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Notes

A study of sodium indomethacin-calcium hydrogen phosphate precipitation

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Summary

The aim of this study was to establish the elemental composition of the precipitate formed in the reaction between sodium indomethacin and calcium hydrogen phosphate. A scanning electron microscope combined with an energy-dispersive microanalyzer was used in the study. The precipitate was found to consist of indomethacin and calcium, suggesting it to be the calcium salt of indomethacin.

The aim of this study was to establish the elemental composition of the precipitate formed in the reaction between sodium indomethacin (Merck, Sharp & Dohme, U.K.) and calcium hydrogen phosphate (Ph. Eur.). The characterization of this precipitate would help to explain the results obtained in the dissolution of sodium indomethacin from film-coated granules containing various fillers (Eerikäinen et al., 1991). These studies showed that calcium hydrogen phosphate dihydrate had a marked retarding effect on sodium indomethacin dissolution from granules when compared with other fillers. It was assumed that a sparingly water-soluble calcium salt of in-

domethacin was formed during the dissolution test.

In order to identify the composition of the supposed calcium salt of indomethacin formed during the dissolution test, a precipitation experiment was performed. The sodium salt of indomethacin was dissolved in the aqueous dissolution medium (pH 7.2) and the solution was combined with a saturated solution of calcium hydrogen phosphate at pH 7.2. The precipitate formed was collected, filtered and dried at room temperature for 24 h. The possible formation of precipitate between indomethacin and calcium hydrogen phosphate was also examined, but no such precipitate was found.

The sodium indomethacin-calcium hydrogen phosphate precipitate was studied using a scanning electron microscope (JEOL JSM-840, Japan)

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combined with an energy-dispersive microanalyzer. A special technique, thin window EDX, was used to demonstrate the presence of elements with atomic numbers lower than that of sodium in the sample (Goldstein, 1991). The samples studied were indomethacin, sodium indomethacin, calcium hydrogen phosphate dihydrate and the precipitate referred to above. A small quantity of powder was placed onto the SEM sample substrate metal pedestal. Double-

sided sticky Scotch tape was used as mounting resin. The sections were coated with a carbon layer to show the specimen's topography undisturbed by flare or distortion caused by thermal effects and insufficient grinding. The coating was made using a Balzers carbon evaporation coater (SEA-030, Balzers GmbH, Liechtenstein). The acceleration voltage used in the scanning electron microscope was 20 keV and the electron beam current was approx. 1×10^{-10} A. An area of

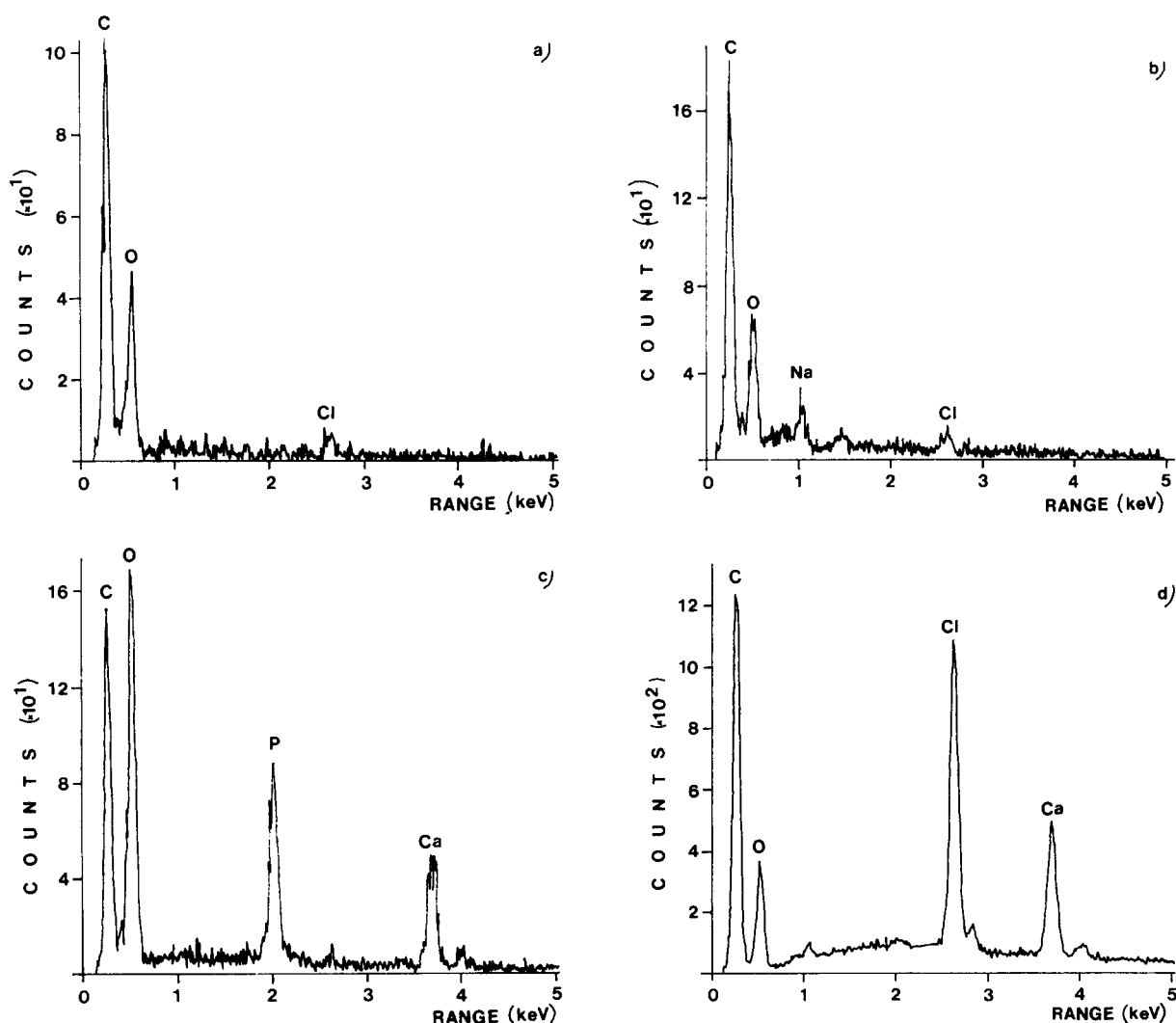


Fig. 1. The X-ray spectra of the samples. (a) indomethacin, (b) sodium indomethacin, (c) calcium hydrogen phosphate dihydrate, (d) the precipitate.

10 × 10 mm of the sample was used as a target for X-ray emission. An aluminium-coated thin window was used in the Si(Li) X-ray detector, giving the elemental scale from boron to uranium. The EDX 'fingerprint' spectra of the samples were analyzed and the characteristic X-ray lines were identified.

The composition of the samples was determined using an EDX microanalyzer. The spectra are shown in Fig. 1. Comparison of the X-ray spectrum of the precipitate with the other spectra (indomethacin, sodium indomethacin, calcium hydrogen phosphate dihydrate) showed it to contain peaks of carbon and oxygen, as did the indomethacin and sodium indomethacin spectra. The precipitate spectrum also had a peak for calcium but not for sodium, unlike sodium indomethacin. It should also be noted that the ratio of the heights of the Ca and Cl peaks is about 1:2 and that the integrated peak areas of 4501 and 9935 counts also correspond quite well to the

ratio 1:2. Although this method is far from quantitative, the results indicate that the precipitate contains Ca and Cl atoms in the ratio 1:2.

These results clearly demonstrate that the precipitate is calcium indomethacin, a sparingly water-soluble salt formed in the dissolution medium. If this calcium salt is formed during the dissolution test of film-coated granules, as might be expected, then it is understandable that its formation would retard drug dissolution from the granules (Eerikäinen et al., 1991).

References

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