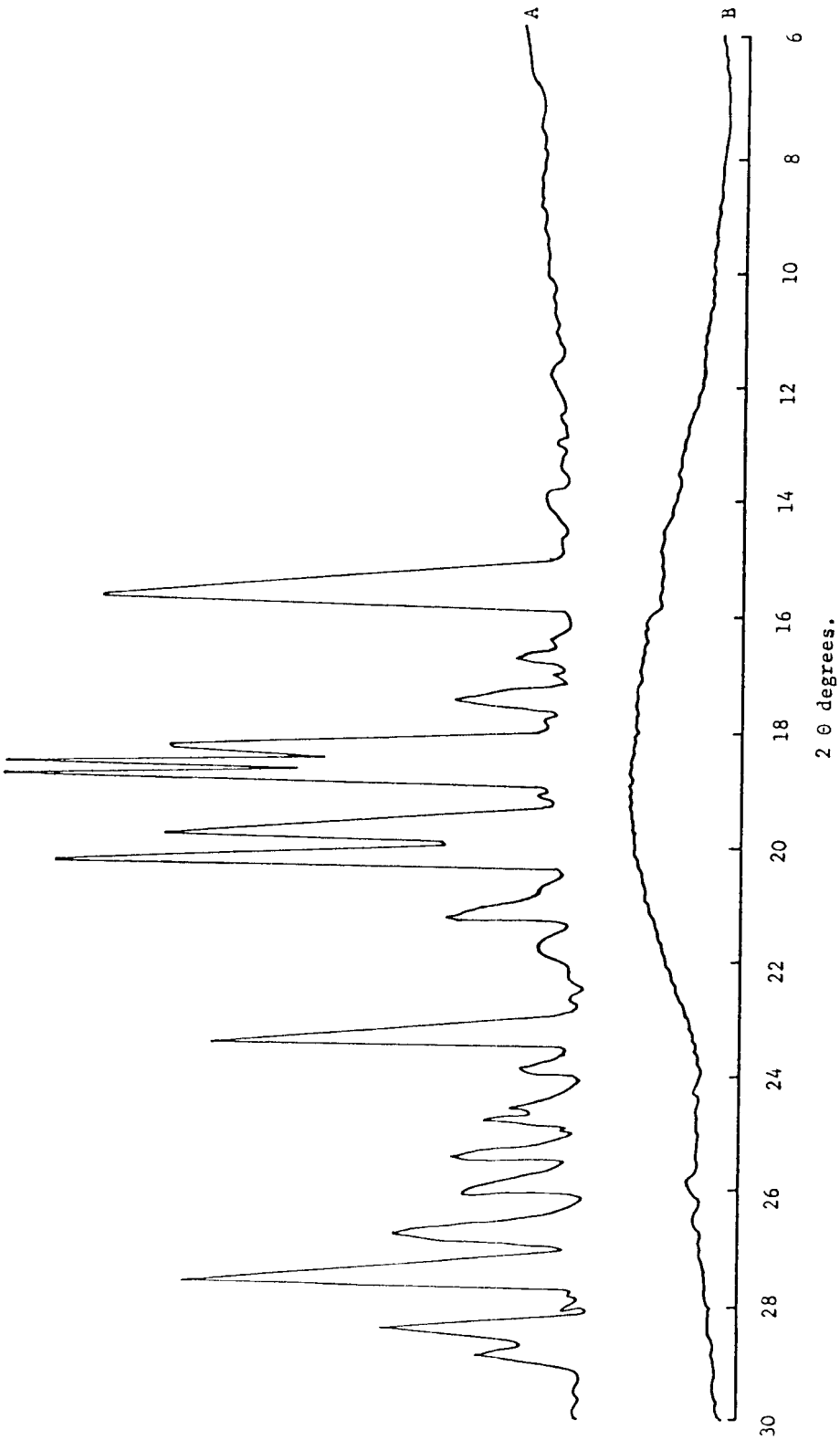


FIGURE 7

X-ray diffraction patterns for hydroflumethiazide samples - A, Non spray dried; B, Spray dried.

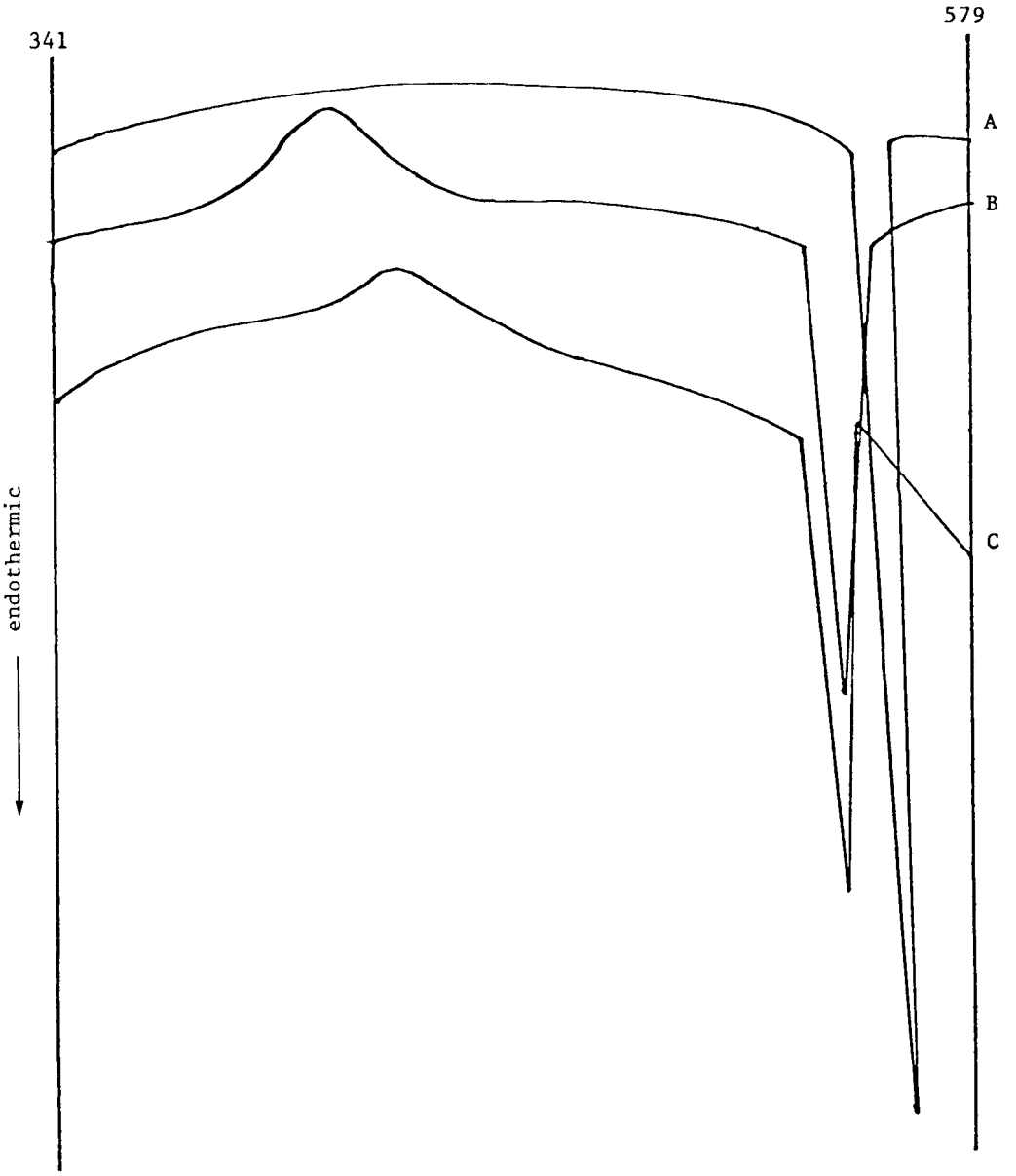


FIGURE 8

DSC thermograms of hydroflumethiazide samples ($^{O}K$)

A, non spray dried; B, spray dried; C, spray dried from 10% PVP solution.

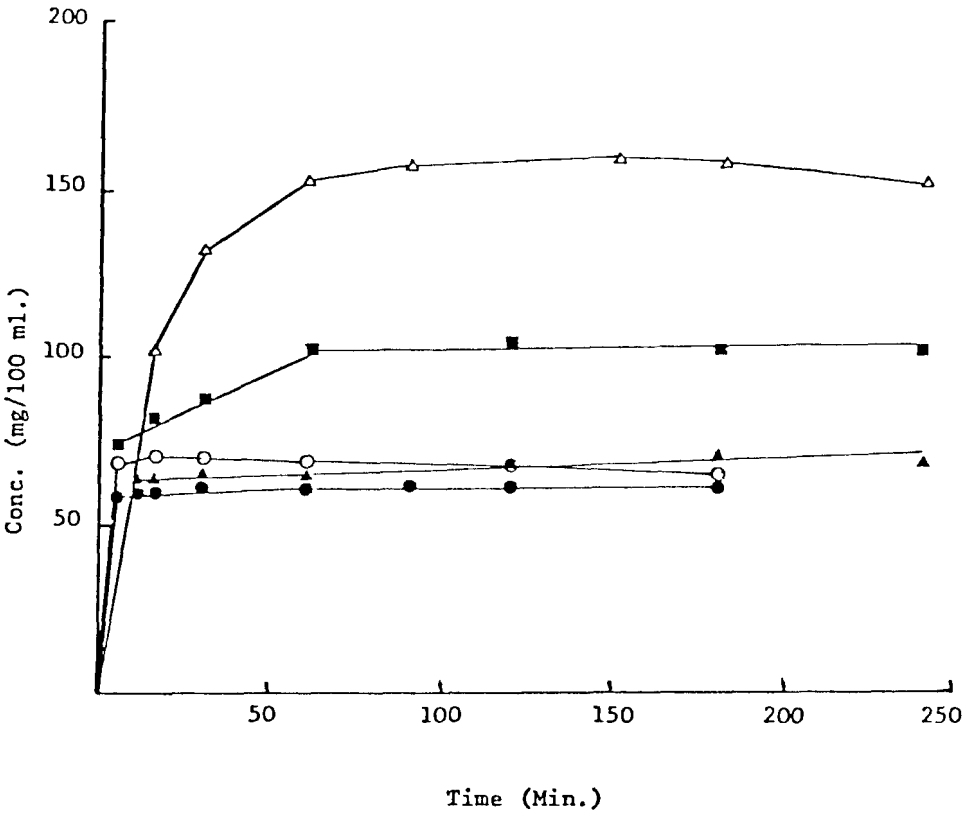


FIGURE 9

Solubility profiles of hydroflumethiazide samples at 37°

(●) Non spray dried and (○) spray dried in 0.1 NHCl media. (▲) Non spray dried and (■) spray dried in a media containing 1% PVP. (△) Spray dried from 10% PVP solution in a media containing 1% PVP.

hydroflumethiazide was therefore spray dried in the presence of low concentrations of PVP. The spray dried materials thus produced were also shown to be amorphous on X-ray analysis. As the concentration of PVP present in the spray dried solid increased, changes occurred in the DSC profiles. The exothermic peak decreased in size and moved to a higher temperature while the endothermic peak decreased and shifted to a lower temperature

(Fig. 8). Amorphous hydroflumethiazide-PVP systems can therefore be prepared by spray drying at much lower PVP weight fractions than those obtained on coprecipitation (20) and these systems appear to contain both amorphous drug and amorphous drug-PVP complex.

The solubility profile of a spray dried hydroflumethiazide system containing 10% PVP is included in Fig. 9. The solubility of this system was higher than that of the pure amorphous material being 2.5 times that of the crystalline drug. Whether this increase in solubility results from the formation of a pure hydroflumethiazide amorphous phase with a higher thermodynamic activity than the pure spray dried form, or from a hydroflumethiazide-PVP complex is unclear and currently under investigation.

Phenobarbitone is known to exist in a glass form (15) although we could not produce such a form by spray drying pure solutions of phenobarbitone. Therefore alcoholic solutions of phenobarbitone were spray dried in the presence of increasing amounts of PVP. The DSC scan for the system containing 10% PVP is included in Fig. 3. The presence of an exothermic peak suggested that the material was amorphous.

In conclusion, our experience with phenobarbitone and hydroflumethiazide has demonstrated that, in addition to changes in the micromeritic properties of a drug, spray drying, either in the presence or absence of excipients, can result in the formation of high energy drug polymorphs and/or amorphous phases not normally obtained by conventional precipitation procedures.

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