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SEMIQUANTITATIVE INVESTIGATION OF TABLET COATS BY ELECTRON PROBE MICROANALYSIS.

Dr. D.T. Brown, School of Pharmacy, Portsmouth Polytechnic, Portsmouth, Hampshire, PO1 2DZ, England.

ABSTRACT

The combined, non-destructive techniques of scanning electron microscopy and electron probe X-ray microanalysis were used to investigate the composition of commercial tablets containing a) film and b) sugar coats, before and after a series of processes designed to challenge the integrity of the coat.

Elemental analysis and estimations of coat thickness and integrity were rapidly made with a single tablet. Using the process of X-ray mapping, it was possible to identify chemically, discrete subcoats of the sugar coat which were indistinct on the electron micrograph. Analyses of these substrata may prove useful in assessing adherence to correct coating procedures.

INTRODUCTION

Tablet coats are employed in pharmaceutical manufacture to provide both physical and chemical protection and for identification purposes[1,2]. In addition, the coating can mask the taste of an obnoxious ingredient or provide a means of separating two in-

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compatible ingredients by including one in the core and the other in the coat.

The choice of coat formulation and therefore its method of application, depend upon the functions which the coat is asked to fulfil in the final dosage form. At one end of the scale are the relatively thick, often multi-layered, sugar coats which contribute significantly to the weight of the finished product. Successive sugar coats, applied by pan coating are built upon several initial foundations or subcoats, containing water, sugar, acacia or gelatin, separated by dusting powders of calcium sulphate, calcium carbonate, talc or kaolin. The sugar ('grossing') coats themselves may contain pigments, lakes or colours and opacifiers.

At the other extreme, the applied coat is so thin (10-100 μm) that it is best described as a film or membrane, consisting of a film-forming, high molecular weight polymer such as hydroxypropyl methylcellulose[2,3]. This is dispersed in a suitable solvent blend together with a plastisizer and colours, and opacifiers if required, and sprayed onto the tablet core. The solvent system is chosen to provide a controlled deposition of solids onto the core surface.

To ensure an effective and coherent film, each of the ingredients should be dispersed uniformly throughout the polymer matrix. Of the insoluble pigments used, titanium dioxide (TiO_2) has proven to be the opacifier of choice because of its superior whiteness and excellent stability. There is evidence that small changes in TiO_2 concentration can result in variations in the mechanical properties of the coat[4], its resistance to moisture permeation[5] and adhesion to the underlying core[6]; all of which may affect its performance during storage and use.

Tablet coats of all kinds must therefore perform in a predictable and satisfactory way and there is a need for close con-

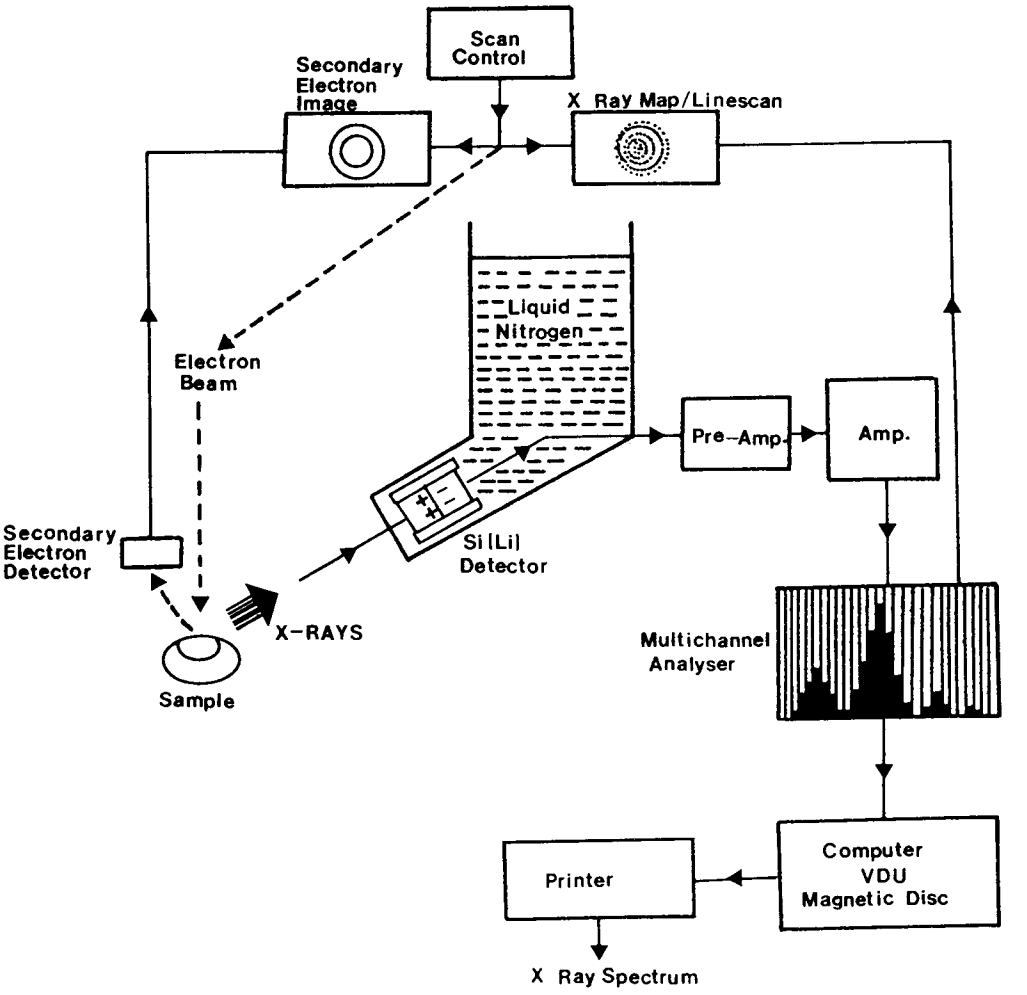


FIGURE 1

Schematic representation of the SEM/EPMA system.

trol to ensure correct chemical composition, homogeneity, integrity and thickness in the final product.

We have evaluated the combined techniques of scanning electron microscopy and electron probe microanalysis (EPMA) in achieving the above objectives.

METHODS

1. Electron Probe Microanalysis

The EPMA technique is described in detail elsewhere[7,8] and only a brief description is given here. The method relies on the fact that when high-energy primary electrons of the scanning electron microscope (SEM) beam collide with atoms in the surface layers of a solid specimen, X-rays are generated which are characteristic of the atomic number of the elements in the specimen. Consequently, if the X-rays can be detected, identified and quantified by means of a suitable apparatus, so can the elements in the sample.

The SEM can be used to obtain a conventional micrograph based on the secondary electron image of a relatively large area ($\doteq$ 10 mm^2) of the specimen, and then the beam can be directed at a very small area (< .25 μm^2) to obtain a rapid, non-destructive analysis in-situ. In addition, it is possible to select for X-rays of a particular element of interest and produce an X-ray map showing the distribution of that element which can be compared with a conventional electron micrograph of precisely the same area.

A JEOL JSM 35C SEM was used, with an attached energy dispersive, solid state detector (EDS) coupled to a multi-channel analyser and microprocessor for data handling and storage (Link 860, 500 MK2 system, Link Systems, England). The general layout is shown in Figure 1.

In this study, the EPMA system was used in three different ways: 1, point spectral analysis and 2, X-ray mapping for a single element as described above; 3, line scanning, where an analysis for a single element based on X-ray counts was made as the electron beam traversed the specimen in a cross-sectional line.

2. Specimens

Two tablets were chosen for investigation on the basis of their contrasting formulations: Tablet A, a film coated propranolol hydrochloride B.P. tablet (Imperial Chemical Industries, England) and Tablet B, a sugar coated, ferrous gluconate B.P. tablet (Antigen, Ireland). All tablets tested were taken from single, quality-controlled production batches, less than 6 months old. The original containers had not previously been opened.

3. Specimen Treatment

3a. Controls

Sample tablets were selected from the batch with no further treatment, unless oven-drying was included in the treatment procedure. In such cases, a control tablet was placed in the oven together with the treated specimens. (See 3d. below)

3b. Section

Elaborate cutting techniques were avoided. Tablets were bisected radially by applying gentle pressure to a #10 stainless steel scalpel blade.

3c. Abrasion

Two abrasion procedures were used. Twenty tablets were placed in an Erweka friabillator (Erweka, West Germany) at 25°C and the tablets gently and continuously, tumbled for 24 hours. Any accumulated dust was then removed by passing dry, filtered air over the tablet surface. In a second experiment, the tablet was lightly abraided with size P600 silicon carbide abrasive paper (3M Company, U.S.A.) so that the underlying tablet core was just visible to the naked eye. Dust was then removed with a jet of air as before.

3d. Dissolution

Individual tablets were placed in a basket of a B.P. disin-

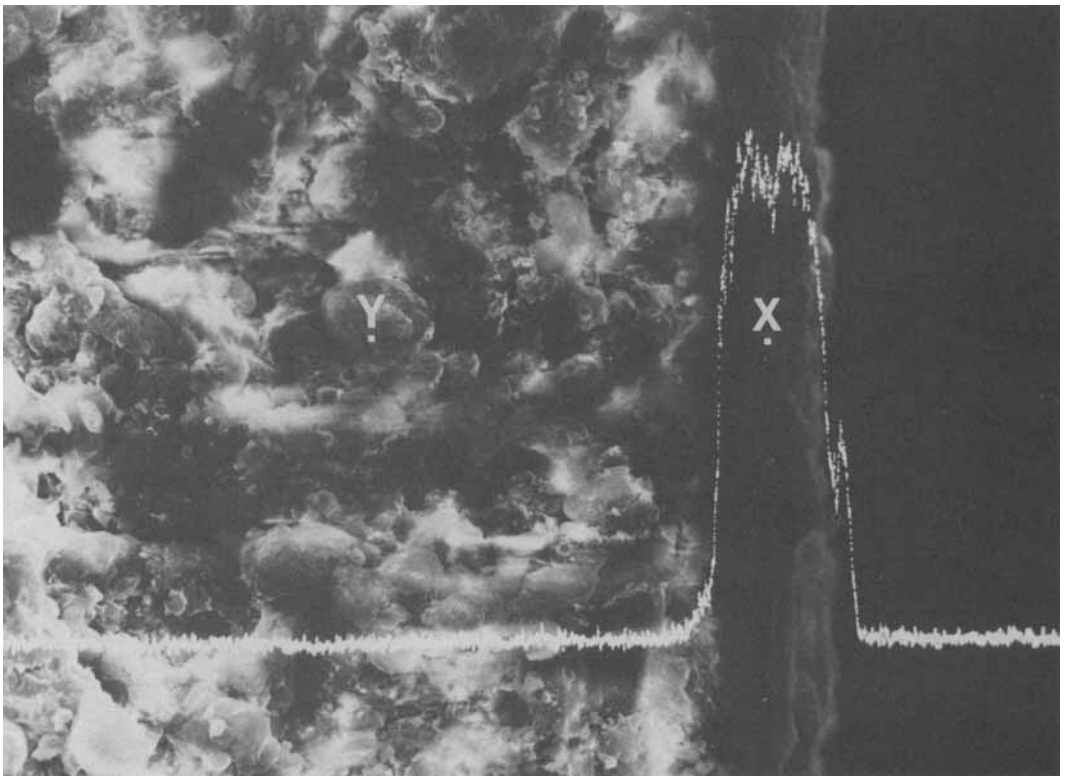


FIGURE 2A

Micrograph of film coated tablet section with overlayed X-ray linescan for Ti, Kα. BAR = 100 μm.

tegration apparatus (Manesty, England) which contained triple-distilled, deionised water, at 25°C, adjusted to a pH of 4 with hydrochloric acid (Analar, BDH Chemicals, England) to provide a gentle, etching medium. After the tablets had undergone a specified number of immersion cycles in the dissolving fluid, they were gently removed with forceps, dipped once into distilled water and dried at 25°C in a dessicator over a 50:50 mixture of silica gel and phosphorus pentoxide for 48 hours.

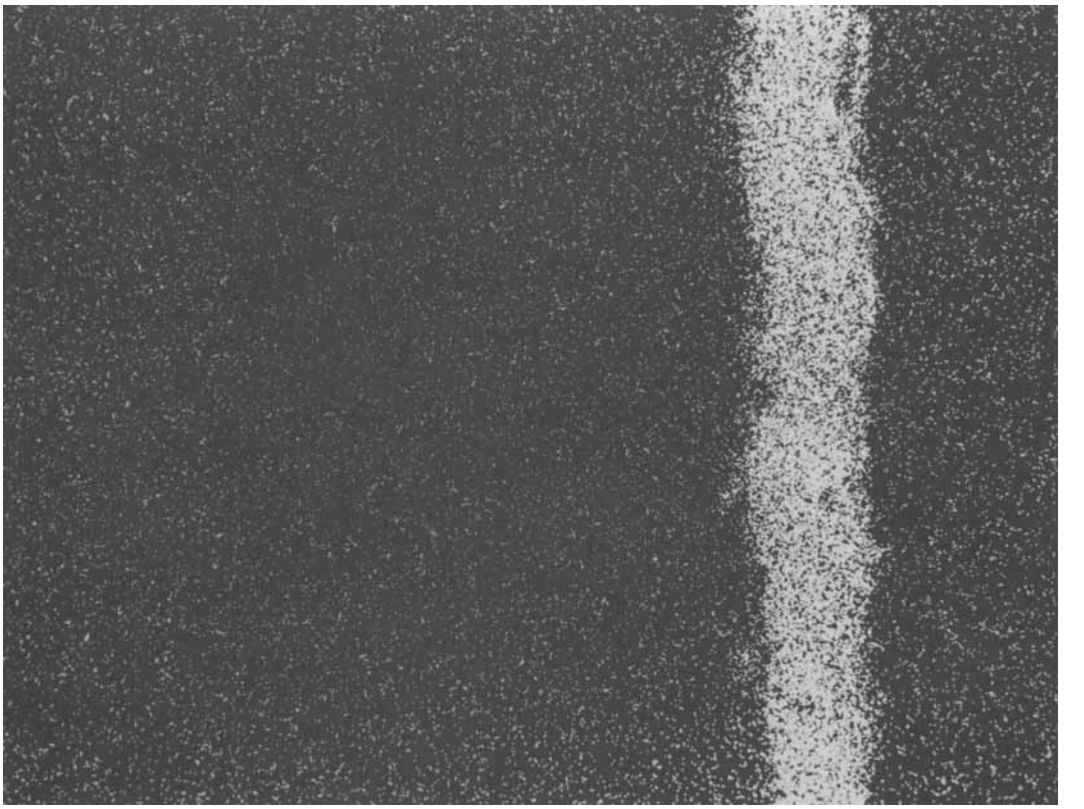


FIGURE 2B

X-ray map of Ti, Kα for same area as in 2A. BAR = 100 μm.

4. Specimen Preparation

With the exception of tablet sections, it was possible to attach the whole tablet to a conventional aluminium SEM specimen stub, pre-coated with carbon paint. Samples were coated with a 300 Å ngstrom thickness of carbon in an Edwards 360 coater (Edwards, England) and then stored in a vacuum of 10^{-1} Torr at 25°C for 48 hours before examination.

RESULTS AND DISCUSSION

Due to the construction of the EDS, X-rays of long wave-

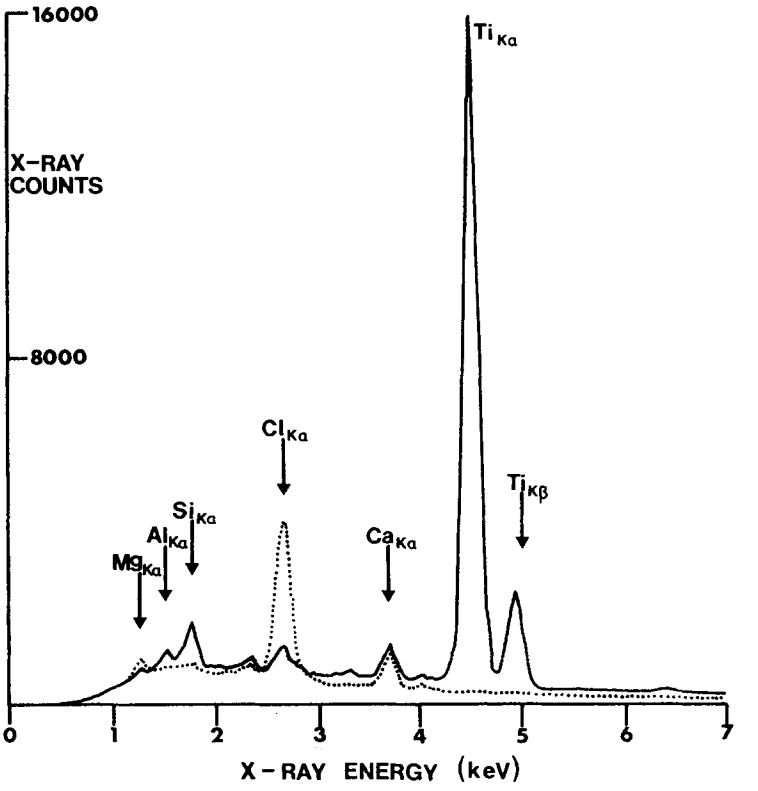


FIGURE 3

Point X-ray spectral analyses taken at locations X (————————) and Y (·····) in 2A.

length are not detected and it is impractical to use X-rays of less than keV for analysis; this rules out elements lighter than sodium, including the carbon in the applied coat. Quantitative analysis is further hampered by the presence of a continuous spectrum of radiation caused by deceleration of beam electrons in the fields of specimen nuclei. It is this 'white radiation' which forms the background, particularly at the lower end of the energy spectrum, on which the major spectral lines are superimposed.

With the above limitations in mind, the EPMA/SEM combination revealed semi-quantitative differences between the tablet cores and their applied coats. Conditions for all analyses (ie. beam current, specimen to detector distance, specimen tilt and count time) were kept constant.

1. Film Coated Tablets

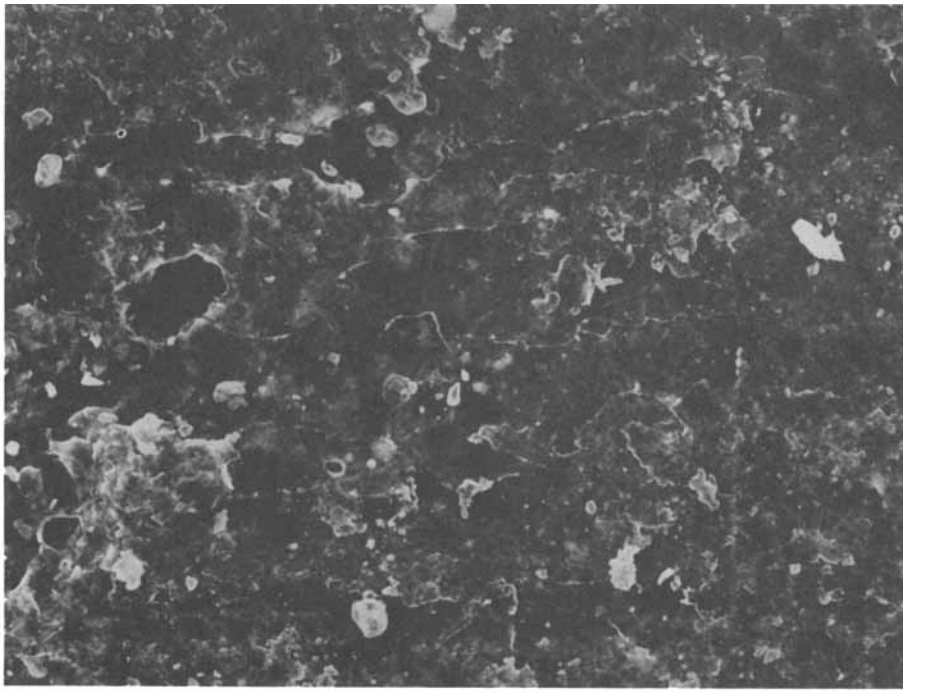
1a. Section

Figure 2A shows a micrograph of an area of tablet core and coat after fracturing. Transposed on the micrograph is an X-ray linescan, specific for the Kα X-ray energy for Ti. An X-ray map for the same area, specific for Ti appears in Figure 2B. Point spectral analyses, taken at locations X and Y in Figure 2A are shown in Figure 3. The major elemental Kα and Kβ peaks are marked. Figures 2 and 3 demonstrate the ability of the system to visualize sharp changes in composition (eg. Ti) when passing from core (high in Mg, Cl and Ca) to coat (high in Al, Si and Ti). A coat thickness of approximately 55 μm was observed on the X-ray linescan, which corresponds closely with the coat image in the underlying micrograph. The X-ray map clearly shows the coating as an area of high Ti concentration relative to the background.

1b. Dissolution

Micrographs were taken from a small area (0.3 mm^2) located at the apex of the convex tablet face. Figure 4A shows a control micrograph of an untreated tablet and a corresponding X-ray map for Ti appears in Figure 5A. Figures 4B/5B, 4C/5C and 4D/5D show matching micrographs and X-ray maps for tablets at various stages in the dissolution process. Figures 6A-D are the X-ray spectra corresponding to the areas shown in the micrographs above. Note that the X-ray count scale has been progressively expanded to visualise the spectra at long dissolution times.

A



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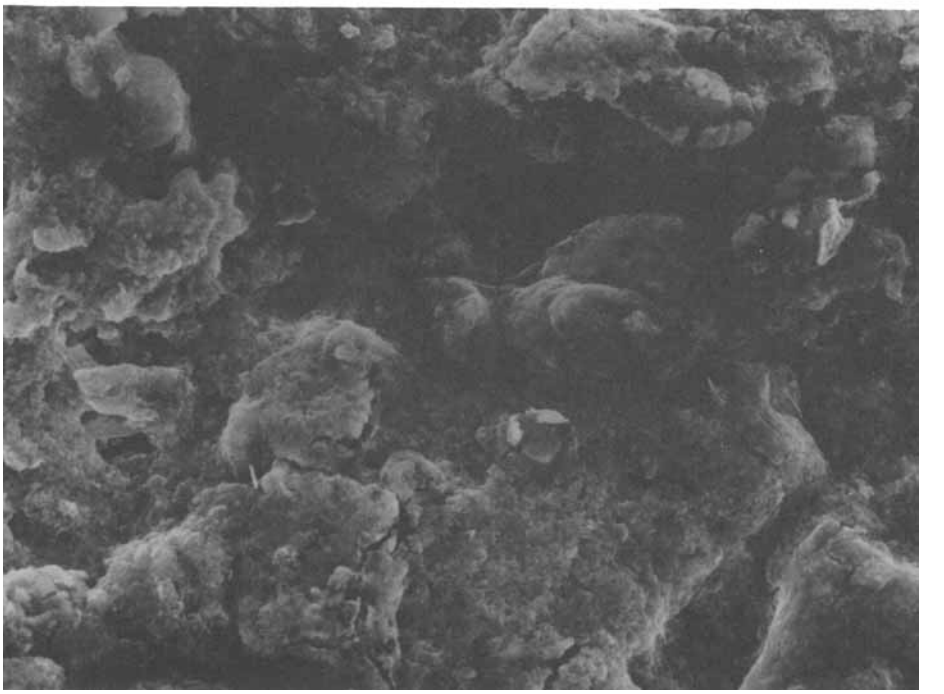
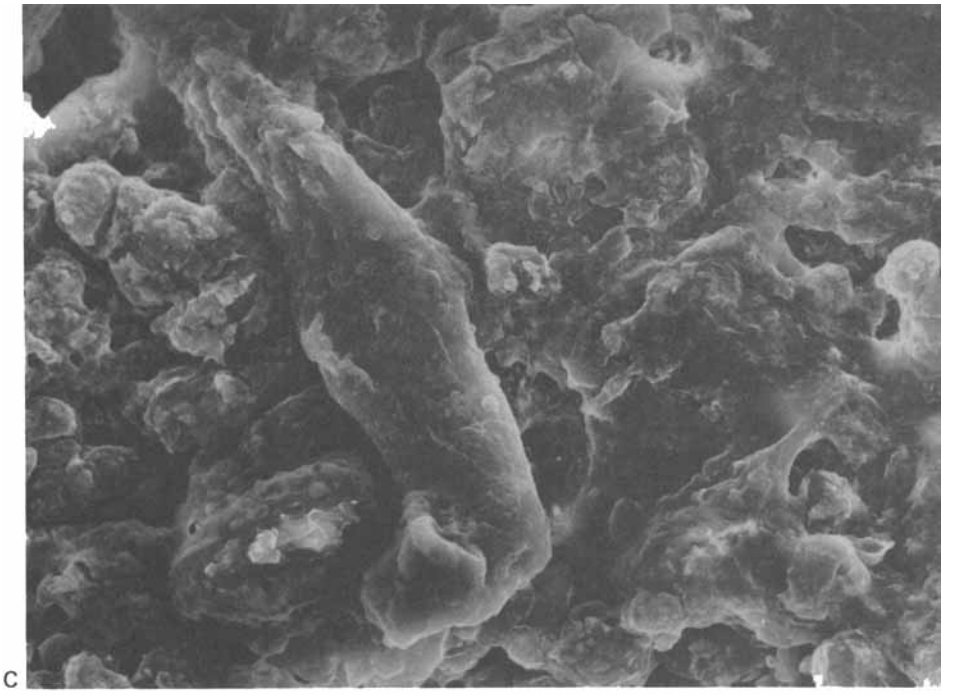
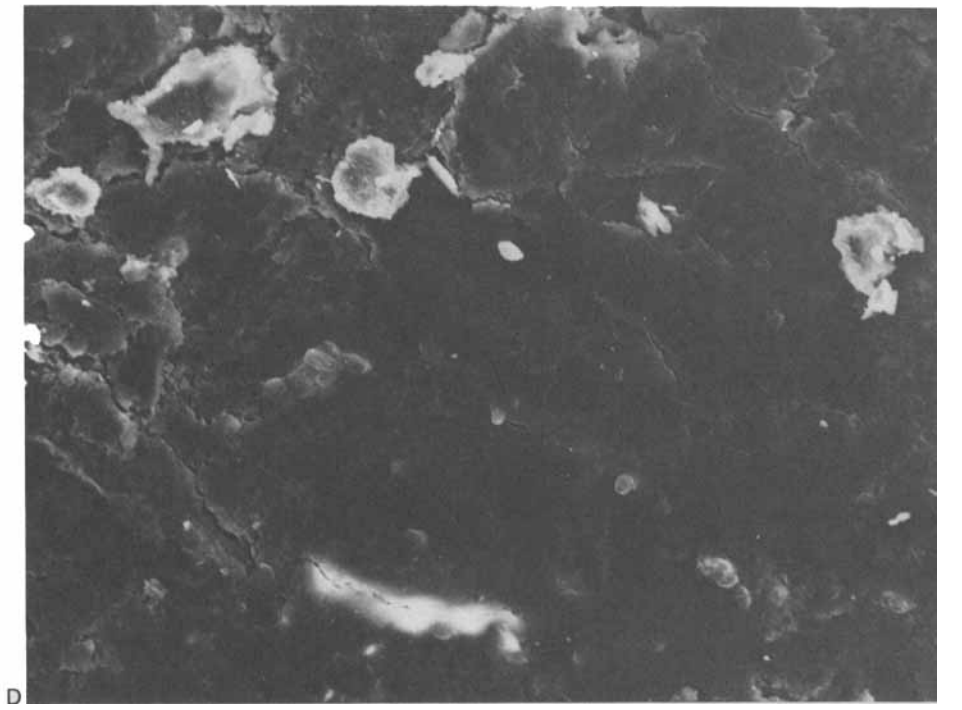


FIGURES 4A-D

Micrographs of film coated tablet surface:
4A, 0 cycles; 4B, 7 cycles; 4C, 15 cycles; 4D, 30 cycles
in a B.P. dissolution apparatus. BAR = 10 μm.

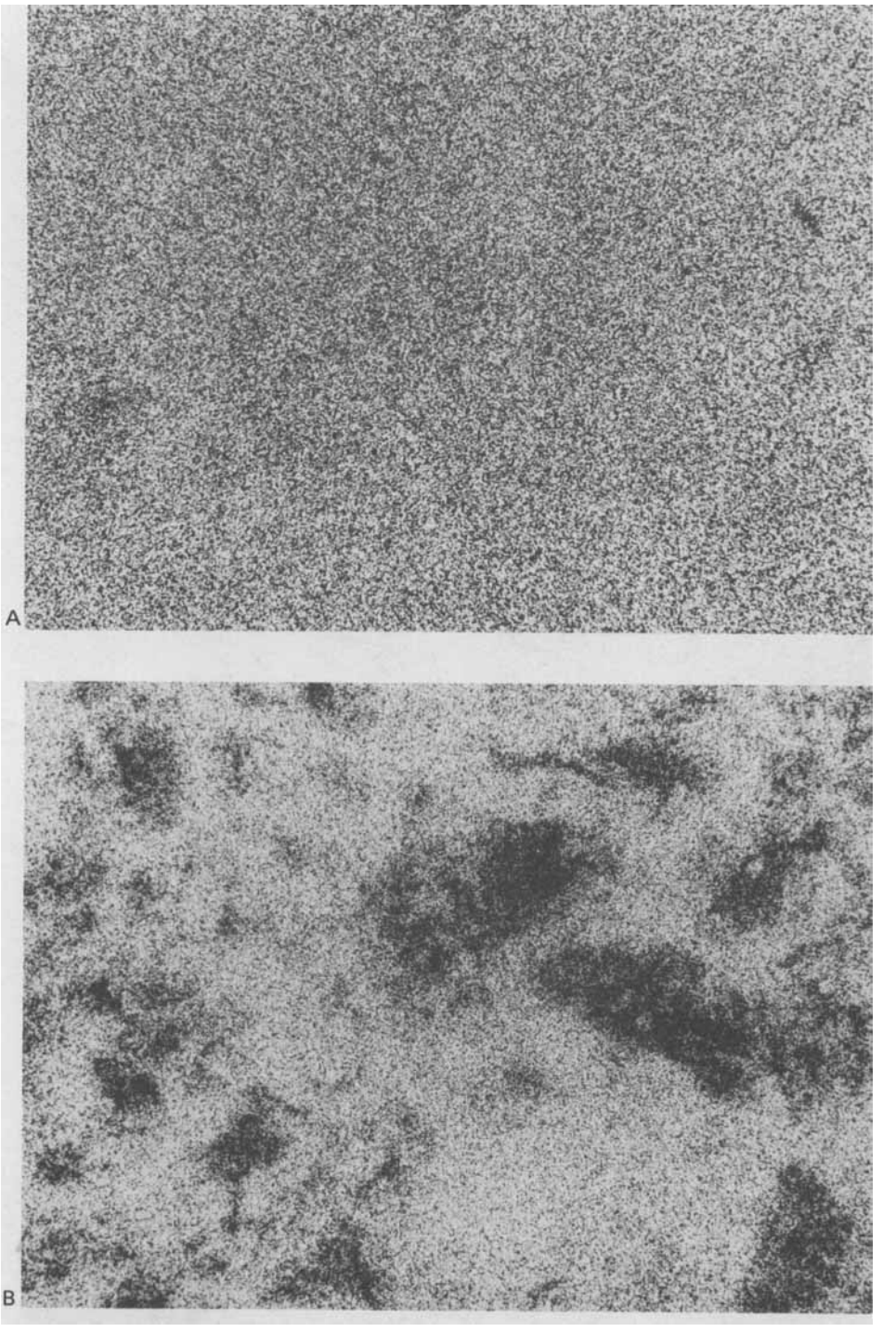


C



D

Figure 4 Continued



FIGURES 5A-D

Corresponding X-ray maps for Ti Kα for the areas shown in Figures 4A-D. Showing progressive disappearance of Ti. BAR = 10 μm.

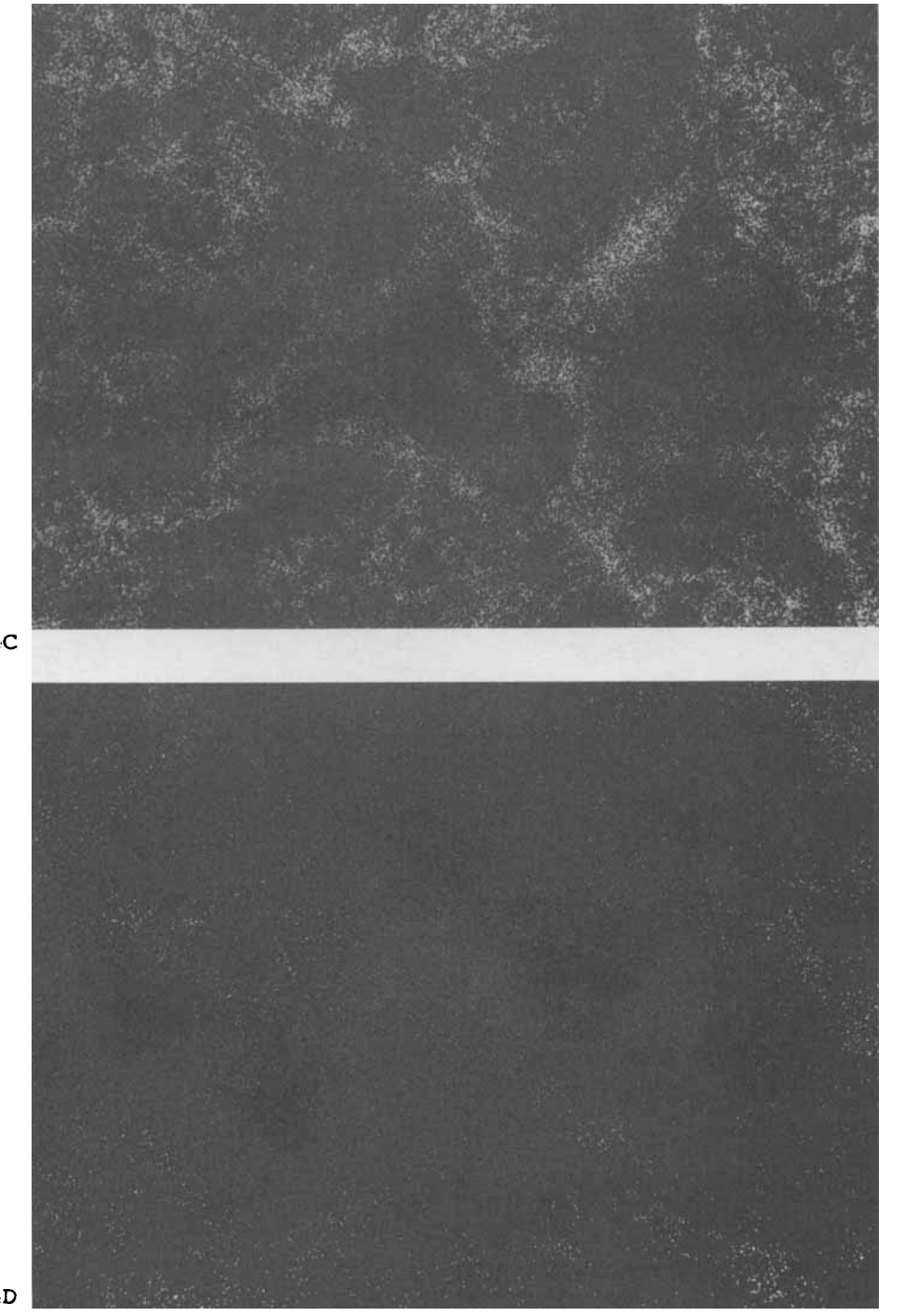
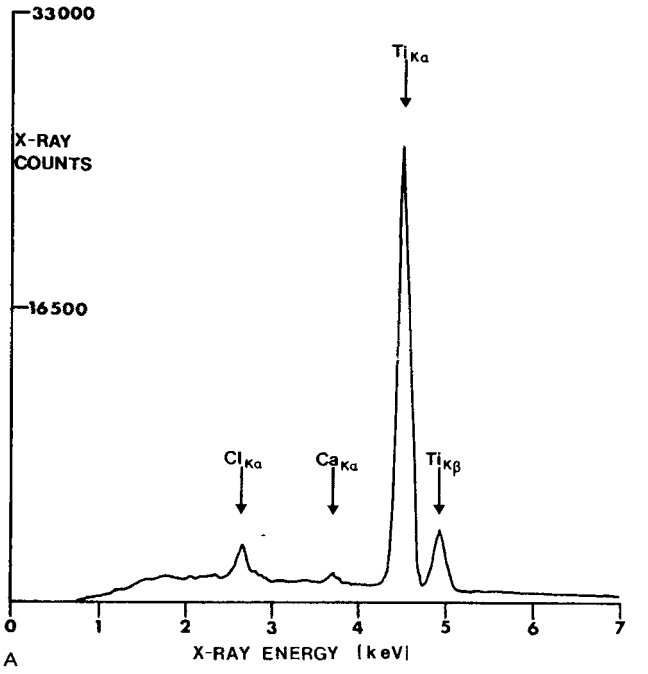
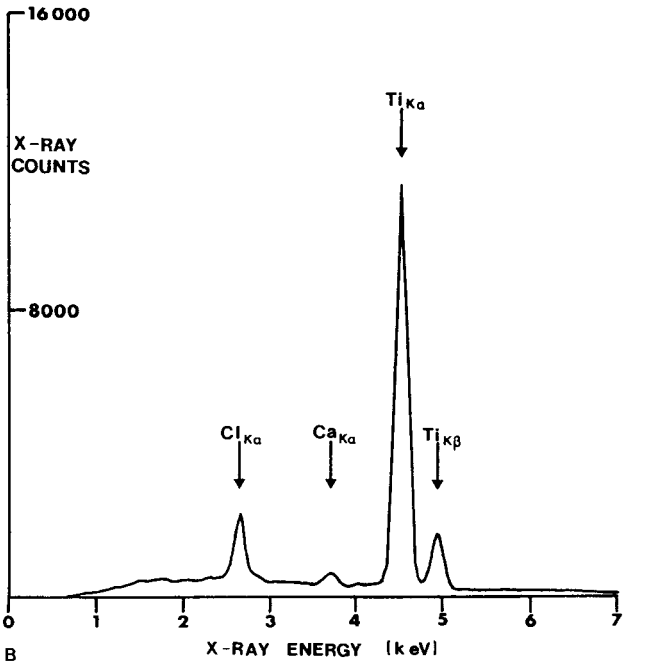


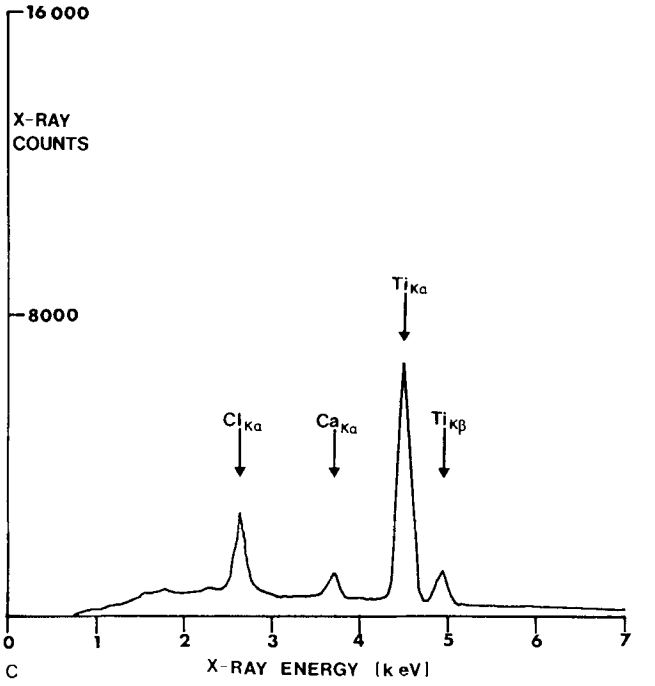
Figure 5 Continued





FIGURES 6A-D

X-ray spectra for the areas shown in Figures 4A-D. Showing progressive disappearance of Ti.



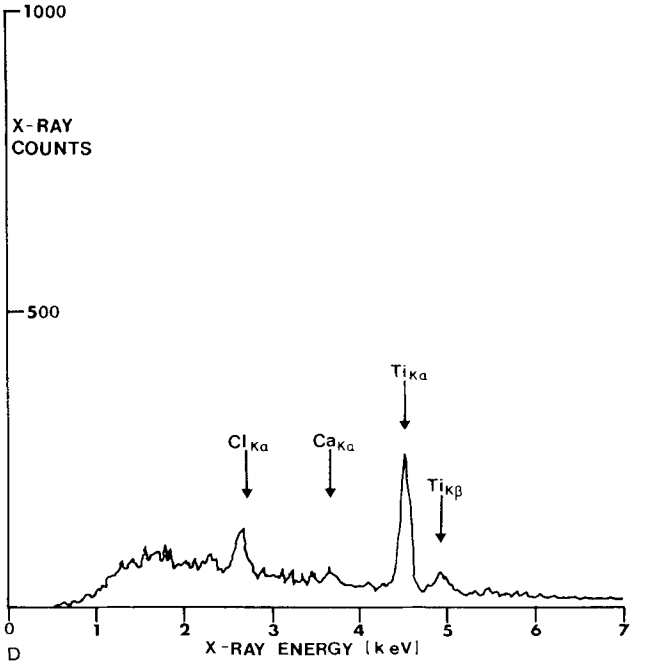


Figure 6 Continued

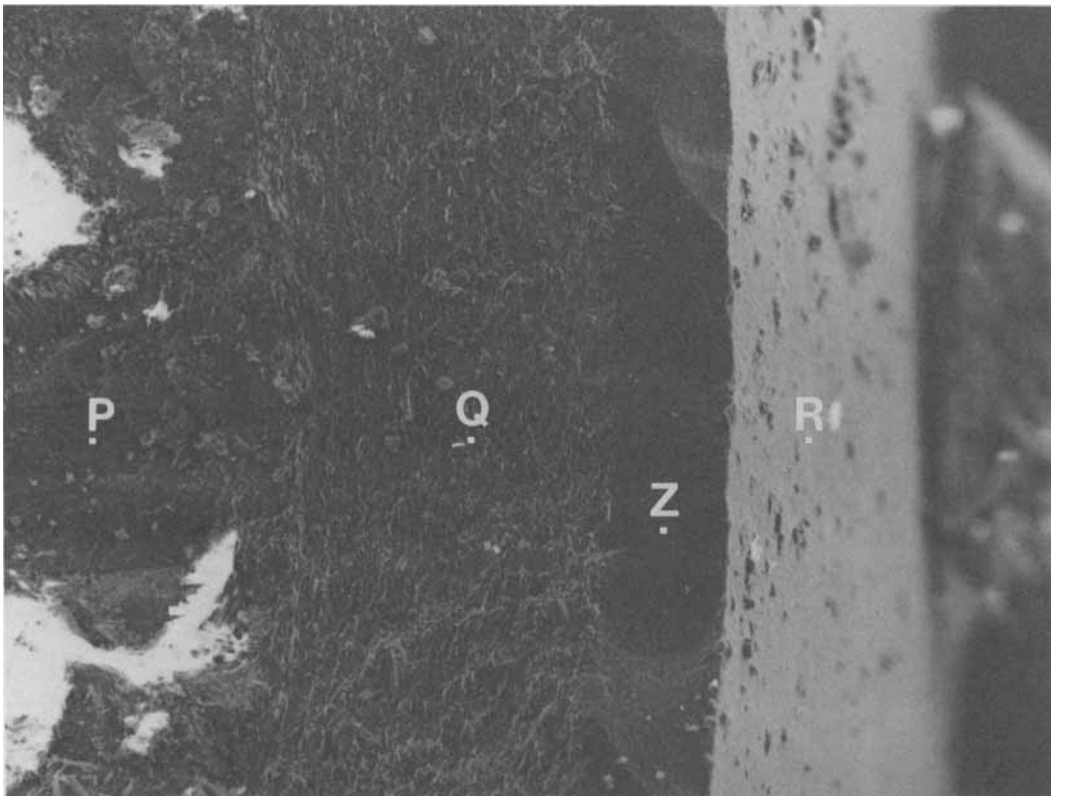


FIGURE 7A

Micrograph of sectioned sugar coated tablet. BAR = 100 μm.

As dissolution of the coat proceeds, so the X-ray spectrum changes, reflecting an increasing contribution from the underlying tablet core. Figures 6A-D show a decreasing Ti peak accompanied by increasing peaks for Ca and Cl.

No change was observed in the X-ray maps and spectra, or the micrograph, for film coated tablets treated with friabillation, indicating that the coat was highly resistant to these conditions.

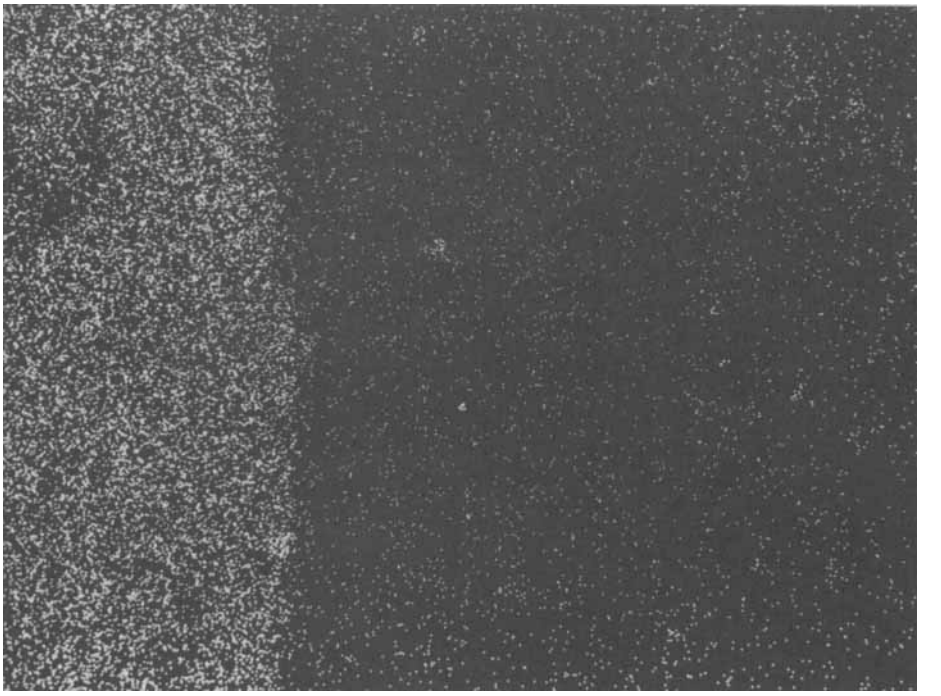


FIGURE 7B

X-ray map for Fe, Kα of area of sugar coated tablet shown in Figure 7A. BAR = 100 μm.

2. Sugar Coated Tablets

2a. Section

Figure 7A shows a micrograph of a sectioned ferrous gluconate tablet, which indicates an outer coat thickness of some 200 μm. Figure 7B shows an X-ray map for Fe and 7C, for Si. Together, these two maps identify a layer (Q) with a high Si content lying between the core (P) and sugar coat (R), which also appears on the micrograph. This is confirmed by the point X-ray spectra for each layer. The tablet core itself, with Fe

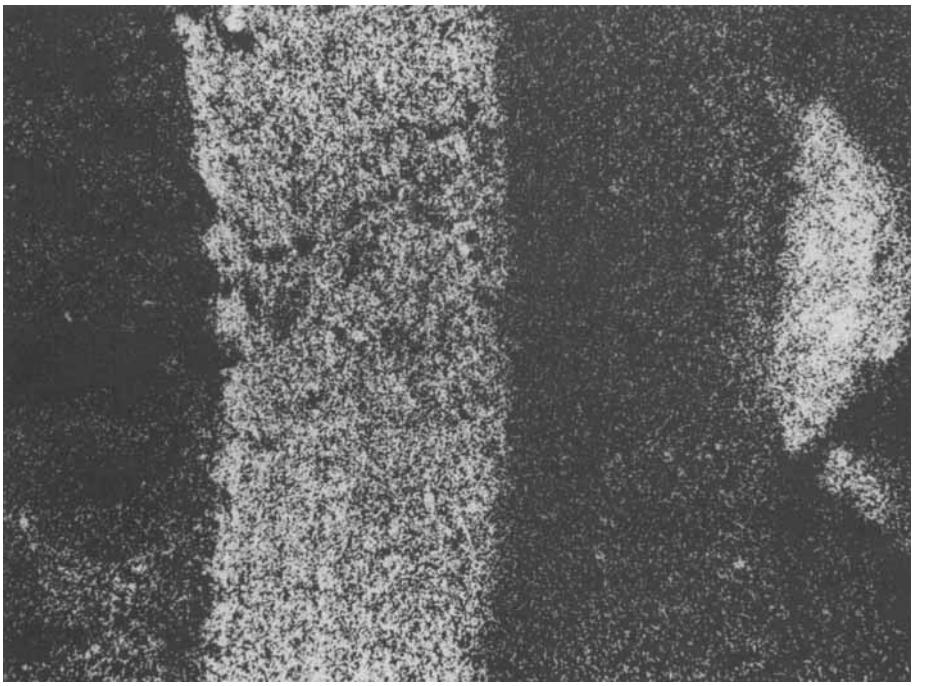


FIGURE 7C

X-ray map for Si, Kα/β of area of sugar coated tablet shown in Figure 7B. BAR = 100 μm.

Kα and Kβ peaks predominating (Figure 8P), underlies the intermediate or sub-coat, low in Fe but high in Al and Si (8Q), and finally the outer coat, devoid of iron but having a different composition from the sub-coat (8R). An air pocket Z (see Fig. 7A) separates the sub- and outer coats at this point on the tablet surface. A small fragment, having a similar Si content to layer Q is shown to the right of the sugar coat.

2b. Abrasion

Gentle abrasion of the sugar coat revealed similar substrata to those found in 7A. Figure 9A shows a micrograph,

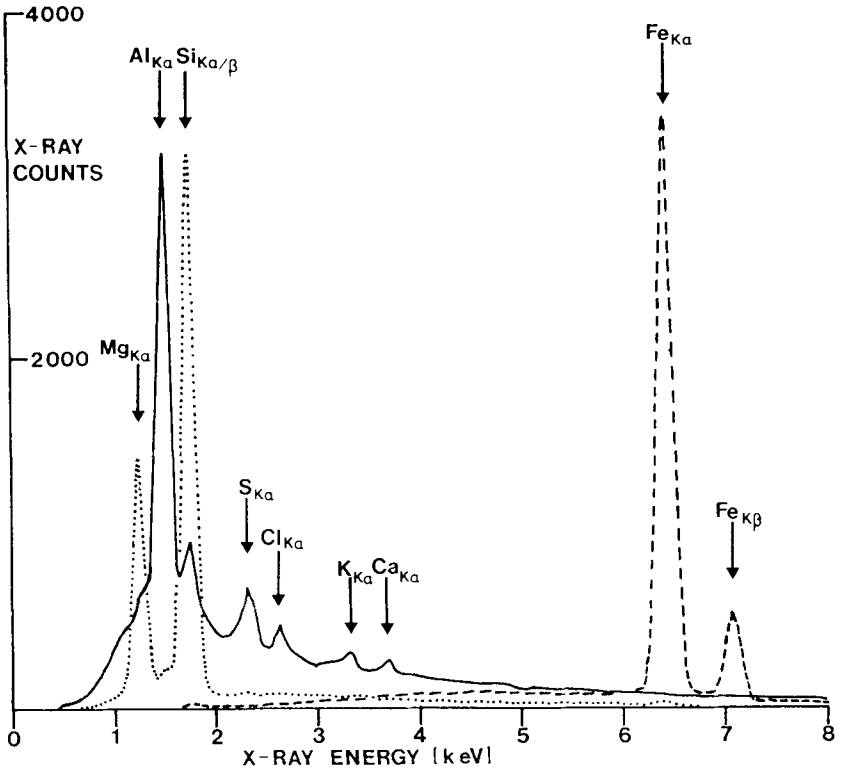


FIGURE 8

Section of a sugar coated tablet. X-ray spectra for points P (– – – – – – –), Q (————————) and R (·····), as shown in Figure 7A.

taken close to the edge of an abraided area. Figures 9B and 9C are the corresponding X-ray maps for Fe and Si respectively. X-ray spot analyses for each zone were almost identical to those in Figures 8P, Q and R. It is not possible to estimate the coat thickness because, in contrast to the fractured samples, the specimen is being viewed obliquely. Friabillation produced no significant changes in micrograph, X-ray map or spot analyses when compared with the control.

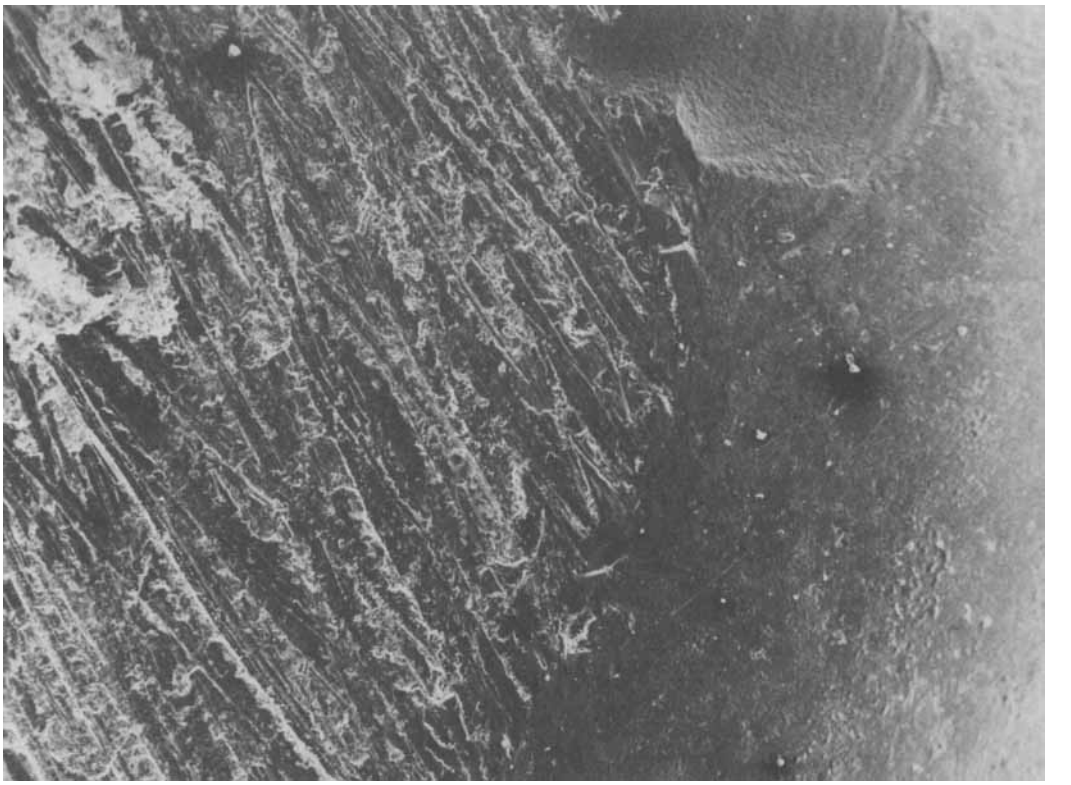


FIGURE 9A

Micrograph of abraided sugar coated tablet. BAR = 1000 μm.

2c. Dissolution

When examined with the SEM, tablets removed at successive stages of the dissolution process showed progressive coat erosion and consequent surface rugosity. X-ray spectra were obtained under standard conditions from relatively large (800 μm^2) areas from fields which were judged to be representative of the general surface appearance. Figures 10A-D clearly show the emergence of the detectable iron core as outer coats are dissolved away.

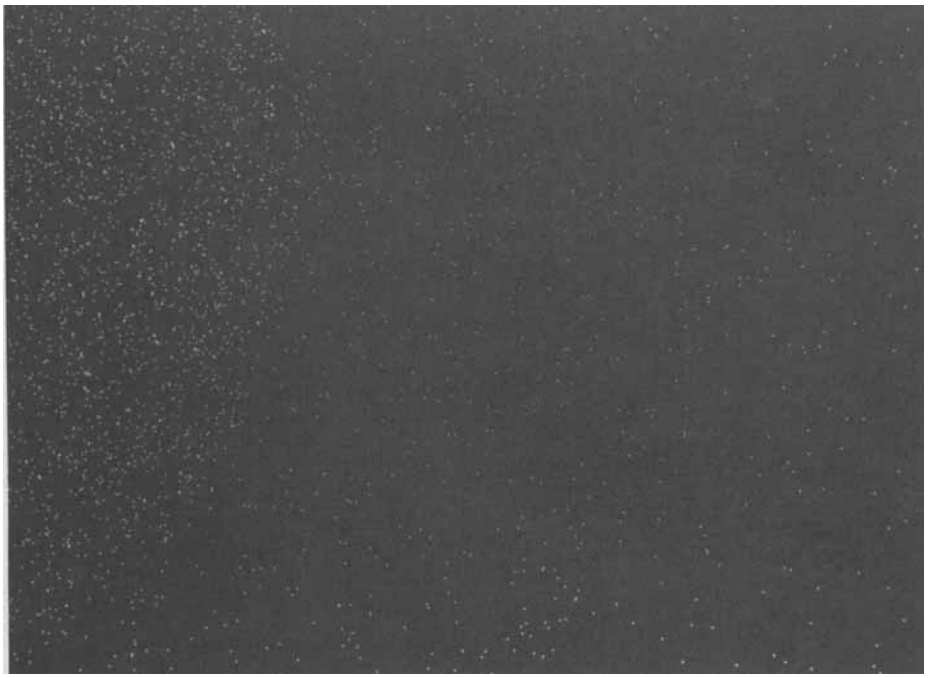


FIGURE 9B

X-ray map for Fe, Kα of area of sugar coated tablet shown in Figure 9A. BAR = 1000 μm.

CONCLUSION

This study has assessed the usefulness of EPMA in conjunction with SEM in the investigation of tablet film coats. It has been clearly demonstrated that changes in coating thickness in response to various agents (dissolution media and abrasion) can be monitored by a combination of both techniques, by 'sensitizing' the EDS to an element of relatively high concentration either in the coat itself (eg. Ti) or in the tablet core (eg. Fe).

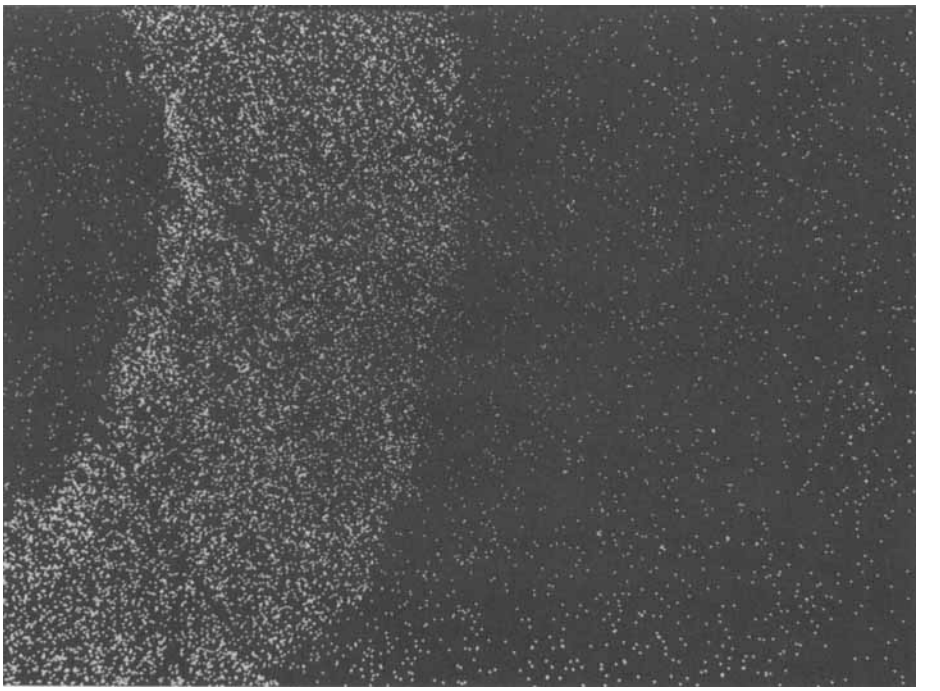


FIGURE 9C

X-ray map for Si, Kα/β of area of sugar coated tablet shown in Figure 9A. BAR = 1000 μm.

We have shown that the EPMA system is of value in assessing coat uniformity, integrity and thickness and suggest that it may be of use in coated tablet manufacture, stability testing, and quality control. The technique appears to be particularly useful in chemically identifying discrete sub-coat layers which may appear as mere shadows on a conventional electron micrograph.

EPMA may provide a rapid means of tablet identification, provided details of coating formulations are available, and the problems involved in truly quantitative analysis, such as surface rugosity and curvature, are overcome. These objectives are the topics of a second paper.

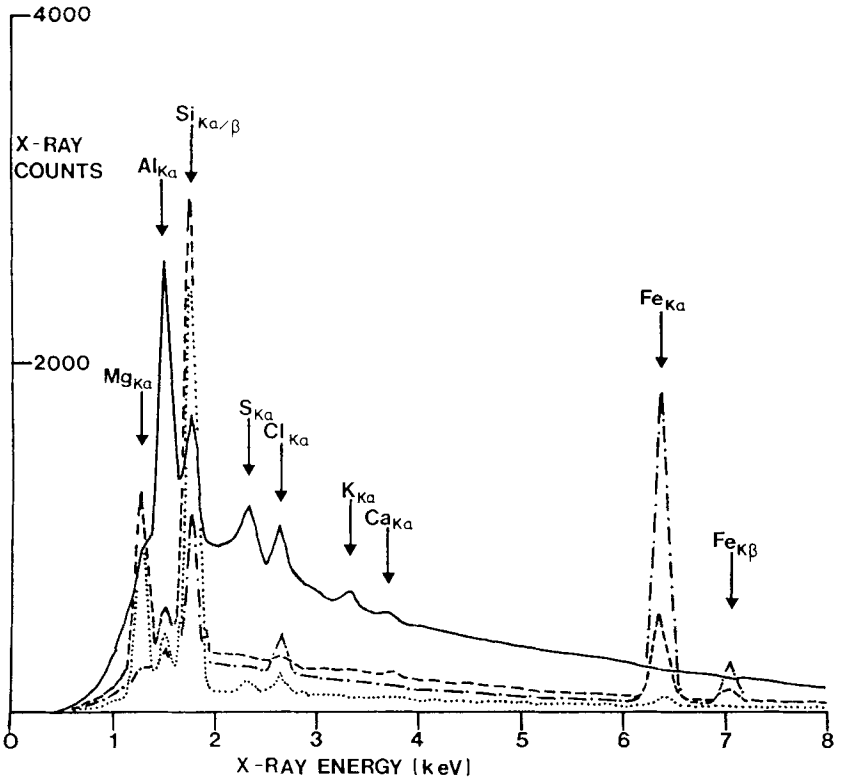


FIGURE 10

X-ray spectra for sugar coated tablet surfaces after progressive dissolution in a B.P. disintegration apparatus.
10A, 0 cycles (————————); 10B, 300 cycles (.....); 10C, 450 cycles (– – – – – – – –); 10D, 900 cycles (—·—·—·—).

ACKNOWLEDGEMENTS

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