International Journal of Pharmaceutics, 62 (1990) 97–103
Elsevier

IJP 02079

Research Papers

The in-situ chemical analysis of polymer film coatings using static secondary ion mass spectrometry (SSIMS)

M.C. Davies [1], I.R. Wilding [1], R.D. Short [1], C.D. Melia [1] and R.C. Rowe [2]

[1] *Department of Pharmaceutical Sciences, Nottingham University, Nottingham NG7 2RD (U.K.) and* [2] *ICI Pharmaceuticals, Alderley Park, Macclesfield SK10 2TG (U.K.)*

(Received 6 October 1989)
(Modified version received 21 December 1989)
(Accepted 27 December 1989)

Key words: Polymer film coating; Static secondary ion mass spectrometry; Cellulose ether; Cellulose ester; Poly(methacrylate) copolymer; Chemical analysis, in situ

Summary

The SSIMS (static secondary ion mass spectrometry) analysis of a range of cellulose ethers, esters and poly(methacrylate) copolymers used as film coating agents in the pharmaceutical industry is described. Certain ions generated in the positive and/or negative SSIMS spectra appear to be characteristic of the particular polymer investigated, reflecting both the monomeric composition of the backbone chain and in particular the side-group substituents that are present. As a result, it appears that SSIMS is capable of positively identifying different film coating polymers when cast as films.

Introduction

Film coating technology is well established as an integral part of solid dosage form manufacture. An understanding of the fundamental principles of film formation coupled with a knowledge of solid state interactions has solved specific coating problems and enabled guidelines for formulation and process development to be established (Rowe, 1984). Standard techniques for the bulk analysis of polymers are inappropriate for the provision of in-situ surface chemical information.

Over the last decade, a number of sophisticated surface analysis techniques have emerged, including static secondary ion mass spectroscopy (SSIMS), which allow the in-situ solid-state chemical analysis of materials. In the SSIMS process, the polymer surface is bombarded with primary ions causing the spluttering of secondary ions from the uppermost 1 nm of the surface. These ions may be elemental or molecular and are detected using a mass spectrometer. SSIMS analyses have successfully been shown to provide detailed information from the positive and negative ion mass spectra of a range of the standard and biomedical polymer surfaces which have been interpreted using conventional mass spectrometry rules (Briggs, 1986; Hearn et al., 1987, 1989; Davies et al., 1989a, b).

In this paper, we illustrate the potential of SSIMS for the chemical identification and analysis of both cellulose derivatives and methacrylate ester copolymers commonly employed in film coating technology.

Correspondence: M.C. Davies, Department of Pharmaceutical Sciences, Nottingham University, Nottingham NG7 2RD, U.K.

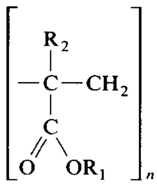
Materials and Methods

All materials were used as received without further extraction or purification. Eudragit E and RS, and methacrylate copolymers, were supplied by Rohm-Pharma (Darmstadt, F.R.G.) and are listed in Table 1.

The cellulose ethers were supplied as follows: ethylcellulose (EC) (Ethocel E grade) and hydroxypropylmethylcellulose (HPMC) (Methocel E50 grade), Colorcon Ltd (Orpington, U.K.); hydroxypropylcellulose (HPC) (Klucel E5), Hercules B.V. (Rijswijk, The Netherlands); HPMC acetate succinate (HPMCAS) and hydroxypropylmethylcellulose phthalate (HP-55F), Shin-Etsu Ltd (Tokyo, Japan); and methylcellulose (MC) (Methocel A50), Dow Chemical Co. (MI, U.S.A.).

TABLE 1

Structure of methacrylate copolymers (Eudragit E and RS)



Eudragit™	Type and relative residue frequency of side group R_1				
	CH_3	C_2H_5	C_4H_9	$CH_2CH_2N(CH_3)_2$	$CH_2CH_2N^+(CH_3)_3$
E	1	-	1	2	-
RS	2	1 *	-	-	0.1

$R_2 = CH_3$ except for * when R_2=H.

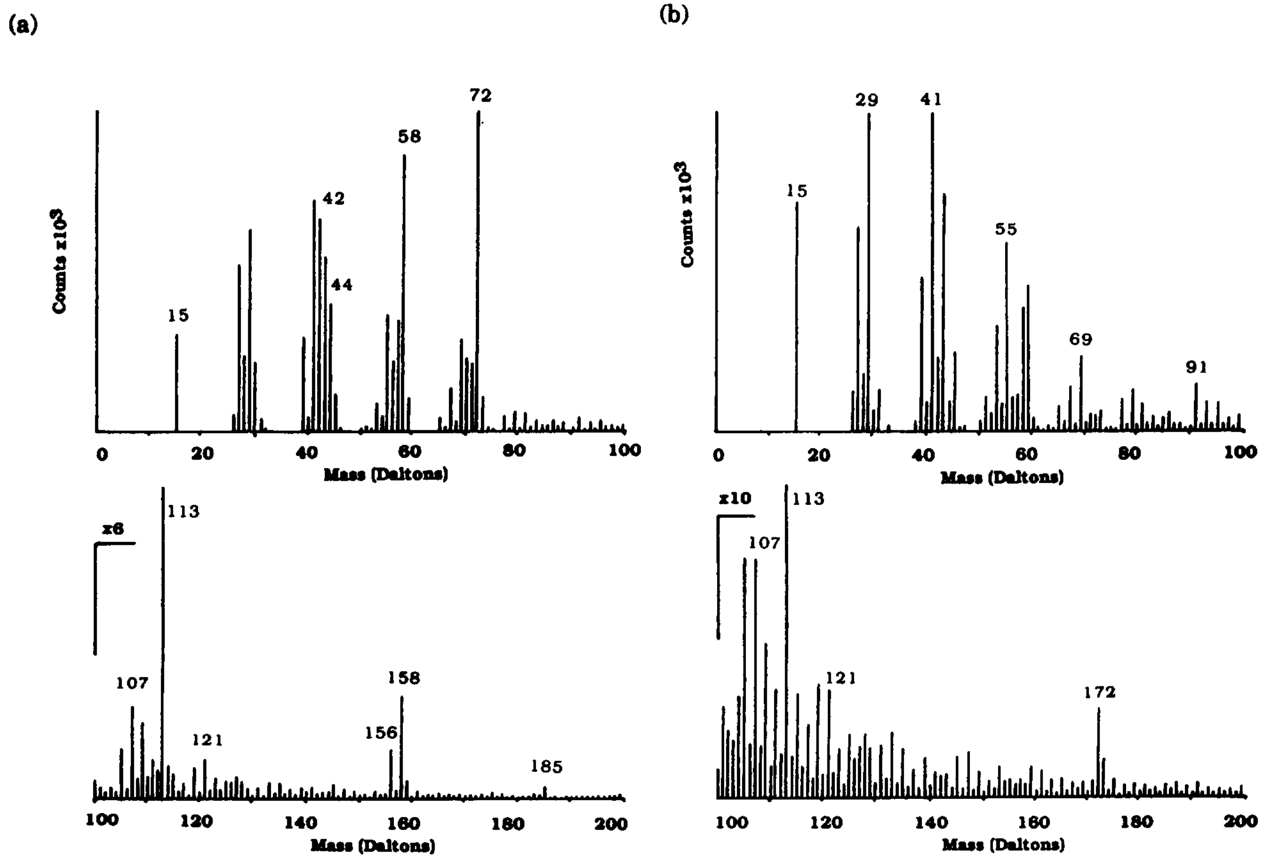


Fig. 1. Positive-ion SSIMS spectra for (a) Eudragit E and (b) RS.

The polymers were studied as thin films, approx. 5–10 μm in thickness, spin cast once from a 1% solution in double-distilled methanol onto a clean aluminium substrate. Samples were analysed within 1 h of casting.

The SSIMS spectra were obtained with a modified Vacuum Generators SIMSLAB which has been described elsewhere (Brown and Vickerman, 1984) using 2 keV argon atoms in a manner outlined in detail previously (Brown and Vickerman, 1986). The total dose for the acquisition of the individual SSIMS spectra fell within the accepted limits for SSIMS analysis of 'undamaged' polymer surfaces (Briggs and Hearn, 1986).

Results and Discussion

For clarity, the methacrylate copolymers (Eudragit E and RS) and the cellulose ether SSIMS spectra will be discussed separately.

Methacrylate copolymers

The positive and negative SSIMS spectra of Eudragit E and RS are shown in Figs 1 and 2, respectively. Previous studies (Wilding et al., 1990) have shown that the fragmentation patterns observed for these copolymers may be interpreted in terms of a general fragmentation model proposed by Hearn and Briggs (1988) for the SSIMS analysis of poly(alkylmethacrylate) homopolymers. Diagnostic ions for each monomer unit of the copolymer are assigned where possible after reference to the SSIMS spectra for the corresponding homopolymer.

In the case of Eudragit E (a copolymer of methyl [25%]-, butyl [25%]-, and dimethylaminoethyl [50%]-methacrylate), the positive ion spectrum in Fig. 1a shows a number of prominent even-mass ions, which are distinctive of the dimethylaminoethyl-methacrylate monomer unit. In particular, ions diagnostic of the side-chain are

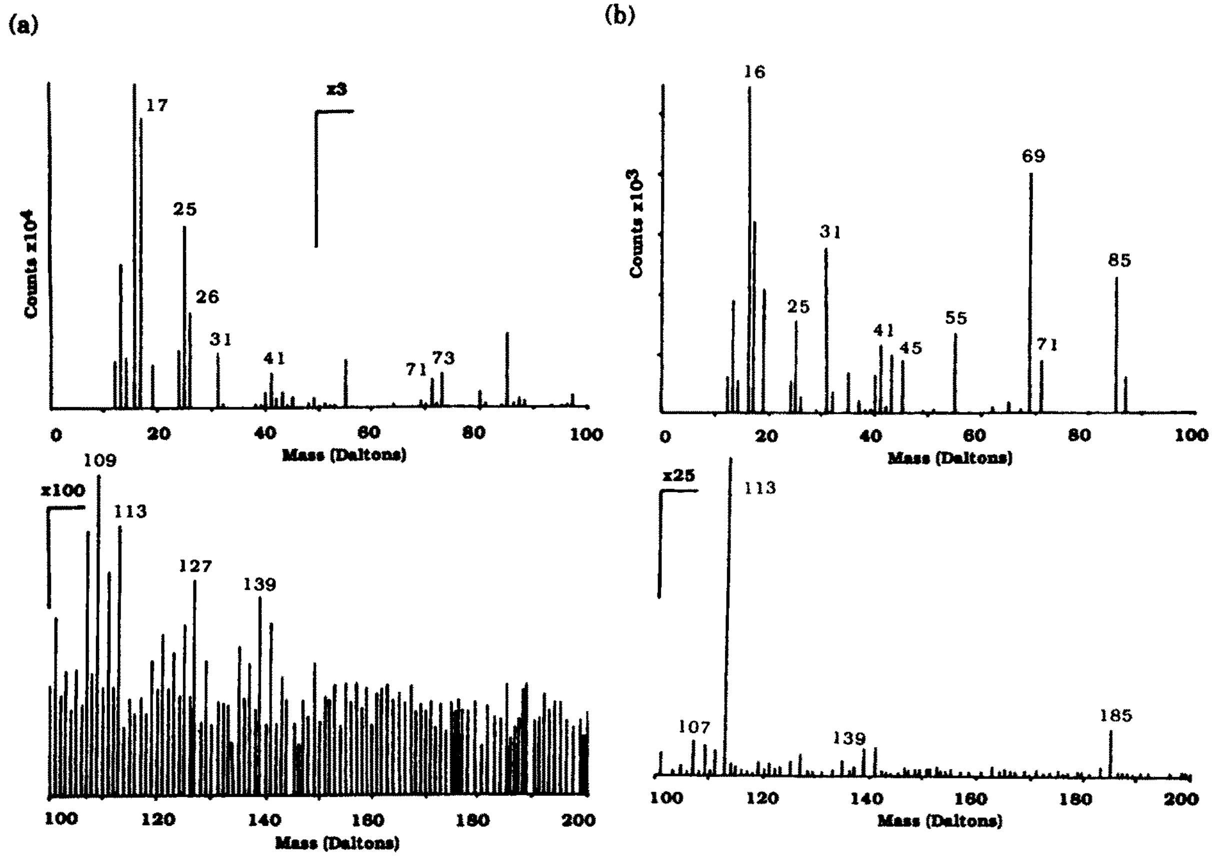


Fig. 2. Negative-ion SSIMS spectra of (a) Eudragit E and (b) RS.

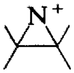
observed at 72, 58, 44 and 42 *m/z* formed by chain cleavage of the ester linkage and its subsequent fragmentation:

$^{+}CH_2CH_2N(CH_3)_2$ $\quad$ $^{+}CH_2N(CH_3)_2$

72 *m/z* $\quad$ **58 *m/z***

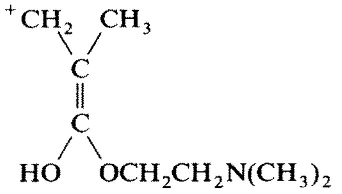
$^{+}N(CH_3)_2$

44 *m/z*

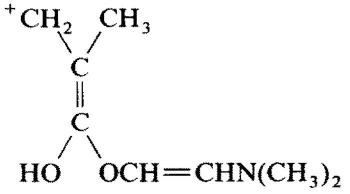


42 *m/z*

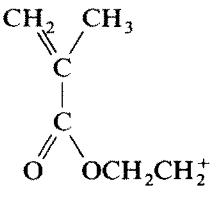
The 69 *m/z* ion is typical of all methacrylate copolymers corresponding to $CH_3C(=CH_2)C^{+}=O$. At higher mass, a number of even-numbered cations are detected at 158/156 *m/z* which are assigned to the dimethylaminoethyl-methacrylate monomer unit and on the loss of the terminal $-N(CH_3)_2$, the 113 *m/z* is formed, i.e.



158 *m/z*



156 *m/z*

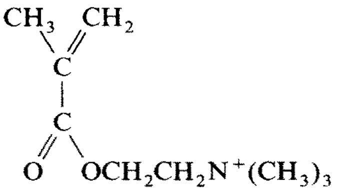


113 *m/z*

The negative ion spectrum in Fig. 2a displays a number of ions diagnostic of both the backbone and the alkyl side-chain species. The ions at 85 and 55 *m/z* have been shown to be characteristic of the methacrylate backbone (Hearn and Briggs, 1988) and ions at 31 and 73/71 *m/z* arise from the methoxyl and butoxyl ions, respectively, and are formed by side-chain cleavage.

No OR^{-} anion was detected from the dimethylaminoethyl-methacrylate monomer unit although nitrile ions, CN^{-}, present at 26 *m/z*, confirm the presence of a nitrogen-containing species within the polymer structure.

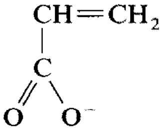
The positive-ion SSIMS spectrum of Eudragit RS (a copolymer of methyl [50%]- and trimethylammonioethyl [0.1%]-methacrylate and ethyl [49.9%]-acrylate) is dominated by the 172 *m/z* ion in the higher mass range. This is attributed to the molecular ion of the trimethylammonioethyl-methacrylate unit which, with the subsequent loss of the terminal $-N(CH_3)_3$, forms the 113 *m/z* cation as observed for Eudragit E.



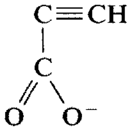
172 *m/z*

The 69 *m/z* ion again indicates the presence of methacrylate structures (Hearn and Briggs, 1988) and the 55 *m/z* ion may in part arise from the corresponding loss of oxygen from the acrylate monomer unit forming the ion, $CH_2=CHC^{+}=O$ (Wilding et al., 1989a).

The negative ion SSIMS spectrum in Fig. 2b is dominated by ions arising from methyl-methacrylate and ethyl-acrylate monomer units. The 85 and 55 *m/z* anions again indicate the presence of methacrylate units whilst the 71 and 69 *m/z* ions arise from acrylate backbone species.



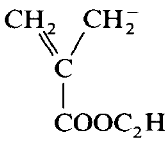
71 *m/z*



69 *m/z*

Again, dominant ions arise from the ester cleavage of the alkoxyl ions at 31 and 43/45 *m/z* for the methyl-methacrylate and ethyl-acrylate units (but not for the nitrogen-containing trimethylammonioethylmethacrylate side-chain).

A number of the higher mass negative ions (87, 107, 109, 111, 127, 139, 141 and 185 *m/z*) are also observed in homopolymers of methyl methacrylate (MMA) and to a lesser extent ethyl acrylate (EA). In particular, the prominent 113 *m/z* probably arises from the ethyl-acrylate monomer unit as follows,



$$\mathrm{CH_2{=}C(CH_2^-)COOC_2H_5}$$

113 *m/z*

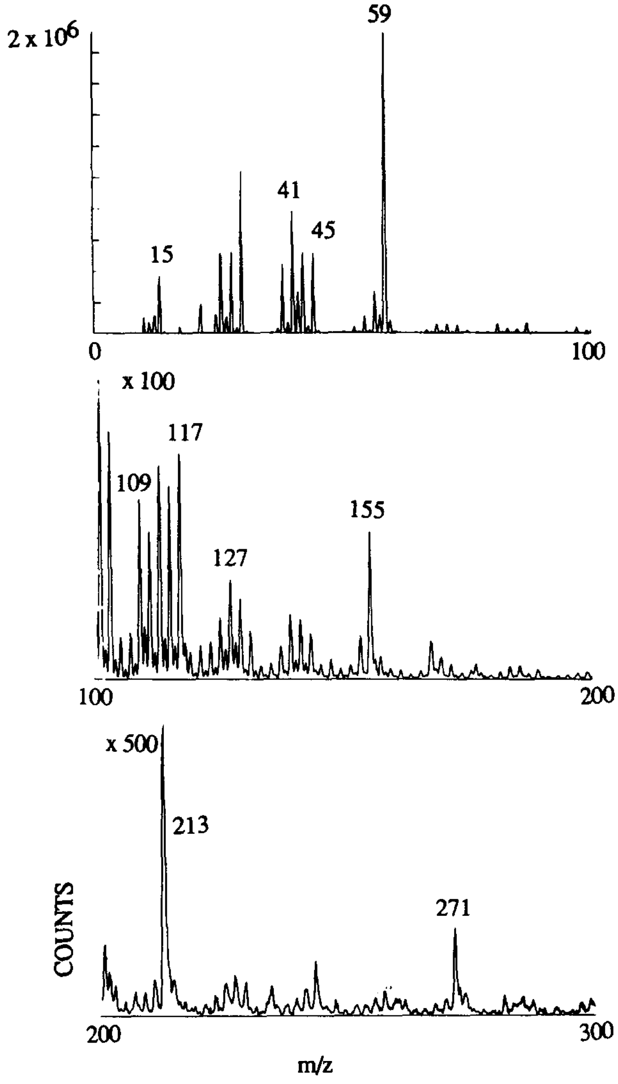


Fig. 3. Positive-ion SSIMS spectrum of HPC.

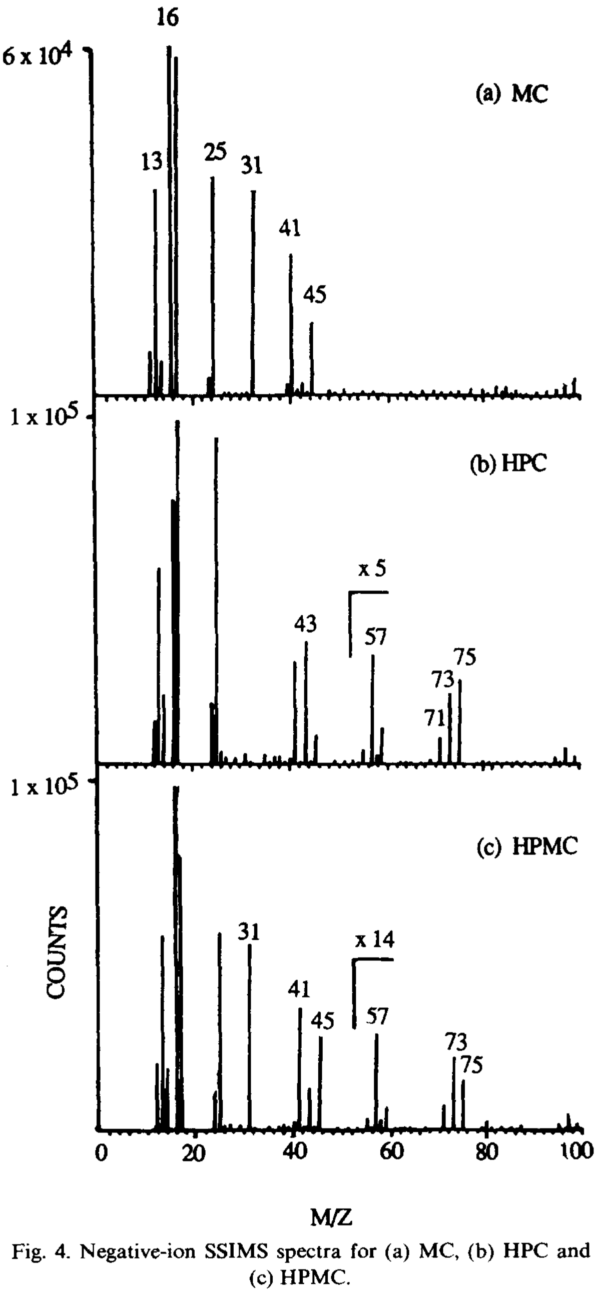


Fig. 4. Negative-ion SSIMS spectra for (a) MC, (b) HPC and (c) HPMC.

Cellulose ethers

For cellulose ethers, the low mass range (0–100 *m/z*) is dominated by hydrocarbon fragments of the type $C_nH_m^+$. This is similar for all cellulose ethers examined. The exceptions are the base peaks attributable to ions formed from cellulose ether side-chain, e.g. the 59 *m/z* ion ($^+CH_2CHOH$-CH_3), in HPC, at 15 and 45 *m/z* (Fig. 3) as (CH_3^+ and $^+CH_2OCH_3$), respectively, for MC, and 45 *m/z* ($^+CH_2CH_2OH$) in EC.

However, the negative ion spectra reveal many diagnostic peaks which may be ascribed to the substituted ether side-chain. The negative-ion SIMS spectra of MC, HPC and HPMC are shown in Fig. 4a–c, respectively. The intense peaks at *m/z* 12–14, 16, 17, 24–25 and 41 correspond to C^-, CH^-, CH_2^-, O^-, OH^-, C_2^-, C_2H^- and C_2HO^-, respectively. In the MC spectrum (Fig. 4a), an additional prominent peak is observed for the methoxyl ion CH_3O^- at 31 *m/z*. In Fig. 4b, there are a number of diagnostic fragments of the hydroxypropyl unit at 57, 73 and 75 *m/z* attributable to $CH_2{=}CO^- - CH_3$, $^-OCH{=}COHCH_3$ and $^-OCH_2CHOHCH_3$, respectively. As one would expect all these ions are present in the HPMC negative-ion spectrum (Fig. 4c).

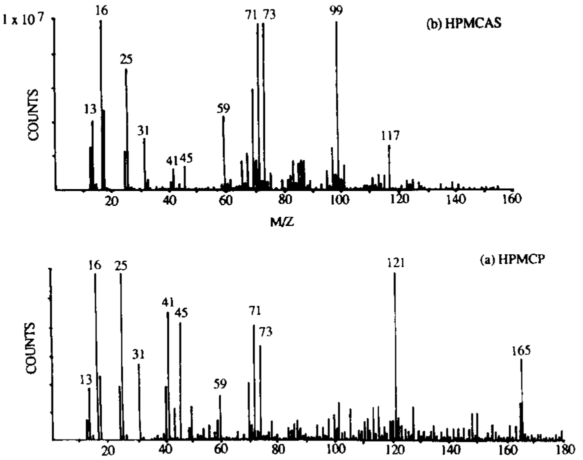
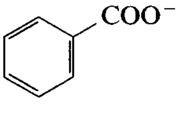
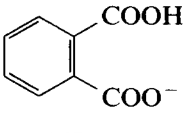


Fig. 5. Negative-ion SSIMS spectra of (a) HPMCP and (b) HPMCAS.

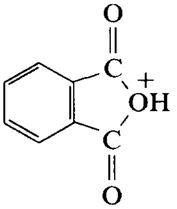
Where the cellulose ether substitution is extended to include acetate, succinate and phthalate groups as with HPMCP and HPMCAS, ions specific to these groups may also be detected. In Fig. 5a, the negative-ion HPMCP spectrum, ions at 121 and 165 *m/z* are thought to be diagnostic of the phthalate substituent. Additionally, a characteristic 149 *m/z* ion in the corresponding positive-ion spectrum (not shown) is known to be diagnostic of the phthalate species generally and corresponds to the stable phthalate anhydride ion, i.e.



121 ***m/z***

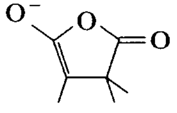


165 ***m/z***

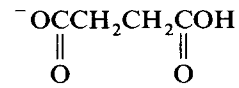


149 ***m/z***

With reference to cellulose acetate SSIMS spectra, we are able to identify peaks attributable to the acetate substituent in HPMCAS. In the HPMCAS negative-ion SIMS spectrum (Fig. 5b), the major acetate peak is observed at 59 *m/z*. The ions at 99 and 117 *m/z* are fragments of the succinate substituent. Possible structures for these ions are proposed below:



99 ***m/z***



$$^{-}\mathrm{O}\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{CH_2CH_2}\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{OH}$$

117 ***m/z***

The ions specific to methoxyl and hydroxypropoxyl substituent noted above are also observed in the HPMCP and HPMCAS negative spectra in Fig. 5.

General Conclusions

In this work, SSIMS has provided detailed chemical structural information from the surfaces of film-coating polymers. The identification of the different monomer units within the Eudragit copolymers and also the substituents on single and multi-derivatised cellulose ethers demonstrates the power of the technique for the in-situ solid-state characterisation and identification of polymer films.

The data presented in the SSIMS spectra are essentially qualitative. The influence of 'matrix effects' on relative ion yields within the mass spectrum prevents a quantitative analysis of the monomer composition in the Eudragit series or the level of substitution for the cellulose ether derivatives. However, it is clearly possible to identify and distinguish between the different film coating polymers using the 'fingerprint' spectra obtained from SSIMS. A further advantage is the possible detection of low molecular weight excipients within the polymer films by the presence of their molecular ion and/or diagnostic fragments, e.g. plasticizers (Wilding et al., 1989), drugs (Davies et al., 1988), lubricants (Davies et al., 1987) and pigments.

References

Briggs, D., SIMS for the study of polymer surfaces. *Surf. Interface Anal.*, 9 (1986) 391–404.

Briggs, D. and Hearn, M.J., Interaction of ion beams with polymers, with particular reference to SIMS. *Vacuum*, 36 (1986) 1005–1010.

Brown, A. and Vickerman, J.C., Static SIMS for applied surface analysis. *Surf. Interface Anal.*, 6 (1984) 1–14.

Brown, A. and Vickerman, J.C., A comparison of positive and negative ion static SIMS spectra of polymer surfaces. *Surf. Interface Anal.*, 8 (1986) 75–81.

Davies, M.C., Brown, A. and Newton, J.M., Chemical characterisation of lubricant films. *J. Pharm. Pharmacol.*, 39 (1987) 122P.

Davies, M.C., Brown, A., Newton, J.M. and Chapman, S.R., SSIMS and SIMS imaging of a drug delivery system. *Surf. Interface Anal.*, 11 (1988) 591–595.

Davies, M.C., Short, R.D., Khan, M.A., Watts, J.F., Brown, A., Eccles, A.J., Humphrey, P., Vickerman, J.C. and Vert, M., A XPS and SIMS analysis of biodegradable biomedical polyesters. *Surf. Interface Anal.*, 14 (1989a) 115–120.

Davies, M.C., Khan, M.A., Short, R.D., Pouton, C. and Aktar, S., A XPS and SSIMS analysis of the surface chemical structure of poly(caprolactone) and poly(β-hydroxybutyrate β-hydroxyvalerate) copolymers. *Biomaterials*, (1989b) in press.

Hearn, M.J., Briggs, D., Yoon, S.C. and Ratner, B.D., SIMS and XPS of polyurethane surfaces. 2. Polyurethanes with fluorinated chain extenders. *Surf. Interface Anal.*, 10 (1987) 384–391.

Hearn, M.J. and Briggs, D., Analysis of polymer surfaces by SIMS. 12. On the fragmentation of acrylic and methacrylic homopolymers and the interpretation of their positive and negative ion spectra. *Surf. Interface Anal.*, 11 (1988) 198–213.

Hearn, M.J., Ratner, B.D. and Briggs, D., SIMS and XPS studies of polyurethane surfactants. 1. Preliminary studies. *Macromolecules*, (1989) in press.

Rowe, R.C., Materials used in the film coating of oral dosage forms. In Florence, A.T. (Ed.), *Critical Report on Applied Chemistry, Vol. 6, Materials used in Pharmaceutical Formulation*, Blackwell Scientific, London, 1984, pp. 1–36.

Wilding, I.R., Melia, C.D., Short, R.D., Brown, A. and Davies, M.C., SSIMS analysis of methacrylate copolymers employed in drug delivery. *J. Appl. Polym. Sci.*, 39 (1990) 1827–1834.

Wilding, I.R., Davies, M.C., Melia, C.D., Brown, A., Humphrey, P. and Rowe, R.C., An investigation using SSIMS of the surface composition of ethylcellulose films plasticized with dialkyl phthalates. J. Appl. Polym. Sci., (1989) submitted.