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Formation of theophylline monohydrate during the pelletisation of microcrystalline cellulose–anhydrous theophylline blends

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Summary

The influence of the degree of wetting, during the granulation step of the pelletisation process, on the drug release from several microcrystalline cellulose-anhydrous theophylline blends was examined. Blends containing 60% theophylline show a release rate inversely related to the amount of water used for granulation. The drug release rate from mixtures prepared with 25% theophylline is less influenced by the degree of wetting. Differences in release rate were correlated with the crystal transition from anhydrous theophylline to theophylline monohydrate.

1. Introduction

Microcrystalline cellulose or microcrystalline cellulose–hydrophilic gum blends are widely used as excipients in the manufacturing of pellets for both controlled release and conventional dosage forms. The release rate of a drug formulated as pellets may be influenced by the choice of the excipients and the processing parameters (O'Connor and Schwartz, 1985).

This paper reports the influence of the degree of wetting, during the granulation step of the extrusion-marumerizer technique, on the drug release rate from different anhydrous theophylline–microcrystalline cellulose blends. In order to simulate the densification of the wet mass during extrusion, the anhydrous theophylline–microcrystalline cellulose blends were granulated and wet compressed.

Materials and Methods

Anhydrous theophylline (micronised theophylline, Boehringer Ingelheim, F.R.G.)–microcrystalline cellulose (Avicel PH 101, F.M.C., Philadelphia, U.S.A.) blends (25 : 75 and 60 : 40; w/w) were granulated, wet compressed and dried.

The powders were dry-blended in a planetary mixer (Kenwood, Type N 901) for 10 min. Several 60 : 40 anhydrous theophylline–microcrystalline cellulose blends were granulated using increasing amounts of water ranging from 25% up to 40%, 60% and 70% of dry weight of the powder material, respectively. Several 25 : 75 blends were granulated using 40%, 60%, 70% and 80% water as granulating liquid. Wet milling was performed

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with a 1500 μm sieve and the granules were wet compressed on an eccentric press (Korsch, Frankfurt, F.R.G.) at a pressure of 90 $kg \cdot cm^{-2}$.

The press was equipped with 10 mm flat punches. As a reference material, pure anhydrous theophylline was directly compressed or granulated and wet compressed while anhydrous theophylline–microcrystalline cellulose blends (60 : 40 and 25 : 75) were directly compressed. All wet compacted masses were dried at 30 °C.

The dissolution testing was performed in 900 ml of distilled water at 37 °C using the paddle method (U.S.P. XXI) at a rotational speed of 50 rpm. Samples were taken frequently and the extinction was measured at 271 nm (Zeiss PM 6 UV-spectrometer, F.R.G.) Scanning electron micrographs of the cross-section of simulated pellets were taken (JEOL, SXA-50, A-electr. probe – Japan). Crystal transitions were detected using X-ray diffractometry (Philips, PA 25 equipped with a copper anti-cathode, 25 mA, 40 kV) and thermal analysis (Perkin Elmer, DSC-2, Norwalk, U.S.A.).

Results and Discussion

Simulated pellets containing 60% theophylline showed a release rate inversely related to the amount of water used for granulation (Fig. 1).

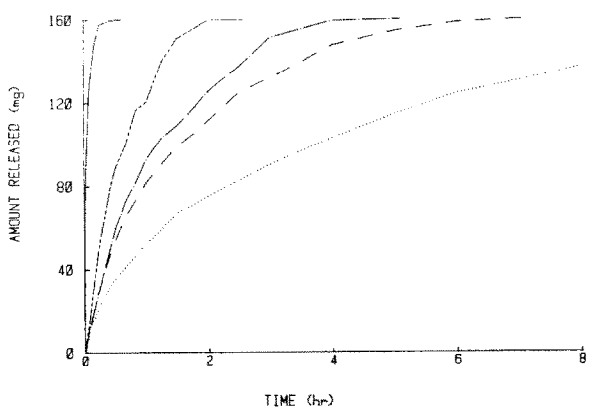

Fig. 1. Dissolution profiles of anhydrous theophylline–microcrystalline cellulose blends (60 : 40): ———, dry blend; granulated blends: — - — - — (25% water); · – · – · (40% water); — — — (60% water); · · · · · · (70% water).

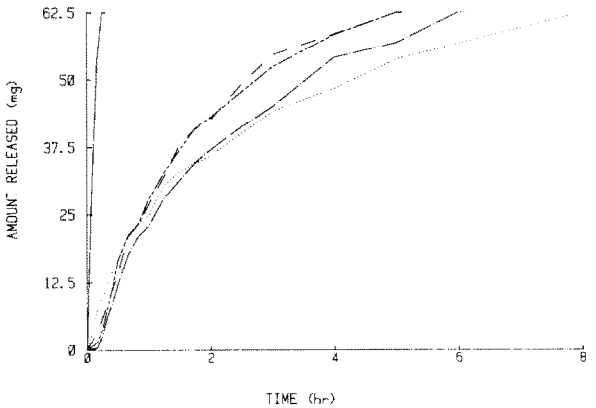

Fig. 2. Dissolution profiles of anhydrous theophylline–microcrystalline cellulose blends (25 : 75): ——— (dry blend); granulated blends: — - — - — (40% water); · – · – · (60% water); — — — (70% water); · · · · · · (80% water).

Increasing the amount of granulating fluid from 25% to 70%, prolonged the 50% drug release level from 25 min to 140 min, respectively. The release rate from simulated pellets containing 25% theophylline was less influenced by the degree of wetting (Fig. 2). No correlation could be found between the apparent density of the simulated pellets and the drug release rate. In comparison to the wet compacted masses, all dry-blended and directly compressed mixtures showed a much faster release rate. No difference was observed in the dissolution behaviour of granulated-wet com-

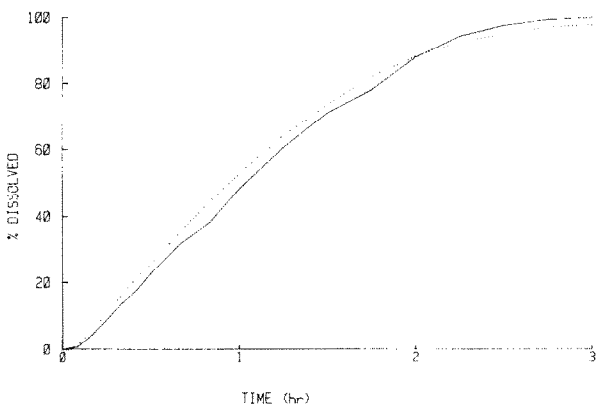

Fig. 3. Dissolution profiles of directly compressed anhydrous theophylline (· · · · · ·) and granulated anhydrous theophylline (———).

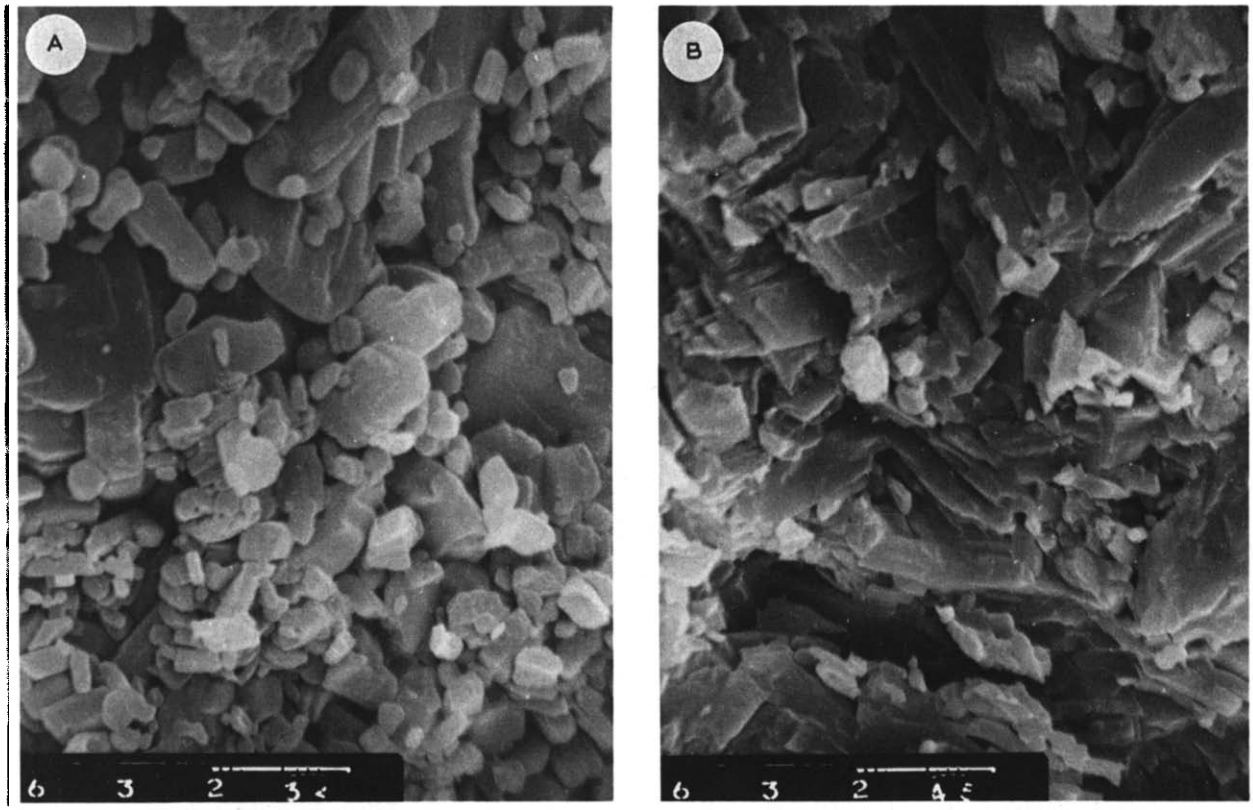

Fig. 4. Scanning electron micrographs of the cross-sections of directly compressed (A) and wet compressed (B) anhydrous theophylline (×3000).

pressed and directly compressed pure anhydrous theophylline (Fig. 3), indicating that the presence of microcrystalline cellulose induced the differences in release rate of the simulated pellets. Although granulation of pure anhydrous theophylline converted the cubic crystals into flake-shaped particles (Fig. 4), no changes in X-ray patterns were observed, indicating that no changes in crystallinity occurred.

X-Ray patterns of the directly compressed theophylline–microcrystalline cellulose blends were similar to those of anhydrous theophylline, as one could expect. On the contrary, the X-ray patterns of theophylline–microcrystalline cellulose blends (60 : 40) granulated with 70% water and all granulated blends (25 : 75) were similar to the one of theophylline monohydrate (Shefter et al., 1973) (Fig. 5). This confirms that wetted anhydrous theophylline was converted to theophylline monohydrate only in the presence of microcrystalline cellulose. The insignificant differences in drug release rate observed for the different anhydrous theophylline–microcrystalline cellulose (25 : 75) blends indicate that nearly all theophylline was converted into the monohydrate form, even when the lowest amount of granulating fluid (40%) was used.

Differential scanning calorimetry could not be used to confirm these results. Although pure theophylline monohydrate showed a dehydration peak at 79 °C, the presence of microcrystalline cellulose interfered with the detection of this dehydration endotherm. The differences observed in the release rate of anhydrous theophylline–microcrystalline cellulose blends can be explained by the lower dissolution rate of theophylline monohydrate

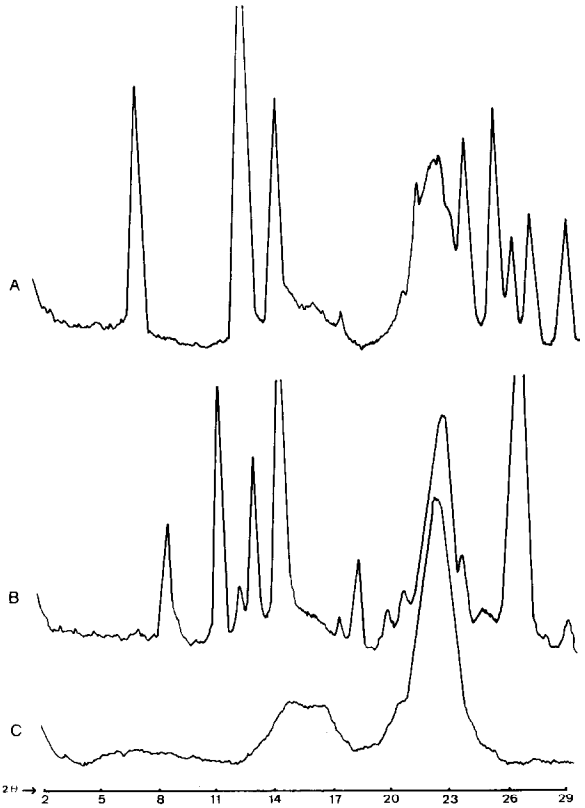

Fig. 5. Parts of the X-ray patterns of directly compressed (A) and wet compressed (B) anhydrous theophylline–microcrystalline cellulose (25 : 75) blends and pure Avicel pH 101 (C).

drate versus anhydrous theophylline (Shefter et al., 1963).

Conclusion

The drug release rate of pellets containing anhydrous theophylline and microcrystalline cellulose may be influenced by the conversion of anhydrous theophylline into theophylline monohydrate. This conversion is quantitatively influenced by the amount of anhydrous theophylline, the choice of the excipients and the degree of wetting during the granulation step.

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