SSIMS Analysis of Methacrylate Copolymers Employed in Drug Delivery

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Synopsis

This study reports on the use of static secondary ion mass spectroscopy (SSIMS) to chemically characterize complex methacrylate copolymers used in the pharmaceutical industry for controlled drug delivery. Ions diagnostic of the component monomer residues were detected, which could be interpreted using a fragmentation model for alkylmethacrylate homopolymers proposed previously. This model is extended to include the SSIMS analysis of nitrogen-containing methacrylate copolymer residues.

INTRODUCTION

Since the early 1980s, static secondary ion mass spectrometry (SSIMS) has emerged as a complementary technique to X-ray photoelectron spectroscopy (XPS or ESCA)[1-3] for the surface analysis of a range of polymeric materials. It has been clearly demonstrated that, under nondamaging conditions, the SSIMS spectra of many polymers yield a number of diagnostic ions arising from the monomer repeating units, the side-chain species present, and/or the fragments of these ions.[4-22] Thus, it has been shown that SSIMS may distinguish many different classes of polymer systems in a qualitative[4-22] and, in the case of certain copolymer compositions, a quantitative manner.[8]

In this work, we examine a range of complex methacrylate copolymers which are employed as film-forming materials in controlled release drug delivery. These methacrylates are used for taste masking of orally administered drugs, protection of pH-sensitive materials from the acid contents of the stomach (enteric coating), and as rate-controlling membranes for controlled-release dosage forms. The different members of this series vary principally in the type and relative ratio of their ester side group substituents (Table II), which play an important role in their functional properties *in vivo*.

Prior to a surface analysis study of film coatings of these polymers on drug delivery systems, we present a report on the characterization of the surface chemical structure of isolated films by SSIMS.

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EXPERIMENTAL

The methacrylate random copolymers were used as supplied from Rohm-Pharma Gmbh (Darmstadt, West Germany) and are listed in Tables I and II.

The polymers were studied as thin films, spin-cast once from a 1% solution in double distilled methanol (Analar grade, BDH, Poole) onto aluminium foil. Samples were analyzed within 60 min of casting.

The SSIMS spectra were obtained using a VG SIMSLAB[11] consisting of an ion/atom gun,[14] a secondary ion energy analyser after the design of Wittmaack,[15] and a quadrupole mass spectrometer (VGMM 12-12, 0–1200 daltons). SSIMS spectra were acquired using 2 keV argon atoms with a flux density of 3×10^9 particles cm^{-2}. In accordance with previous work,[12] an electron beam of 1–10 nA cm^{-2} current was used to optimize negative ion yields. A PDP111 computer system was used for the acquisition, manipulation, and storage of secondary ion mass data. The total dose for both positive and negative ions per sample was of the order of 2×10^{12} particles per sample,

TABLE I
Methacrylate Copolymers Used in This Study

Trade name	IUPAC name
Eudragit S	Poly(methacrylic acid, methyl methacrylate)
Eudragit L	Poly(methacrylic acid, methyl methacrylate)
Eudragit E	Poly(butyl methacrylate (2-dimethylaminoethyl) methacrylate, methyl methacrylate)
Eudragit RS	Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride)

TABLE II
Copolymer Structure and Composition

$$\left[\begin{array}{c} R_2 \\ | \\ -C-CH_2- \\ | \\ C \\ {}^{\diagup} {}^{\diagdown} \\ O \quad OR_1 \end{array} \right]_n$$
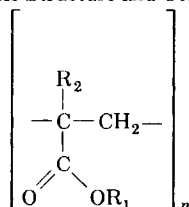
Type and Relative Residue Frequency of Side Group R_1 [a]

| Eudragit	H	CH_3	C_2H_5	C_4H_9	$CH_2CH_2N(CH_3)_2$	$CH_2CH_2\overset{+}{N}(CH_3)_3$
S	1	2	—	—	—	—
L	1	1	—	—	—	—
E	—	1	—	1	2	—
RS	—	2	1*	—	—	0.1

[a] $R_2 = CH_3$ except for * when $R_2 = H$

with a combined setting-up and spectral acquisition time of 600 s. This time period and treatment falls within the accepted limits for SSIMS analysis of "undamaged" polymer surfaces.[20]

RESULTS AND SPECTRAL INTERPRETATION

For clarity, the spectra for the differing polymer structures will be discussed individually.

Eudragit L and S will be considered together as they differ only in the relative ratios of methacrylic acid (MAA) and methyl methacrylate (MMA) residues (1 : 1 and 1 : 2, respectively), and, in both the positive and negative ion spectra, there appears to be no discernable difference in the relative ion intensities between the two copolymers.

Figure 1(a) shows the positive ion spectrum for Eudragit S over the range 0–200 D. The 69D ion is typical of all methacrylates, corresponding to $CH_3C(CH_2)C^+ = O$, and is a dominant feature of the spectrum. The intense CH_3^+ peak reflects the presence of poly (methyl methacrylate) (PMMA) in the structure. In the 100–200 D range, a number of intense ion clusters are observed; however, the relative ion intensities, in general, do not mirror those seen for PMMA previously,[21] with the exception of the 101, 109, and 186 D peaks, for which the following structures have been assigned:

101 D   109 D   186 D
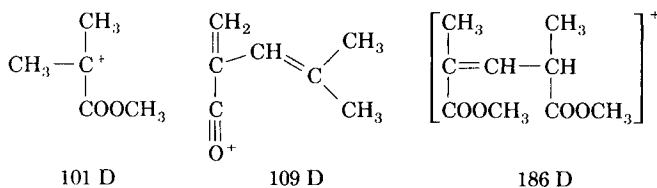
The negative ion spectra for Eudragit L, from 0 to 200 D, is shown in Figure 2(a). Typical of all methacrylates, the ions at 41, 45, 55, and 85D attributable to the methacrylate backbone[12] dominate the lower mass range of the spectrum. The methoxyl ion, CH_3O^-, formed by ester cleavage of the methacrylate units of PMMA, is seen at 31 D. At higher masses (100–200 D) there are a number of specific ions attributed by Hearn and Briggs[21] as being characteristic of PMMA and PMAA structures. The 109, 125, 127, 139, and 141 D ions are common to both PMMA and PMAA, but 87, 101, and 185 D are unique to PMMA and 97 and 113 D are considered diagnostic of PMAA. However, it is
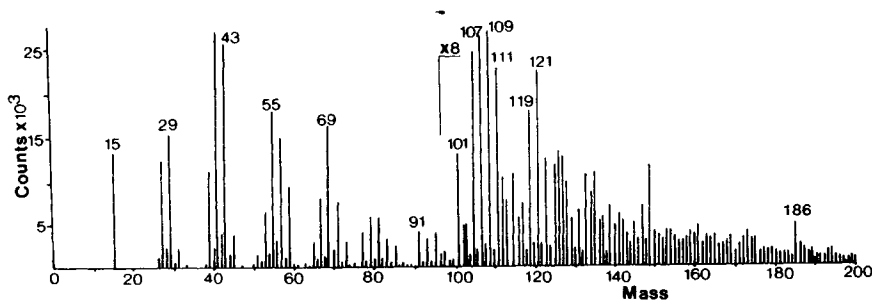

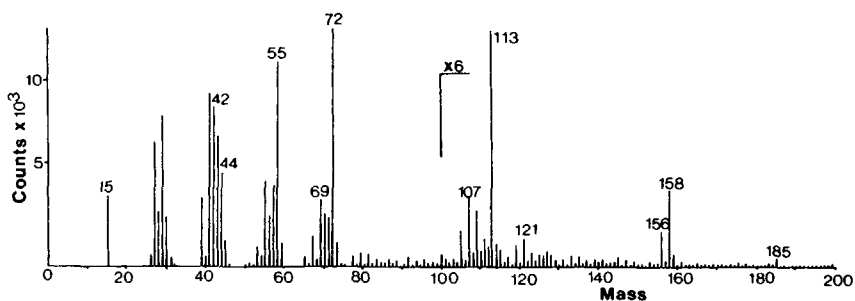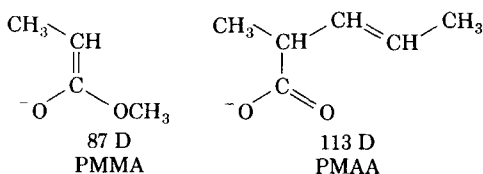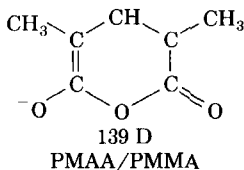Fig. 1(a).   Positive ion SSIMS spectra of Eudragit S.

Fig. 1(b). Positive ion SSIMS spectra of Eudragit E.

interesting to note that other ions diagnostic of PMAA (151 and 158 D), are not prominent in the L spectra as may have been anticipated from previous work,[21]

87 D
PMMA

113 D
PMAA

The limited number of ions diagnostic of PMAA, 97 and 113 D, within the L negative ion spectra, reflects the structural similarity between PMAA and PMMA and their subsequent fragmentation. In certain cases, once cleavage of either the methyl or methoxyl unit has occurred, the resulting ions and fragments are identical, e.g., 109, 125, and 139 D:

139 D
PMAA/PMMA

Such overlap of the fragmentation patterns makes definitive identification of PMAA fragments difficult.

The positive and negative ion SSIMS spectra for Eudragit E are shown in Figures 1(b) and 2(b), respectively. In the positive ion spectrum, prominent
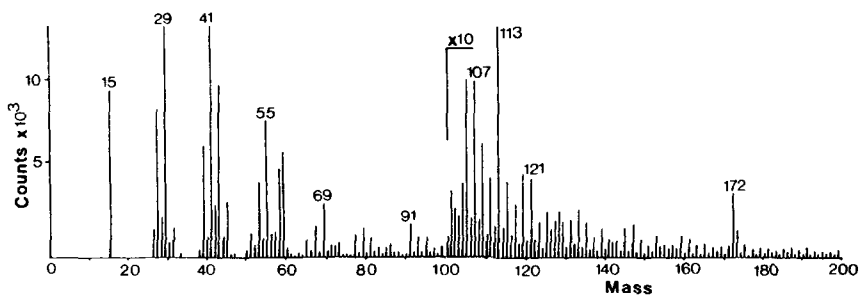

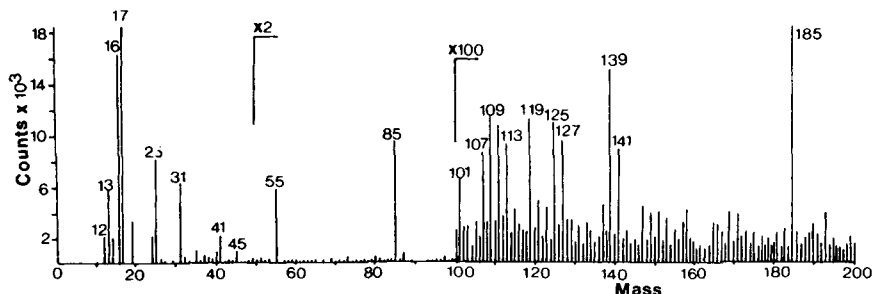Fig. 1(c). Positive ion SSIMS spectra of Eudragit RS.

Fig. 2(a).   Negative ion SSIMS spectra of Eudragit L.

ions are observed at 72, 58, 44, and 42 D at lower mass, together with the characteristic hydrocarbon fragments. These even-numbered ions are diagnostic of nitrogen-containing fragments from the dimethylaminoethyl side chain:

$$^+CH_2CH_2N(CH_3)_2 \qquad ^+CH_2N(CH_3)_2 \qquad (CH_3)_2\overset{+}{N}$$

72 D   58 D   44 D   42 D
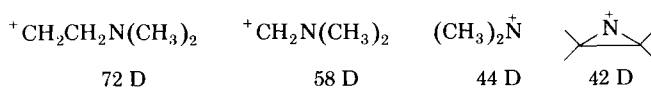
Although methyl methacrylate units comprise some 25% of all residues, no ions diagnostic of PMMA (as seen for L and S) or for poly(butyl methacrylate) (PBMA)[21] are observed in the 100–200 D range. However, there are a number of even-numbered ions at 156 and 158 D which may be assigned to a cation derived from the complete dimethylaminoethyl methacrylate monomer unit, and on loss of the terminal $-NH(CH_3)_2$, the 113 D ion is formed, i.e.,

158 D

156 D

113 D
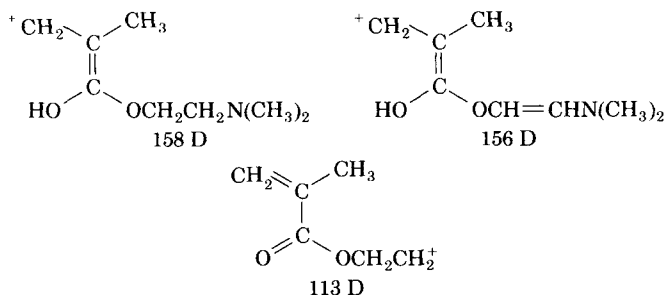
In the negative ion spectrum [Fig. 2(b)], the principle diagnostic fragments of the methacrylate backbone are again prominent at 41, 55, and 85 D. The formation of alkoxyl ^-OR ions by cleavage of the ester linkage occurs in both PMMA and PBMA monomer units ($^-OCH_3$ at 31 D for PMMA, and the butoxyl, $C_4H_9O^-$ and the resonance stabilized species $C_4H_7O^-$, at 73 and 71 D, respectively, for PBMA). In the case of the dimethylaminoethyl methacrylate unit, a prominent ^-OR ion at 88 D is not seen, although the presence of nitrile ions, CN^- at 26 D, confirms the presence of nitrogen-containing residues. In the higher mass region, while ion clusters are observed around 109, 127, and 139 D, previously noted for both PMMA and PBMA,[21] few intense diagnostic fragments characteristic of either monomer (e.g., 185 D for PMMA or 183 D for PBMA) are detected. No prominent ions from the dimethylaminoethyl methacrylate monomer are detectable above 100 D.
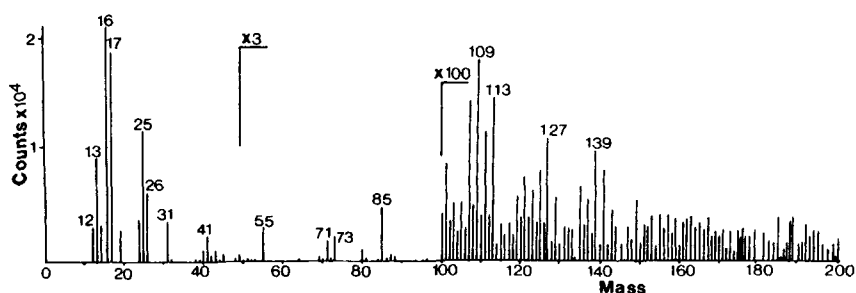
Fig. 2(b).   Negative ion SSIMS spectra of Eudragit E.

In Figure 1(c), the positive ion spectra for Eudragit RS is shown from 0–200 D. The 69 D ion is again diagnostic of the methacrylate structure whereas the prominence of the 55 D ion may in part be attributable to the corresponding loss of oxygen from the acrylate monomer unit $CH_2=CHC^+O$.[22] Ions typical of PMMA and polyethylacrylate (PEA) are not observed at higher masses. The even numbered 172 D ion may be attributed to the molecular ion of the trimethylammonioethyl methacrylate unit. The subsequent loss of $-NH(CH_3)_3$ generates a further peak at 113 D, as seen in Eudragit E:

172 D
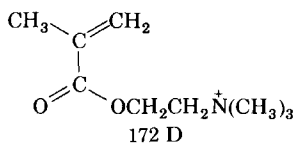
The prominence of the peaks, despite the very low bulk concentration of these residues (approximately 2.5%), may be due in part to either the preferential surface orientation of the charged species and/or the generation of highly stable precharged ion from the monomer.

Few significant ions associated with PMMA and PEA are seen in the positive ion spectrum of Eudragit RS. In contrast, the negative ion spectrum, shown in Figure 2(c), contains a number of ions (87, 101, 109, 111, 127, 139, 141, and 185 D) which are also observed in PMMA and to a certain extent
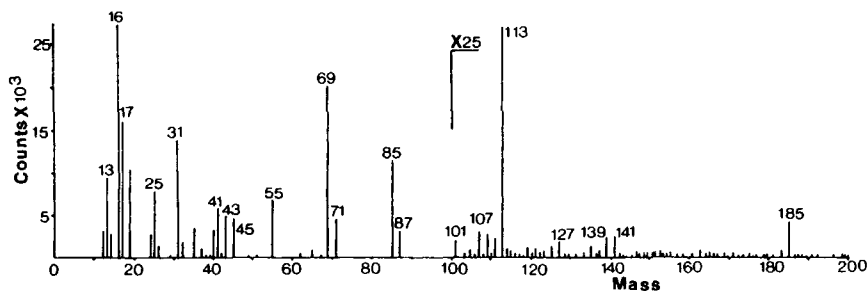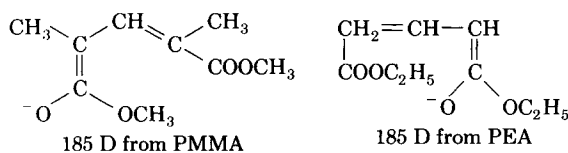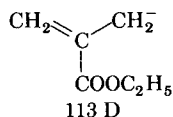

Fig. 2(c).   Negative ion SSIMS spectra of Eudragit RS.

in PEA[22]:

CH$_3$—C(=C(—OCH$_3$)(O$^-$))—CH=C(CH$_3$)(COOCH$_3$)

185 D from PMMA

CH$_2$=CH—CH(COOC$_2$H$_5$)—C(—O$^-$)(OC$_2$H$_5$)

185 D from PEA

However, the higher mass range is dominated by the 113 D ion, which may arise principally from the ethylacrylate monomer unit, i.e.,

CH$_2$=C(COOC$_2$H$_5$)—CH$_2^-$

113 D

Negative ions diagnostic of the methacrylate backbone and acrylate residues are evident at 85 and 55 D and 71 and 69 D, respectively:

HC=CH$_2$ — C(=O)(O$^-$)   71 D

C≡CH — C(=O)(O$^-$)   69 D
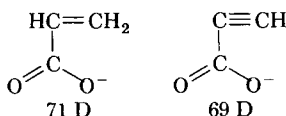
Prominent ester side-chain fragments are seen as $^-$OR at 31 D for methoxyl and 43 and 45 D for ethoxyl units, but no corresponding ion is seen for the trimethylammonioethyl methacrylate monomer.

GENERAL DISCUSSION

A number of interesting conclusions can be drawn from this study. Many of the prominent ions observed in the SSIMS analysis of these copolymers are those previously seen by Hearns and Briggs[21] for pure alkylmethacrylate homopolymers. For most of the copolymers examined, the monomeric units yielded diagnostic fragments which, for alkylmethacrylates, correlated well with those documented previously for the corresponding homopolymers.[21] The low mass fragments in the negative ion spectra demonstrate the ability of SSIMS to distinguish methacrylate (55 and 85 D) and acrylate (69 and 71 D) monomer units and also the chemical nature of the non-nitrogen-containing alkyl side chain substituents, following ester cleavage.[12, 21] These ions are complimented by a number of high mass fragments (> 100 D) in both the positive and negative SSIMS spectra, which may be interpreted in terms of linear and cyclic ions from the fragmentation model proposed by Hearn and Briggs.[21] However, it is evident that careful judgement is needed to distinguish between PMMA and PMAA species in the SSIMS spectra of L and S, due to the similarity of many of the ion fragments for both systems. Similarly,

no changes in relative ion intensities were observed, despite the differences in the monomer ratios between L and S.

A particularly interesting feature of this study is the SSIMS spectra of nitrogen-containing methacrylates. A number of cations are formed which arise from the monomer unit of the nitrogen-containing species, even at low bulk concentration as is the case for RS. This indicates that the sequence of fragmentation, depolymerization followed by ionization, is similar for these nitrogen-containing species as that evoked by Hearn and Briggs for alkyl-methacrylate homopolymers.[21] Fragments generated from these nitrogen-containing residues dominate the positive ion spectra to the virtual exclusion of peaks arising from the alkylmethacrylate monomers, even when the latter are present in higher relative concentrations. However, no characteristic ions, including those formed from ester cleavage, are seen in the negative ion spectra except CN^-.

Although the interpretation of the fragmentation patterns of these poly-methacrylate copolymers yields much interesting information on their molecular structure, the data should be viewed as essentially qualitative. Marked differences between anticipated (from homopolymer analysis) and actual relative ion intensities may be due in part to possible surface segregation of one of the copolymer monomer species. Alternatively, the relatively high stability of certain charged ions, e.g., the nitrogen-containing species in the positive ion spectra, will also cause them to dominate the mass spectra, over and above less stable ions derived from species present at a higher bulk composition. The intense peak from precharged ions in the positive ion spectrum of the RS copolymer (despite a low bulk content) could conceivably arise from either of these points. The determination of the lowest detectable limits in the SSIMS analysis of these monomer units at the polymer surface is an interesting goal. Model polymer systems are currently being synthesized within our laboratories to address this problem.

Although a more comprehensive surface analysis would encompass complementary surface techniques, this work shows the ability of SSIMS to provide information identifying the different polymer types used in controlled drug delivery.

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