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PHYSICOCHEMICAL PROPERTIES OF INDOMETHACIN AND RELATED COMPOUNDS CO-SPRAY DRIED WITH POLYVINYL-PYRROLIDONE.

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ABSTRACT

The spray drying of indomethacin produced a viscous liquid phase which then solidified to an amorphous glassy solid mass. This amorphous phase was physically unstable and converted on storage to crystalline indomethacin forms II and I. Co -spray drying indomethacin with up to 20% PVP also gave a fused amorphous solid. Apparent solubility and dissolution studies illustrated the higher energy of indomethacin in these systems. The presence of PVP in the solid retarded conversion of indomethacin to a crystalline phase, the effect increasing with increasing PVP content. Scanning electron microscopy revealed the growth, with time, of needle-like whiskers on the surface of the amorphous products. Co-spray drying indo-

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methacin with more than 20% PVP resulted firstly in products composed of a fused network of spherical particles, then partially coalesced spheres and ultimately, above 25% PVP, in individual agglomerated microspherical particles. The spray drying of either naproxen, ketoprofen or ibuprofen did not result in the formation of an amorphous glassy solid. Co-spray drying with PVP led to reduced crystallinity; the size of the melting endotherm decreased with increasing PVP content and became absent at 50% PVP. As the PVP percentage increased a microspherical product also developed, but at PVP levels greater than that observed for indomethacin.

INTRODUCTION

Spray drying is increasingly used in the production of pharmaceutical products and this process can alter biopharmaceutically relevant drug properties[1]. Previously we investigated the physicochemical properties of a number of spray dried thiazide diuretics[2,3]. These compounds had melting points in the range 200 - 340°C and, on spray drying from ethanolic solution, gave microspherical amorphous glassy particles of varying physical stability with higher activities than the normal crystalline drug forms[3]. Both these pro-

perties, namely small particle size and higher activity, offer potential biopharmaceutical advantage. We have exte nded these investigations to other drug groups including a number of non-steroidal anti-inflammatory agents of low melting point (M.P.) i.e. indomethacin (158-162°C) naproxen (156°C), ketoprofen (94.5°C) and ibuprofen (75-77.5°C). Indomethacin is known to exist in a number of polymorphic states and also in an amorphous form[4] which has a significantly higher solubility than the crystalline phases[5]. The amorphous form is, however, unstable, being converted to crystalline form I and II[5]. The dissolution kinetics of indomethacin-polyvinylpyrrolidone coprecipitates have also been investigated[6,7]. Recently the stabilization of amorphous indomethacin formed in indomethacin-polyvinylpolypyrrolidone (1:3) systems was reported[8]. Solid dispersion systems of indomethacin and polyethylene glycol (PEG) have also been examined[9,10] and drug dissolution rate related to its degree of crystallinity in the sample[10]. Solid dispersions of ketoprofen have also been investigated and the freeze dried ketoprofen:PVP (1:2) system reported to contain amorphous drug[11]. In contrast, ketoprofen:urea solid dispersions had the characteristics of a simple eutectic mixture[12]. In this communication, the physicochemical

properties of indomethacin and a number of related anti-inflammatory agents, each spray dried both in the presence and absence of PVP, are reported.

MATERIALS AND METHODS

Preparation of Spray Dried Samples

Materials to be spray dried were dissolved in alcoholic solvent. The solution was dried using a Buchi Minispray 190 spray drier, as previously described[2]. Indomethacin, naproxen, ketoprofen and ibuprofen of B.P. grade were used without further purification. PVP (plasdone c-15) of approximate molecular weight 10,000 was used.

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 (SEM) and a Hitachi S-520 SEM.

Solubility and Dissolution Rate

Solubilities and apparent solubilities in phosphate buffer pH 6.6 were determined by the modified method of Shefter and Higuchi[13] as previously described[2]. Apparent solubilities of metastable systems were also determined in media containing 1% PVP in order to inhibit transformation of the metastable phase.

Dissolution profiles were determined from compressed discs of drug mounted in paraffin wax as previously described[14]. Drug in solution was assayed by UV spectroscopy.

Thin Layer Chromatography

Ethanolic solutions of indomethacin spray dried systems were each spotted on 0.3 mm silica gel 60 GF 254 plates. Plates were developed with methanol-strong ammonia solution 100:1.5, air dried and visualized under UV light.

RESULTS AND DISCUSSION

Indomethacin

On spray drying indomethacin from ethanolic solution a highly viscous phase formed, mainly in the cyclone separator above the collecting vessel, which then solidified to give a glassy amorphous form of drug. Spray dried systems containing

indomethacin were slightly yellow in colour. However, only one spot was detected by TLC, the spray dried material having the same R_f value as pure indomethacin. Both samples were equivalent on U.V. assay indicating insignificant decomposition on spray drying. X-ray diffraction (Fig. 1) and DSC (Fig. 2) scans of indomethacin confirmed the amorphous nature of the spray dried product. Thus it appears that the liquid droplets of drug formed during the spray drying process have insufficient time to solidify and coalesced on contact in the cyclone separator. The product, although amorphous, was in sharp contrast to the microspherical amorphous particles which were recovered from the collecting vessel on spray drying the high melting point thiazide diuretics[3].

Amorphous indomethacin developed crystallinity within a week. DSC profiles of freshly spray dried indomethacin (Fig. 2) had three peaks, an exotherm, corresponding to reversion of the amorphous phase to form II, a first endotherm suggesting conversion of form II to form I and a second endotherm indicating melting of form I. On storage the size of the exotherm and of the form II endotherm decreased. X-ray diffraction scans of a sample in transition showed traces of peaks of both form

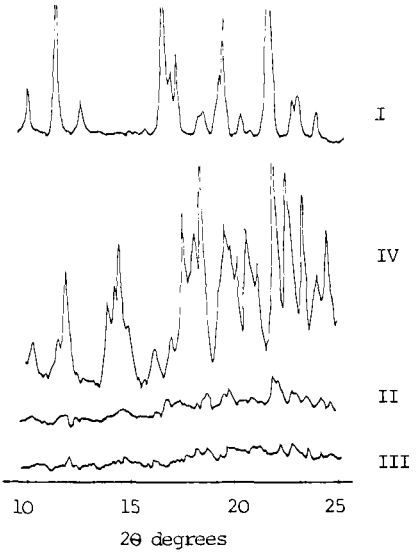

FIGURE 1

X-ray diffractograms of indomethacin systems. I, crystalline drug (form I); II, spray dried drug; III, drug spray dried with 10% PVP and IV, drug spray dried with 5% PVP and stored for two months.

II and form I. Therefore it is not clear whether conversion of the amorphous phase to form I occurs directly or via form II. DSC thermograms obtained on spray dried samples after one year's storage at room temperature still revealed traces of form II.

Indomethacin:PVP Spray Dried Systems

Samples prepared by co-spray drying indomethacin and PVP from ethanolic solutions were also amorphous. The high activity of these amorphous systems was confirmed by dynamic solubility and intrinsic dissolution rate experiments. The sol-

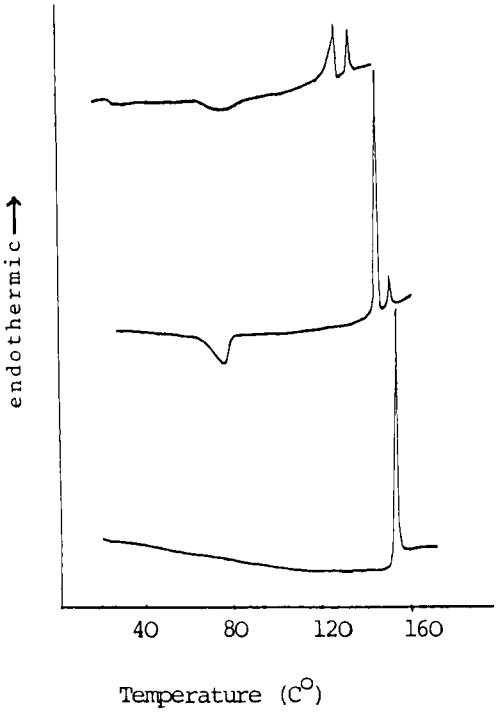

FIGURE 2

DSC scans of I, indomethacin (form I); II, spray dried indomethacin and III, indomethacin spray dried with 5% PVP (freshly prepared).

ubility profile for the amorphous system containing 1% PVP is compared to that of crystalline (form I) in Fig. 3. The amorphous system containing 1% PVP had a peak indomethacin solubility approximately five times that of form I. The inclusion of PVP in the solubility medium to retard crystallization, increased the solubility of both crystalline and amorphous drug indicating soluble complex formation between indomethacin and PVP in solution. Co-spray

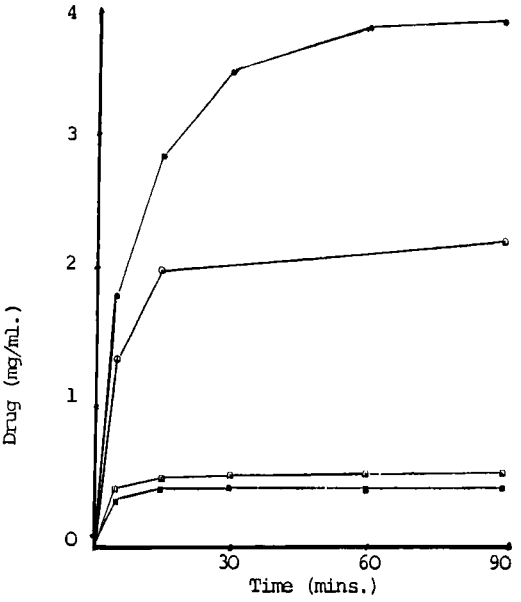

FIGURE 3

Solubility profiles for indomethacin systems. Key: ■ indomethacin (non spray dried), o spray dried sample (indomethacin:PVP 99:1), □ indomethacin (non spray dried) in dissolution medium containing 1% PVP and ● spray dried sample (Indomethacin:PVP 99:1) in dissolution medium containing 1% PVP.

drying indomethacin with higher percentages of PVP gave products with even higher apparent peak solubility. However these systems were physically less stable, rapidly crystallizing from solution even in media containing 1% PVP.

Fig. 4 shows the dissolution profiles of an indomethacin:PVP (10% PVP) co-spray dried system, the corresponding crystalline drug:PVP physical mixture and pure indomethacin (form I) obtained using constant surface area discs. The release rate from

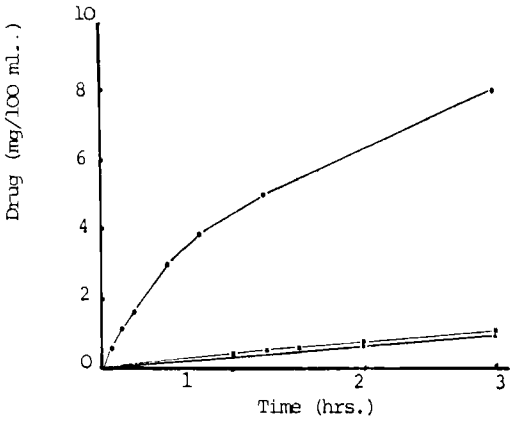

FIGURE 4

Dissolution profiles of constant surface area discs. Key ● indomethacin spray dried with 10% PVP, ▲ physical mixture containing 10% PVP and ■ crystalline indomethacin.

the amorphous phase was over twenty times that observed for crystalline form I.

The physical stability of indomethacin as an amorphous phase improved when the drug was co-spray dried with PVP, the effect increasing as the proportion of PVP in the solid increased. As little as 1% PVP retarded the conversion to crystalline indomethacin. Some conversion to the crystalline phase was evident after twelve days storage in the case of the system containing 1% PVP. Furthermore, when crystallization occurred in PVP containing systems, form I was not the dominant phase as can be seen from the X-ray diffraction pattern for a 2 month-old system spray dried to contain indomethacin with 5%

PVP (Fig. 1). Scanning electron micrographs of these systems revealed the growth of whisker-like, needle-shaped projections on the solid amorphous glassy phase surface (Fig. 5). These whiskers, which appeared to develop less rapidly as the proportion of PVP co-spray dried with the drug increased, became more numerous with time. The growth of needle-shaped crystals in indomethacin systems has been reported to be commensurate with form II indomethacin[4,9]. Surprisingly, even when substantial surface whisker growth was evident from scanning electron microscopy in the 10% PVP system, the sample appeared amorphous by the X-ray diffraction method. While the development of hairlike or whisker-like growths has long been known in inorganic systems[15], it appears to be less common in organic systems systems. In the pharmaceutical area, whisker growth on the surface of ethenzamide and caffeine anhydride tablets has been reported[16]. Technological interest in whiskers has centered on their reported ultra high strength and potential use in high strength, light weight whisker reinforced composite materials. Whether they have direct pharmaceutical applications remains to be explored.

In addition to improving the stability of the amorphous product, co-spray drying with PVP also

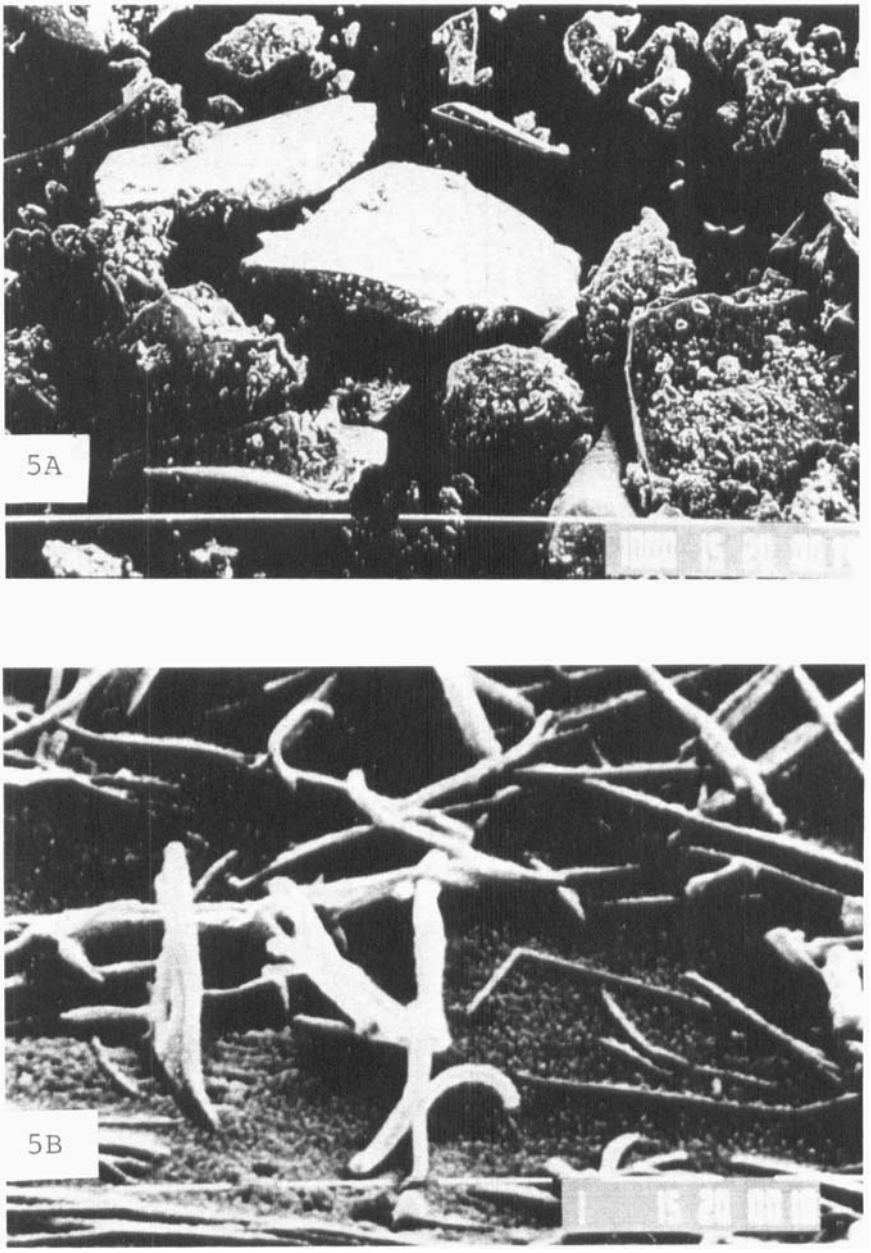

FIGURE 5

Scanning electron micrographs of indomethacin spray dried with 5% PVP. A : bars represents 1000 μm, B : bars represents 1.0 μm.

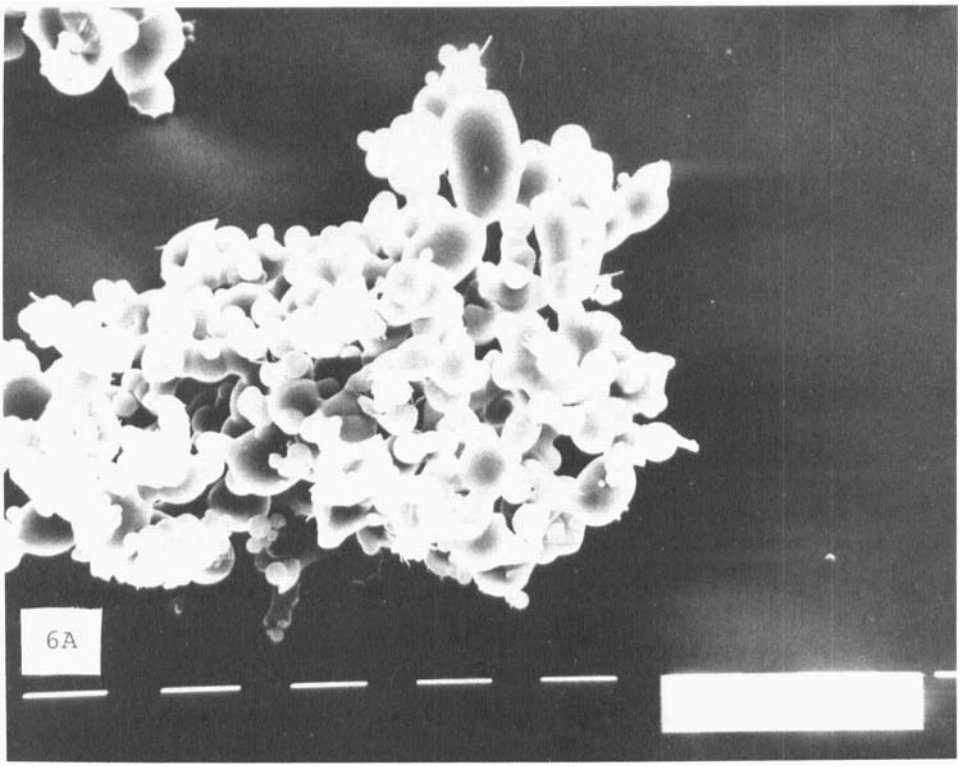

FIGURE 6

Scanning electron micrographs of indomethacin samples spray dried with PVP.
A and B : 20% PVP, bars represent 10 μm
C : $33^1/_3$ % PVP, bars represent 10 μm
D : $33^1/_3$ % PVP, bars represent 1.0 μm

dramatically altered the physical properties of the spray dried material. Indomethacin:PVP spray-dried systems containing up to 20% PVP were physically similar to pure spray-dried amorphous indomethacin in that the dried spray droplets coalesced during drying to form an amorphous coating of product in the cyclone separator. When the

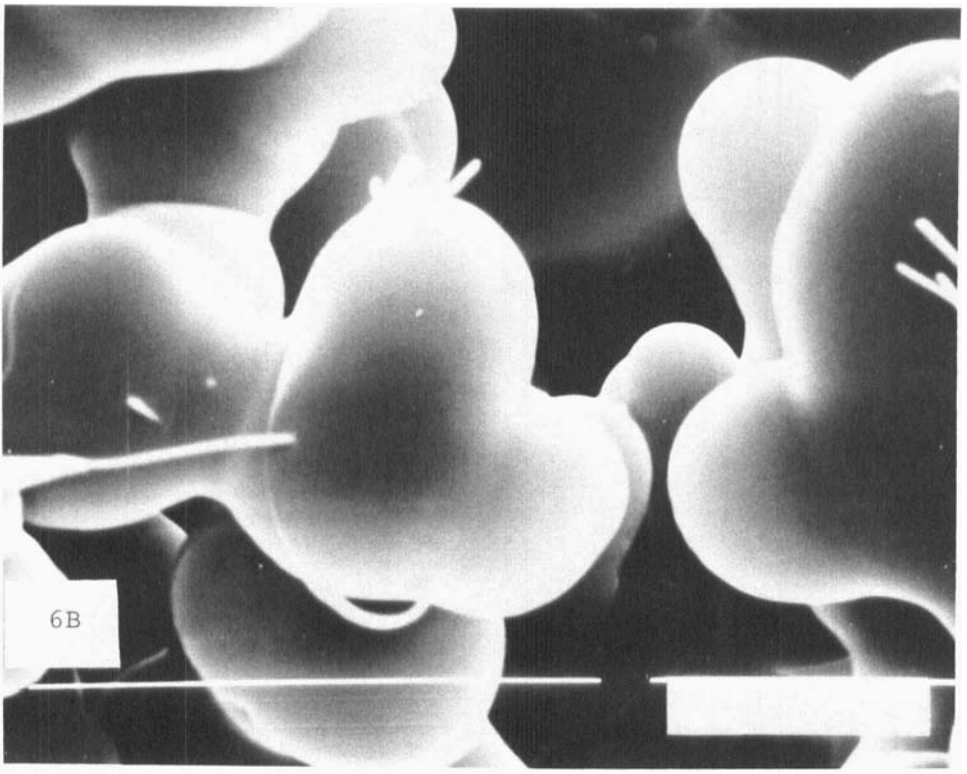

Figure 6 (Continued)

proportion of PVP co-spray dried with indomethacin was further increased, i.e. in the range 20-35%, a change in the properties of the resultant solid occurred. At these higher PVP percentages, a powder formed in the collecting vessel which proved under SEM to be agglomerated microspherical amorphous particles (Fig. 6). At intermediate PVP percentages, the transition from an amorphous slab to a more open network of partially coalesced spheres was

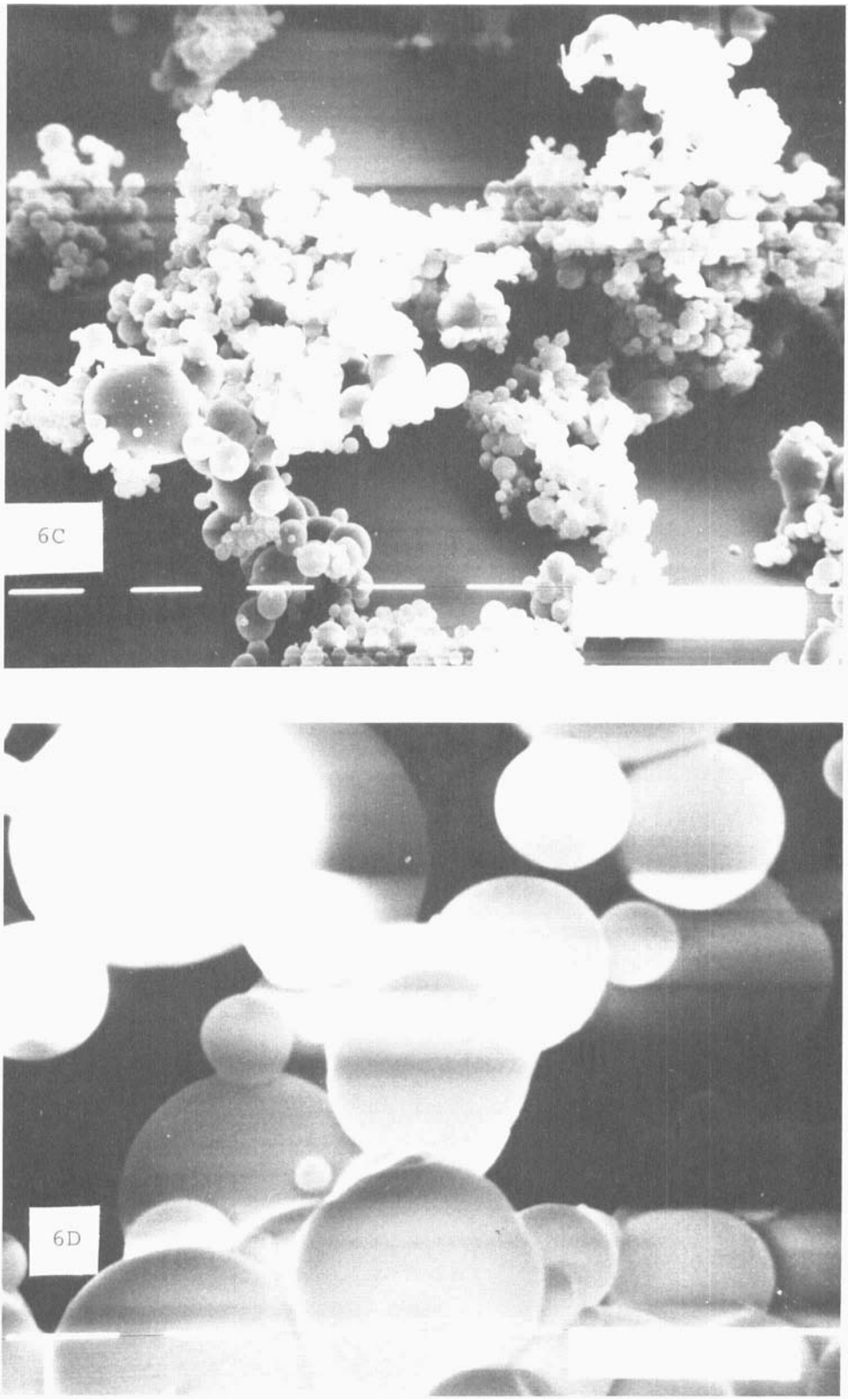

Figure 6 (Continued)

evident. The growth of needle-like whiskers was not evident in systems containing 25% or more of PVP.

Naproxen

A crystalline product was formed on spray-drying naproxen in ethanolic solution. Crystallinity was confirmed by both X-ray diffraction and D.S.C. methods. Co-spray drying this drug with increasing amounts of PVP resulted in a decrease in crystallinity. No endothermic peak was evident in the thermogram at 40% PVP. X-ray diffraction peak intensities also decreased with increasing PVP content, only a trace of the major peak being detectable at 40% PVP. However scanning electron microscopy of naproxen:PVP spray dried samples revealed the presence of surface crystals of drug even in systems containing up to 60% PVP, the formation of true amorphous microspherical particles only occurring in systems containing as much as 70% PVP (Fig. 7).

Although naproxen has a similar melting point to indomethacin, it has a much smaller molecular weight. We have previously observed that lower molecular weight compounds less readily form an amorphous phase.[3]

Ketoprofen and Ibuprofen

The products produced on spray drying either ketoprofen or ibuprofen were highly viscous transparent liquids. In contrast to indomethacin and

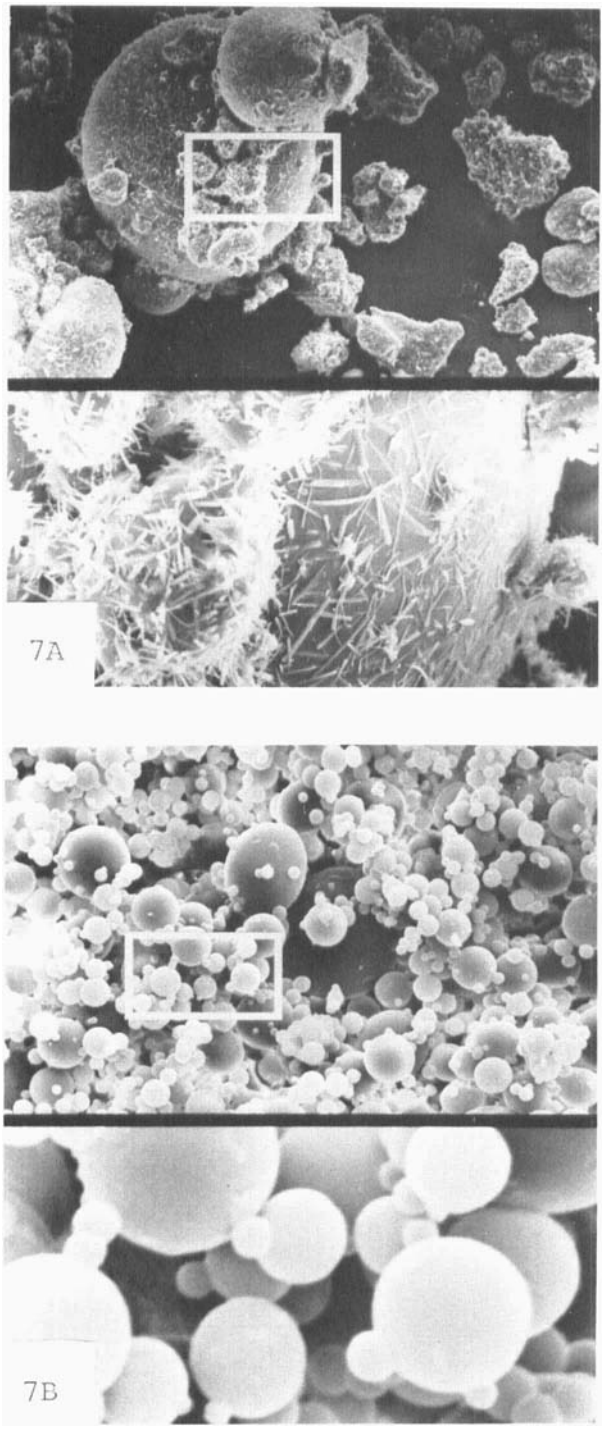

FIGURE 7

Scanning electron micrographs of naproxen spray dried with PVP.

A : 40% PVP magnifications x 130 and x 650
B : 75% PVP magnifications x 1,040 and x 5,200

naproxen both ketoprofen and ibuprofen have melting points below 100°C. Co-spray drying ketoprofen or ibuprofen with sufficient PVP gave amorphous solid products. An aglomerated powder was formed at 50% PVP with ketoprofen, while ibuprofen systems of similar composition were still fluid. When co-spray dried with 75% PVP both drugs gave products which were microspherical on SEM examination.

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REFERENCES

1. E. Nurnberg, Acta Pharm. Techn., 26, 39 (1980).
2. O.I. Corrigan, K. Sabra and E.M. Holohan, Drug Devel. Ind. Pharm. 9, 1 (1983).
3. O.I. Corrigan, E.M. Holohan and K. Sabra, Int. J. Pharm. (in press), 18, 195 (1984).

4. L. Borka, Acta Pharm. Suecica, 11, 295 (1974)

5. H. Imaizumi, N. Nambu and T. Nagai, Chem.Pharm. Bull. 28, 2565 (1980)

6. K. Takayama, N. Nambu and T. Nagai, Chem. Pharm. Bull. 28, 3309 (1980)

7. K. Takayama, N. Nambu and T. Nagai, Chem. Pharm. Bull, 29, 2718 (1981)

8. H. Imaizumi, N. Nambu and T. Nagai, Chem. Pharm. Bull, 31, 2510 (1983)

9. J. L. Ford and M. H. Rubinstein, Pharm. Acta Helv. 53, 93 (1978)

10. D. J. Allen and K. C. Kwan, J. Pharm. Sci. 58, 1190 (1969)

11. K. Takayama, N. Nambu and T. Nagai, Chem. Pharm. Bull. 30, 3013 (1982)

12. J. A. Rogers and A. J. Anderson, Pharm. Acta Helv 57, 276 (1982)

13. E. Shefter and T. Higuchi, J. Pharm. Sci., 52 781 (1963)

14. O. I. Corrigan and R. F. Timoney, J. Pharm. Pharmac. 27, 759 (1975)

15. A. P. Levitt in "Whisker Technology" Wiley-Interscience (1970)

16. H. Yuasa, K. Miyata, T. Ando, Y. Kanaya, K. Asahina and H. Murryama. Yakuzai Gaku 41, 155 (1981).