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Crystal habit modifications and altered tabletting characteristics

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Summary

The crystal habit of a drug is an important parameter that affects the basic physical properties and micromeritic properties of a compounded mixture of powders A novel orally active iron chelator, 1,2-dimethyl-3-hydroxypyrid-4-one (DMHP), has been synthesized as orthorhombic crystals which have very poor flow properties and do not tablet well The crystal habit could not be changed in its pure state Hence, incorporation of additives by coprecipitation was used as an approach to induce habit modification. Commonly used pharmaceutical excipients (gelatin, PEG 4000, and PVP) were studied at concentrations ranging from 1 . 0 2 to 1 : 2 (DMHP : additive, w/w). The resulting powders were free flowing and formed good tablets Photomicrography revealed spherical aggregates, X-ray diffraction spectra did not show any polymorphic change While gelatin induced spherical aggregation at a concentration of 1 0 2, PEG and PVP were required at higher concentrations (1 2) The dissolution of DMHP from tablets made from these coprecipitates did not show any pH dependence at low additive concentrations but with gelatin at 1 . 2, a near zero-order release was obtained at pH 7.4 The ability of coprecipitation to modify crystal habit, tabletting characteristics, and release rates of drugs is demonstrated.

Introduction

Crystal habit of a drug is an important variable in pharmaceutical manufacturing. A number of basic physical properties such as solubility, dissolution rate, melting behavior, etc. (Doherty and York, 1988; Dahl et al., 1989) and certain micromeritic properties or performance characteristics, e.g., tablet compressibility, mechanical strength, powder flow, etc. (Simmons et al., 1972; Kawashima et al., 1986) depend on the habit modification of a particular drug. Furthermore, these variations can alter the bioavailability and therapeutic response. Although isotropic crystals (cubic, spherical) are the preferred habit modifications, the majority of drugs exist as non-isotropic crystals. Therefore, manipulative procedures to change to a more favorable crystal form are quite often called for.

The technology of particle design of drugs has emerged as one of the areas of active research currently of interest in pharmaceutical manufacturing. Attempts have been made by many researchers to modify the micromeritic properties of powders. The following are some of the commonly used approaches: spherical crystallization

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or spherical agglomeration transforms a microcrystalline drug into an agglomerated form during the crystallization process. The resultant agglomerated crystals assume a spherical form thereby enabling easy compounding with other pharmaceutical powders (Kawashima et al., 1982, 1984, 1986). More recently spherical agglomerates have been prepared by a sophisticated technique, referred to as the quasi emulsion solvent diffusion (QESD) method (Sano et al., 1990). In the solvent change method of spherical agglomeration, the crystallization process is controlled by changing the solvent such that crystalline polymorphs or habits having more advantageous secondary characteristics are produced (Sano et al., 1989). In most cases, solvent-solute interactions play an important role in determining which crystal habit results (Doherty and York, 1988). Incorporation of 'additives', or 'impurities' structurally related to the compound in question has also been used to provide crystal growth inhibition in specific directions, thereby yielding crystals of different morphology (Chow et al., 1984; Chow et al., 1985). Other techniques such as changes in the degree of supersaturation (Haleblian, 1975), temperature (Khamskii, 1976), or conditions of agitation (Garti and Tibika, 1980) have also been used to produce habit modifications.

The crystals of pure DMHP, a highly effective orally active iron chelator, are orthorhombic. Preliminary studies showed poor tabletting properties. Attempts to modify this habit in the pure state by modifying the crystallization conditions (using a range of solvents, changing the degree of supersaturation and rate of cooling) did not yield any different crystal forms. Hence, habit modification in the presence of selected additives was considered as a possible approach. Additives were incorporated into the cyrstals by coprecipitation. The samples were characterized by powder X-ray diffraction, optical microscopy and tablet dissolution profiles.

Materials and Methods

DMHP was synthesized according to a previously published method (Chan et al., 1991). PEG 4000, gelatin and polyvinylpyrrolidone (PVP) were purchased from Fisher Scientific Co., Fairlawn, NJ, U.S.A.

Coprecipitation

This was carried out by dissolving in 95% ethanol, DMHP and any of the following agents: PEG 4000, PVP, or gelatin in various ratios ranging from 1.0:0.2 to 1.0:2.0 (DMHP:additive, w/w). Ethanol was removed by evaporation on a water bath at 50°C with constant stirring. The resulting dry residue was collected, gently ground into a powder, and the powder between an 80 and a 200 mesh (USP standard series of sieves) was collected and compressed into tablets on a single punch tablet press (Model F3, Manesty Machines, Liverpool, U.K.). The tablet weight was adjusted to give 50 mg of DMHP per tablet and a hardness of 6–8 kg.

Powder X-ray diffraction

A Phillips (Model PW 1729) X-ray diffractometer was used at 40 kV, 40 mA and a scanning rate of 6°/min over a range of 5–35° 2θ, using $CuK_{\alpha 1}$ radiation of wavelength 1.5406 Å.

Photomicrography

Photomicrographs of the crystals were taken on a Nikon optical microscope (Model: HFX) equipped with automatic photographic capabilities (Model: FX35A) using a 35 mm, 125 ASA black and white photographic film under a magnification of $\times 12$.

Dissolution studies

A USP Dissolution Test Apparatus no. 2 was used to monitor the dissolution profiles of the tablets. The dissolution medium was 900 ml of either KCl–HCl buffer (pH 2.0) or phosphate buffer (pH 7.4) equilibrated to 37°C. The paddles were rotated at 50 rpm. 2 ml samples were withdrawn from the dissolution flask, immediately centrifuged for 10 s on a bench-top centrifuge to remove any undissolved particles and the supernatant analyzed for DMHP content at 276 nm (pH 2.0) or 278 nm (pH 7.4) on a UV spectrophotometer (Model UV 160, Shimadzu Corporation, Japan).

Results and Discussion

Powder X-ray diffraction patterns of pure DMHP crystals showed the presence of strong peaks in decreasing order of intensity, at 14.9, 13.5, 28.0 and 30.2° 2θ. Every coprecipitate sample showed all these diffraction lines characteristic of DMHP, revealing the presence of crystalline DMHP in the coprecipitate (Fig. 1a–1d). The interplanar spacings corresponding to each of the diffraction lines were identical to the values for pure DMHP. This is interesting in view of the fact that one would expect the lattice spacing to change in the presence of additives. However, in the present situation, because of the large difference in molecular size between DMHP (Mol. Wt 139) and the additives, we could expect crystallites of DMHP interstitially placed in the polymer matrix instead of the polymer occupying sites in the DMHP crystal lattice. The relative peak intensities of the diffraction lines (intensity compared to the strongest peak assigned a value of 100%) were not very different as compared to the values of pure DMHP crystals. Although these results reflect no change in the packing arrangement and structure of DMHP crystals, the results from optical microscopy (Fig. 2) show that the overall shape of a coprecipitate powder particle could be different from that of the constituent drug particles. This is exemplified by the spherical aggregation brought about by a small fraction of gelatin (DMHP : gelatin = 1 : 0.2) in the coprecipitate. PEG 4000 and PVP were also effective in causing crystal modifications but only at higher concentrations as seen in Fig. 2. This difference between gelatin and the other polymers can be attributed to the heterogeneity of gelatin as compared to the more homogeneous nature of PEG or PVP. The presence of multifunctional groups in gelatin makes spherical aggregation relatively easy.

The coprecipitates were free flowing and formed very good tablets as compared to pure DMHP crystals. The tablets had good binding characteristics and hardness of 6–8 kg was readily achieved from the coprecipitates at low compaction forces. The friability of all tablets was typically less than 1% by weight.

The dissolution profiles of tablets made from the coprecipitates are shown in Figs. 3 and 4. In pH 2.0 buffer, nearly 50% of DMHP was re-

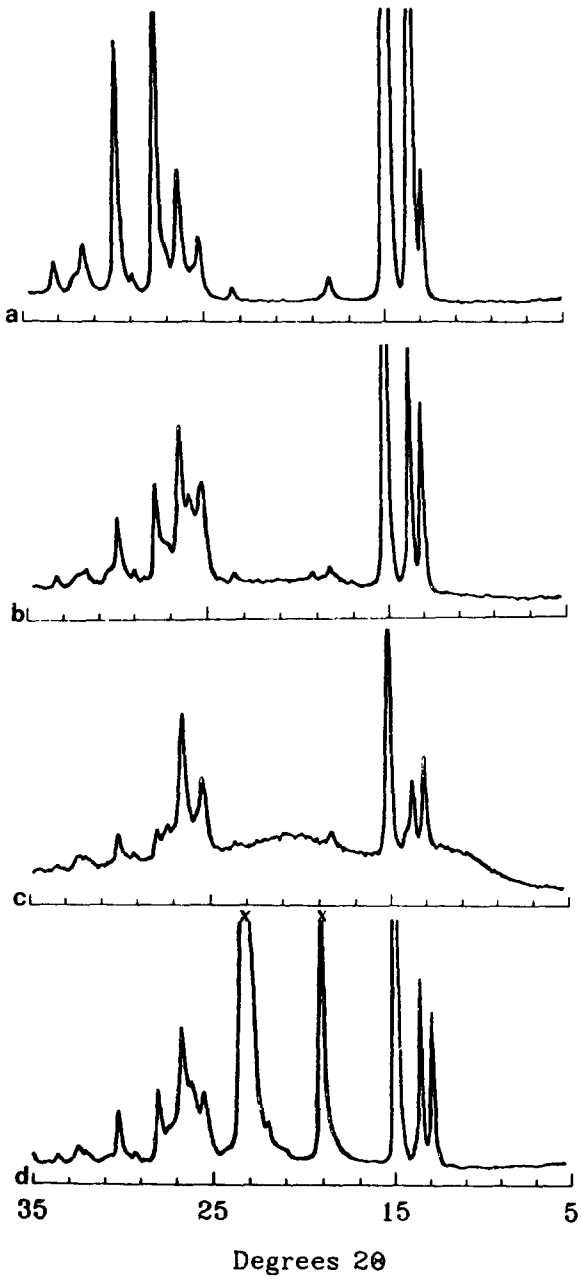

Fig. 1. Powder X-ray diffraction patterns of (a) pure DMHP, and coprecipitates of DMHP with additives. (b) DMHP : gelatin, 1·0.2, (c) DMHP : PVP, 1 2 and (d) DMHP : PEG 4000, 1 . 2 by weight. Peaks marked 'x' are from pure PEG 4000.

leased within 30 min from tablets made from coprecipitates containing only a small amount of the additive (DMHP : additive = 1 : 0.2) as shown in Fig. 3a. The dissolution profiles did not change significantly in pH 7.4 buffer (Fig. 3b). However, by increasing the concentration of gelatin in the coprecipitate to 1 : 1, the dissolution rates were significantly slower at both pH 2.0 and pH 7.4 (Fig. 4a and b). DMHP release in pH 7.4 was nearly linear up to about 100 min of the dissolution run. This is perhaps due to the formation of a viscous layer of gelatin around the tablet forming a rate-controlling membrane in situ. Such a phenomenon was not observed with either PVP

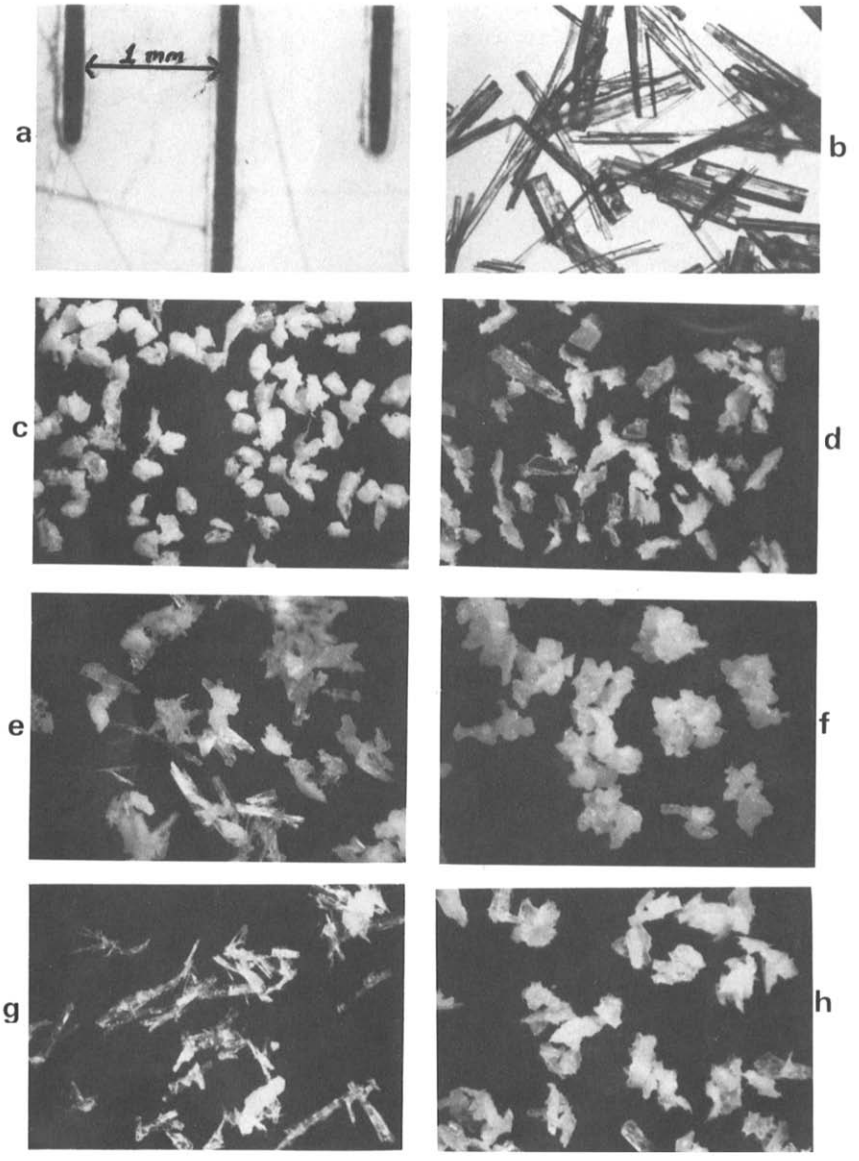

Fig. 2. Photomicrographs of pure DMHP and its coprecipitate powders with various agents under a magnification of ×12. (a) micrometer; (b) pure DMHP; (c,d) DMHP · gelatin 1 : 0.2 and 1 : 2; (e,f) DMHP PVP 1 0 2 and 1 2, and (g,h) DMHP · PEG 4000 1 . 0.2 and 1 · 2, respectively.

or PEG 4000 which demonstrated similar release patterns as seen at the respective lower additive concentration at both pH 2.0 and 7.4. Higher concentrations of gelatin made the coprecipitates extremely hard and difficult to recover from the beaker.

In conclusion, these results demonstrate the utility of coprecipitation to incorporate additives to modify the crystal habit of a drug particularly when the crystal habit of a drug cannot be altered in the pure state. The concentration at which crystal habit modification is produced depends upon the additive. The release rates of the active ingredient from tablets also depend upon the type of additive and some additives are sensitive to pH changes. Finally, interesting results were obtained from gelatin, which produced crystal habit modification at a very low concentration and at a higher concentration was able to provide a near zero-order release from tablets.

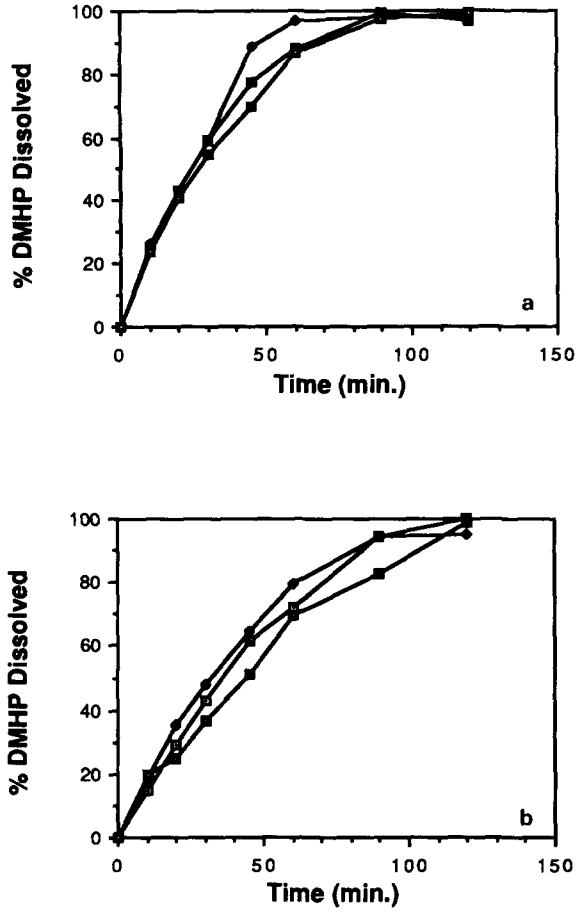

Fig. 3 Dissolution profiles of tablets made from coprecipitates of DMHP with various agents in the ratio of 1:0.2 by weight, in (a) pH 2.0 buffer and (b) pH 7.4 buffer at 37°C (□ ——— □) Gelatin; (◆ ——— ◆) PVP and (■ ——— ■) PEG 4000

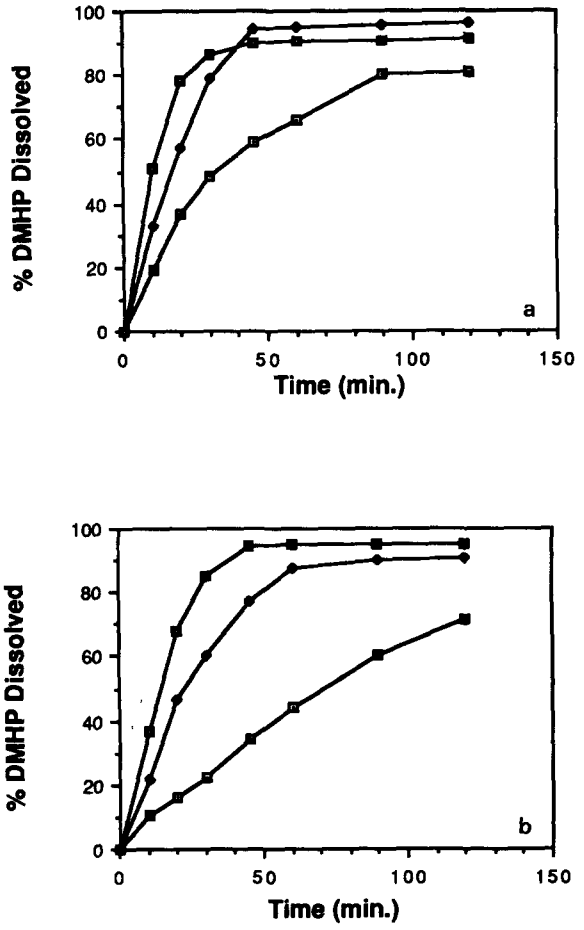

Fig. 4. Dissolution profiles of tablets made from coprecipitates of DMHP with various agents, in (a) pH 2.0 buffer and (b) pH 7.4 buffer at 37°C (□ ——— □) DMHP gelatin,1:1; (◆ ——— ◆) DMHP:PVP 1 2 and (■ ——— ■) DMHP·PEG 4000 1·2 by weight

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