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Behaviour of pH sensitive polymers on metal electrodes

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The behaviour of two different enteric coatings with pH dependent properties has been investigated as a model system for the degradation of polymer coated electrodes using impedance spectroscopy. Since the stability of these polymers depends strongly on pH, it was possible to halt the breakdown at well defined stages, which were investigated systematically. Although both polymers, Eudragit S-100 and a modified maleic anhydride copolymer, have similar chemical structures, they had different breakdown mechanisms. Eudragit S-100 films dissolved, initially forming electrolyte filled pores through which electrolyte penetrated to the gold and spread along the electrode surface. The electrolyte layer between coating and electrode was found to be typically 0.7 μm thick for a 30 μm thick coating with a porosity of 2×10^{-4}. Layers of the modified maleic anhydride copolymer, unlike the Eudragit S-100, did not dissolve, but swelled in the course of the breakdown. It was shown that only positively charged ions can penetrate this polymer during breakdown. For the redox couple $[Ru(NH_3)_6]^{2+}/[Ru(NH_3)_6]^{3+}$ a mean diffusion coefficient of $D = 0.7 \times 10^{-8} cm^{-2} s^{-1}$ in the swollen polymer was determined.

1. Introduction

The properties of polymer coatings, in particular protective coatings, on metals have been explored extensively by the use of impedance spectroscopy. For some time [1, 2] it has been clear that impedance measurements can give quantitative information on the pores in such polymer coatings which are filled with electrolyte. In this present work the behaviour of two different enteric coatings with pH dependent properties have been investigated. These polymers swell or dissolve if the pH is increased above a certain critical value as described below in more detail.They represent a unique model system for the study of the degradation of polymers on metal electrodes since they provide the possibility of halting the breakdown at well defined stages which can be systematically investigated.

1.1. *Enteric coatings*

Enteric coatings are polymers used in the coating of dosage forms for orally administered drugs, with the purpose of delivering drugs to specific regions of the gastrointestinal tract. This article deals with two different polyacids which are stable at low pH, but degrade above a threshold pH because of ionization of the carboxylic side groups. The first polymer characterized in this work is Eudragit S-100, a methyl methacrylate/methacrylic acid copolymer. It begins to dissolve at pH 7 and becomes highly soluble at pH values above 7 [3–5].

The second polymer under investigation is a methyl vinyl ether/maleic anhydride copolymer modified by esterification. This material has found wide interest as an enteric coating because the pH above which it is degraded, and the pH below which it is stable are separated by only 0.25 pH units. The pH sensitivity of the polymer can easily be varied. An increase in the degradation pH can be achieved either by esterifying with a longer chain alcohol or by increasing the degree of esterification [6–9]. The fraction of ionized carboxyl groups necessary to solubilize the polymer ranges between 3 and 99%, and increases as the hydrophobicity of the polymer increases [9]. Heller *et al.* have shown that the more hydrophobic polyacids do not dissolve, but swell above their breakdown pH [9].

Maleic anhydride copolymers esterified with higher alcohols show a very low water uptake of about one molecule of water per polymer unit at pH 2. This indicates that the water is probably not free, but bound to carboxyl groups [9].

The behaviour of enteric coatings below the dissolution pH has been characterized by Raffin *et al.* [10]. An increase in pH leads to a rising flux of sodium ions through cellulose acetate phthalate films exposed to a sodium chloride solution. This is

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accompanied by a decrease in resistance and an increase in the capacitance of the film as shown in impedance measurements. As the carboxyl groups are progressively deprotonated, sodium ions penetrate the polymer balancing the negative charge. At a pH close to the dissolution pH the polymer film becomes a sodium ion conductor. Hence, the behaviour of enteric coatings just below the dissolution pH can be compared to that of ion exchange membranes.

1.2. *Impedance of protective coatings*

A perfect protective coating would behave like a pure capacitance, C_g, with

$$C_g = \varepsilon_r \varepsilon_o \frac{A}{d}$$

because it would have no free ions, water or oxygen in it. Similar behaviour can be predicted for enteric coatings that have been exposed to electrolyte only for a short time.

Defects in protective coatings such as pores or delamination have been widely investigated with impedance spectroscopy [1, 2]. Pores in a coating filled with electrolyte cause an apparent bulk conductivity of the polymer, which can be described by the bulk resistance, R_b. It can be used to calculate the relative porosity, P, of the film:

$$P = \frac{R_{bt}}{R_b}$$

where R_{bt} is the resistance of a layer of electrolyte having the same area and thickness as the polymer coating [2]. Assuming the porosity, P, is identical to the fraction of the wetted metal area, the impedance behaviour of the system can be described with the model shown in Fig. 1. The bulk properties of the coating are represented by the bulk resistance, R_b, in parallel with the geometric capacitance, C_g. The metal/electrolyte interface is described by a charge transfer resistance, R_{ct}, and a double layer capacitance, C_{dl}, in parallel. For many metal/polymer systems it has been found that, after penetrating a pore, electrolyte spreads as a thin film between metal and coating, that is, the fraction of the wetted metal area, W, can be several orders of magnitude larger than the relative porosity [2]. This results in a nonuniform current distribution which is not accounted for in the equivalent circuit shown in the Fig. 1. However, this model can be used to estimate the fraction of the wetted metal area, W:

$$W = \frac{C_{dl}}{C_{dlo}} = \frac{R_{cto}}{R_{ct}}$$

where C_{dlo} and R_{cto} are the values for the bare electrode. As previously shown [2], ignoring the nonuniform current distribution leads to a slight underestimate of the wetted surface area.

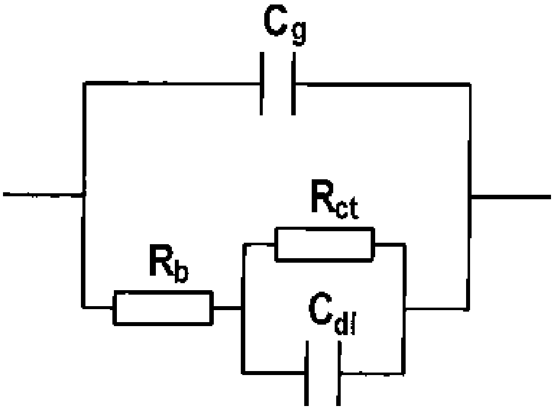

Fig. 1. Equivalent circuit: (C_g) geometric capacitance, (R_b) bulk resistance, (C_{dl}) double-layer capacitance, (R_{ct}) charge-transfer resistance.

2. Experimental details

2.1. *Modification of the maleic anhydride copolymer*

Methyl vinyl ether/maleic anhydride copolymer Gantrez AN 139 (ISP Co. Ltd, Manchester, UK) was esterified with octanol using the following procedure. Some 30 g of the polymer were refluxed with 150 ml of octanol for 48 h, with constant stirring. Thereafter, 20 drops of concentrated sulfuric acid were added to the hot reaction solution which was then refluxed for a further 2.7 h. Work-up was achieved by precipitating the product with methanol, repeated dissolution of the material in acetone and precipitating the product with a methanol/water mixture. Residual solvents were removed by freeze-drying.

2.2. *Polymer deposition*

Gold organometallic ink electrodes were screen printed onto a ceramic substrate by Gwent Electronic Materials Ltd. (Wales, UK). All polymers were deposited onto the electrodes by:

(a) Spray coating of the Eudragit S-100
A 1 g sample of Eudragit S-100 was dissolved in 14 g of acetone. A total of three layers were sprayed over the working area of the electrodes, with each layer being allowed to dry at room temperature for 20 min before the next layer was applied.

(b) Spin coating of the esterified maleic anhydride copolymer (EMAC)
A solution of 1 g EMAC in 14 g of acetone was prepared. Some 40 μl of the polymer solution were applied to the working area of the electrodes before spinning it at a speed of 110 rpm for 2 min. The process was repeated once.

To ensure effective drying of the polymer all electrodes were left for at least 24 h at room temperature before use.

2.3. *Determination of the polymer thickness*

The thickness of the polymer films was determined by taking electron micrographs of a cross section of the electrodes. This was carried out by the Electron Microscopy Unit, University of Newcastle upon Tyne.

2.4. *Impedance measurements*

Impedance measurements were performed using a Schlumberger Solartron 1253 gain-phase analyser and an SI 1186 electrochemical interface (Schlumberger Technologies, Hampshire, UK). Impedance measurements were mostly performed at zero potential in a two-electrode arrangement with a 4 mm diameter glassy carbon electrode as the counter electrode placed opposite and parallel to the polymer coated electrode at a distance of about 3 mm. For impedance measurements in the presence of a redox couple a three-electrode arrangement with a {Ag/AgCl, 1 M NaCl} reference electrode was used. The measurements were carried out with an a.c. amplitude of 30 mV. Eudragit S-100 coated electrodes were characterized in 10 mM phosphate buffer containing 1 M NaCl at pH 5.2. EMAC coated electrodes were characterized in 10 mM phosphate buffer containing 1 M NaCl at pH 7.4.

The breakdown of the polymer was initiated by removing the measuring solution and adding 200 μl of 0.1 M phosphate buffer pH 7.8 in the case of the Eudragit S-100 polymer, and 0.1 M Tris/HCl buffer pH 8.7 in the case of the EMAC. In order to halt the breakdown at different stages, it was interrupted by removing the solution, rinsing with water and adding the same electrolyte as for the initial experiments.

Kinetic measurements of the breakdown of Eudragit S-100 coatings were carried out in 100 mM phosphate buffer pH 7.8 containing 1 M NaCl by running full impedance sweeps every minute. Mathematical fits of the impedance spectra were carried out using the program Equivalent Circuit, Version 4.51 (B. A. Boukamp, 1993, University of Twente, The Netherlands).

2.5. *Coulometric measurements*

Partially broken down Eudragit S-100 films were exposed to a 0.1 M ferricyanide solution containing 1 M NaCl overnight. The coulometric measurement was carried out using a three electrode arrangement. Reduction of the ferricyanide was performed at a constant potential of −0.1 V vs a {Ag/AgCl, 1 M NaCl} reference electrode.

EMAC films were degraded in 1 M NaOH for 30 min. The electrodes were then rinsed with water and exposed to a 20 mM $[Ru(NH_3)_6]Cl_3$ containing 1 M NaCl and 10 mM phosphate buffer pH 7.4 for 1 h. The Ru(III) solution was then removed and 1 M NaCl containing 10 mM phosphate buffer pH 7.4 added. The reduction of Ru(III) within the polymer was performed at a constant potential of −0.4 V.

2.6. *Cyclic voltammetry*

Cyclic voltammograms were obtained using a VersaStat^{TM} (EG&G Princeton Applied Research) controlled by an AT compatible computer via an IEEE interface board. To determine the redox potentials the electrodes were exposed to a 20 mM solution of $[Ru(NH_3)_6]Cl_3$ containing 1 M NaCl. The measurments were performed at a sweep rate of 1 mV s^{-1}.

3. Results and discussion

3.1. *Eudragit S-100 films*

Eudragit S-100 coatings dissolve completely at pH values greater than 7. Exposure of the material to an alkaline solution results in the formation of a clear solution. Basically, three different stages of the polymer coated electrodes were characterized using impedance spectroscopy: the initial film, intermediate stages of partial dissolution of the polymer and the bare gold electrode.

Spin coated Eudragit S-100 films were found to be 30 μm thick. The impedance spectrum of the initial Eudragit S-100 film showed capacitive behaviour over a large frequency region (curve (a) in Fig. 2); i.e. the phase angle was close to 90 ° . This indicated that the Eudragit S-100 films provided good insulating properties. The geometric capacitance of the film calculated from a fit of the spectrum was 177 pF cm^{-2} and corresponded to a dielectric constant of $\varepsilon_r = 7$.

The spectrum of a bare electrode (curve (f) in Fig. 2) shows a phase angle lower than 90 ° at low frequencies. This could be explained by the rough surface of the screen printed gold electrodes [11]. To account for this the double layer capacitance C_{dl} was in all cases fitted as a constant phase element CPE:

$$Z_{CPE} = \frac{1}{Y(j\omega)^{\alpha}}$$

where Z_{CPE} is the complex impedance of a constant phase element, the exponent α is a number between 0 and 1, j is the imaginary number $\sqrt{-1}$ and ω is the rotational frequency.

Therefore, all values of the double layer capacitance were calculated using the approximation $C_{dl} = Y$. Capacitances and resistances given in this paper were all normalized with the geometric surface of the gold electrodes.

For a bare electrode (curve (f) in Fig. 2), a double layer capacitance for the gold/electrolyte interface of 25 μF cm^{-2} ($\alpha = 0.82$) was determined. Impedance spectra of partially dissolved films are represented in curves (b)–(e) in Fig. 2. After partial dissolution the polymer films were stabilized at pH 5.2. Therefore, the system was at steady state when the impedance spectra were taken. For the first stage of breakdown (curve(b)), the geometric capacitance of the polymer was 188 pF cm^{-2}, that is, nearly the same as for the initial state (curve (a)). The low frequency region showed a resistive behaviour, which could be ascribed to the formation of pores in the polymer layer. Therefore, the fit of the spectra could be based on the equivalent circuit in Fig. 1. As shown previously, the relative porosity of the film can be estimated from the resistance of electrolyte in the pores. For curve (b), a

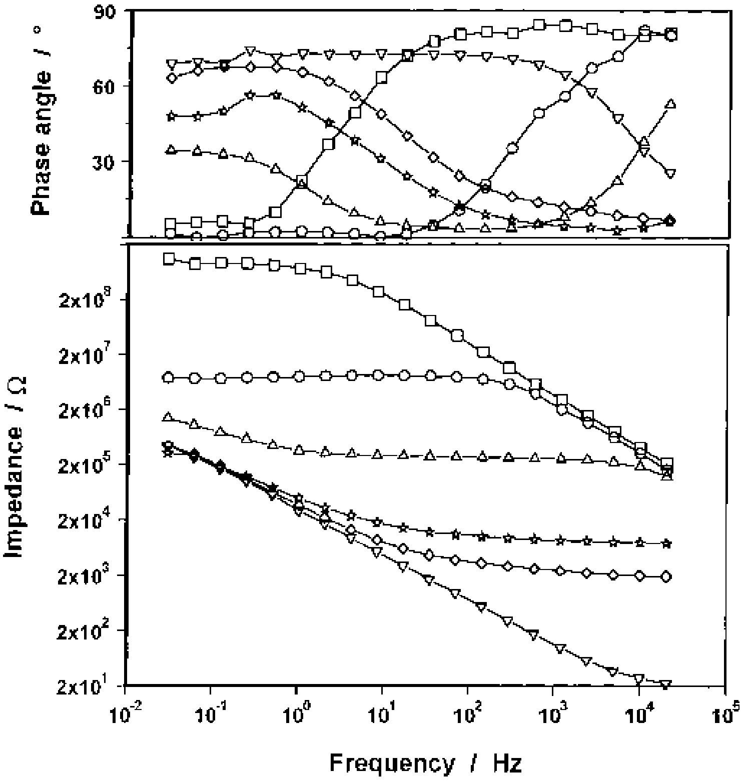

Fig. 2. Bode plots of (a) an Eudragit coated electrode prior to breakdown, (b)–(e) partially degraded Eudragit films and (f) a bare electrode. Key:(a) □, (b) ○, (c) △, (d) ☆, (e) ◇ and (f) ▽.

porosity of 1.7×10^{-8} was obtained. In the frequency range used for the measurements, the limiting low frequency behaviour of curve (b) was purely resistive. Therefore, in this instance the electrolyte did not penetrate the polymer and contact the gold surface (Fig. 3(a)). At later stages of breakdown, as shown in Fig. 2 curves (c)–(e), where the electrolyte had penetrated the polymer film to contact the electrode surface, the low frequency impedance was capacitive and represented the wetted area of the gold electrode.

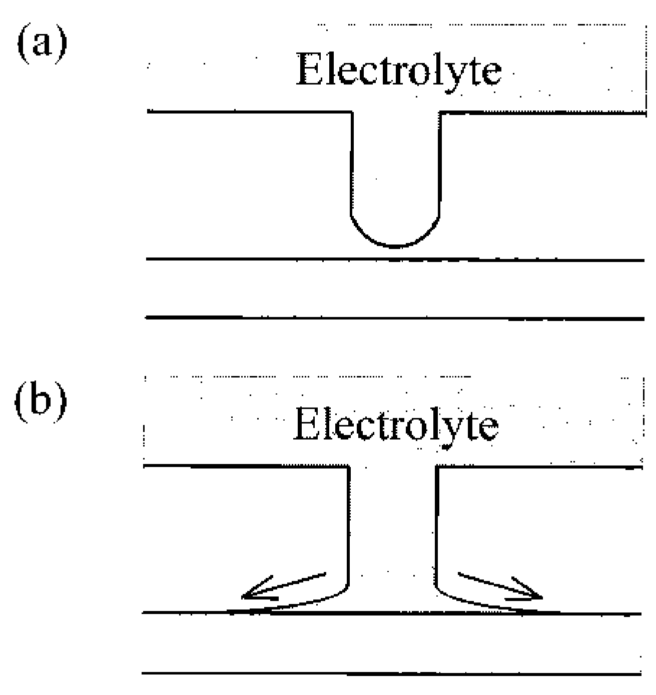

Fig. 3. Schematic diagram showing the proposed mechanism of pore formation in the Eudragit film in alkaline solution.

At the second stage of breakdown (Fig. 2, curve (c)), the geometric capacitance of the polymer was still the same (188 pF cm^{-2}). However, the porosity of the film had increased to 4.9×10^{-7} and the double-layer capacitance, by comparison with that of a bare electrode, showed that ~8.5% of the gold surface was wetted with electrolyte. The relatively high fraction of wetted electrode surface in combination with the small porosity of the film can be explained by spreading of the electrolyte on the gold surface beneath the Eudragit S-100 polymer layer (Fig. 3(b)). This resulted in an inhomogeneous current distribution which accounted for the frequency dispersion of the double layer capacitance in spectrum (c) (Fig. 2). Therefore, the exponent α obtained for this spectrum was 0.57. These results were confirmed by impedance spectra of films which had been broken down further. For curve (d) in Fig. 2 and a porosity of 1.5×10^{-5} were calculated, while ~90% of the surface area was wetted ($\alpha = 0.65$). At the next stage of breakdown, Fig. 2 curve (e), the geometric capacitance could no longer be measured. From the electrolyte resistance in the pores, a relative porosity of $5.6 \times 10^{-5}$was estimated. Since the double layer capacitance obtained from Fig. 2, curve (e) was identical to the capacitance of a bare electrode, essentially 100% of the gold surface was covered with electrolyte.

Figure 4 represents the changes in wetted surface area and porosity with time during the breakdown. The results showed that the electrolyte spreads on the electrode surface before a major increase in the porosity occurs, that is, only a very small porosity was necessary to allow the electrolyte to penetrate the polymer and spread on the surface of the metal electrode. To obtain these kinetic data impedance

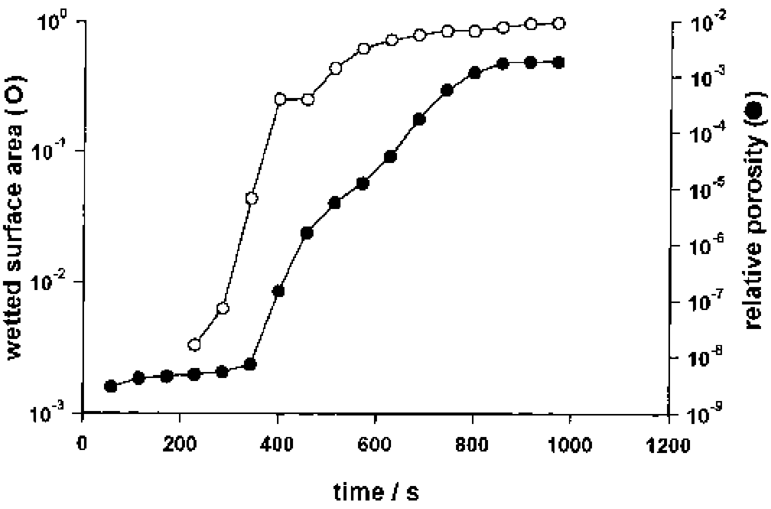

Fig. 4. Changes of wetted surface area and porosity with time.

sweeps were run consecutively during the course of the breakdown. Since the system was not at steady state, impedance sweeps were designed to last less than a minute for these measurements. Therefore, values for the porosity and wetted surface area should be regarded as estimates.

The small ratio of porosity to wetted surface area made it possible to determine the thickness of the electrolyte layer between gold and polymer by means of coulometric measurement. The partially dissolved polymer electrode was exposed to a ferricyanide solution until equilibrium was established. The ferricyanide in the electrolyte layer between gold and polymer was reduced quantitatively. From the resulting charge and the information about the wetted surface area from impedance spectroscopy, the average thickness of the electrolyte layer could be calculated. For a partially degraded film with a wetted surface area of 57% and a porosity of 2×10^{-4}, obtained from an impedance sweep, an average thickness of the electrolyte layer of 0.7 μm was calculated.

3.2. *EMAC films*

Spin coated EMAC films were found to be 19 μm thick. They degraded at pH values greater than 8.4, however, in contrast to the Eudragit S-100, the EMAC coatings did not dissolve, but remained as a film on the electrode. Figure 5 shows the impedance spectrum of an EMAC film after degradation in 1 M NaOH and after exposure to a 20 mM solution of the redox couple $[Fe(CN)_6]^{3-}/[Fe(CN)_6]^{4-}$. There was no evidence of an impedance due to a redox couple, that is, the negatively charged ions could not penetrate the polymer. Since the breakdown of the films is caused by deprotonation of the carboxyl groups this can be explained by the repulsion between negatively charged ions and carboxylate groups. Furthermore this experiment shows that no holes were formed in the EMAC films in the course of the breakdown.

To obtain information about the ion transport properties of the polymer after treatment at a high pH, investigations with the positively charged redox

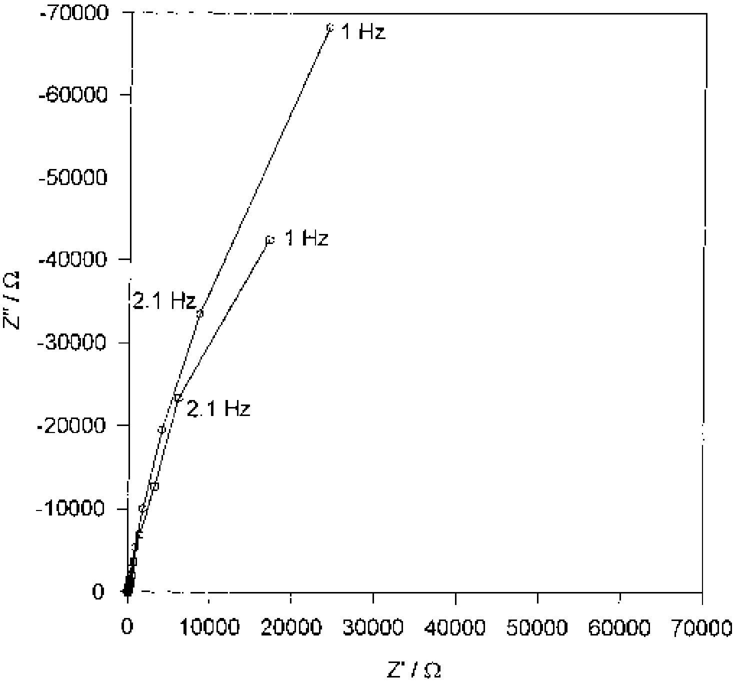

Fig. 5. Nyquist plots for EMAC coated electrodes after breakdown in 1 M NaOH. Impedance spectra were taken in 10 mM phosphate buffer pH 7.4 containing 1 M NaCl in the absence (○) and presence (□) of 20 mM $[Fe(CN)_6]^{3-/4-}$.

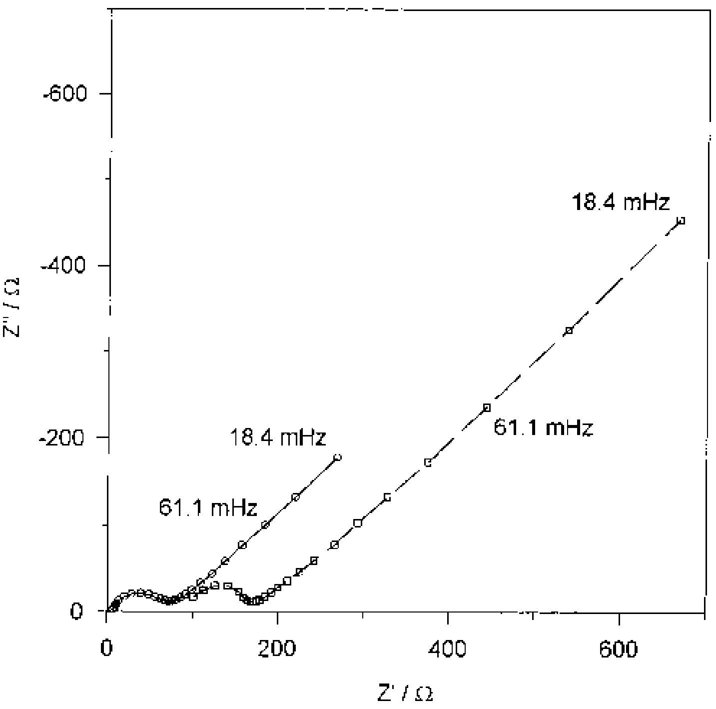

Fig. 6. Nyquist plots for a bare electrode and an EMAC coated electrode after breakdown in 1 M NaOH. Impedance spectra were taken in 20 mM $[Ru(NH_3)_6]Cl_3$ containing 1 M NaCl at the redox potentials for the bare (○) and EMAC coated (□) electrodes.

system $[Ru(NH_3)_6]^{2+}/[Ru(NH_3)_6]^{3+}$ were carried out. From cyclic voltammograms the redox potential for both a polymer coated and a bare gold electrode were determined as the median value of the peak oxidation and reduction potentials. For the EMAC coated electrode a potential of $E = -0.35$ V was obtained, while that for the bare electrode was $E = -0.20$ V The difference between these values was probably caused by the interaction between polymer and positively charged ions and shows that there was no direct contact of the electrolyte solution with the surface of the gold electrode in the case of the polymer coated electrode. Delamination as found for the Eudragit S-100 can therefore be excluded.

As described in the introduction, positively charged ions penetrate the polymer to compensate for the negative charge of the carboxylate groups. It can be expected that ions with a higher charge are bound more strongly to the polymer, i.e. the ratio of Na^+ to $[Ru(NH_3)_6]^{3+/2+}$ should be lower in the polymer than in solution. The amount of Ru(III) in the polymer layer was determined in a coulometric experiment, reducing all of the Ru(III) in the polymer after exposing it to 20 mM $[Ru(NH_3)_6]^{3+}$ containing 1 M NaCl. A concentration of 142 mM Ru(III) in the EMAC layer was obtained, which was seven fold greater than the concentration of Ru(III) in the solution.

Using a redox couple in solution for impedance measurements resulted in a Warburg impedance for an EMAC covered and a bare electrode (Fig. 6). To ensure equal concentrations of both redox partners on the surface of the electrodes, these measurements were carried out at their redox potentials. To obtain the Warburg coefficient, σ, the spectra were fitted with the model shown in Fig. 7. From the Warburg coefficient, the medium diffusion coefficient, D, was estimated using the following equation assuming equal concentrations and diffusion coefficients for $R = [Ru(NH_3)_6]^{2+}$ and $O = [Ru(NH_3)_6]^{3+}$:

$$\sigma = \frac{RT}{n^2F^2\sqrt{2}}\left[\frac{1}{c_R D_R^{1/2}} + \frac{1}{c_O D_O^{1/2}}\right]$$

The diffusion coefficienct is usually lower for cations with a higher charge. Therefore, the values obtained are expected to reflect the diffusion coefficient of $[Ru(NH_3)_6]^{3+}$ rather than $[Ru(NH_3)_6]^{2+}$. For the bare electrode a diffusion coefficient of $D = 0.2 \times 10^{-5}$ cm^2 s^{-1} was calculated, which was slightly lower than would be expected for these species. For the EMAC films a value of $D = 0.7 \times 10^{-8}$ cm^2 s^{-1} was calculated using the concentration of ruthenium ions in the polymer obtained in the coulometric measurement.

Figure 8 shows impedance spectra of an EMAC coating at different stages of breakdown. EMAC coatings initially showed good capacitive behaviour (curve (a), Fig. 8) similar to the Eudragit S-100

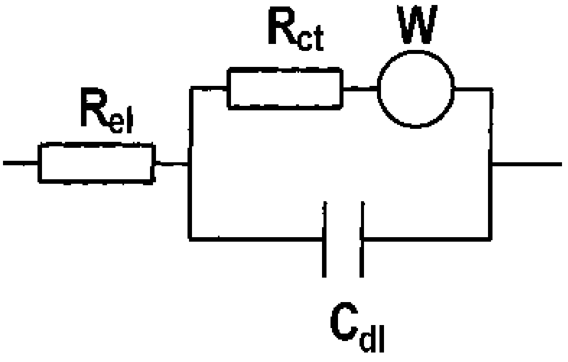

Fig. 7. Equivalent circuit: (R_{el}) electrolyte resistance (bare electrode)/bulk resistance (polymer coated electrode), (C_{dl}) double-layer capacitance, (R_{ct}) charge-transfer resistance, (W) Warburg impedance.

coatings (curve (a), Fig. 2). However, the spectra obtained at different stages of breakdown (curves (b)–(e), Fig. 8) were less clearly structured than those for Eudragit S-100 (curves (b)–(e), Fig. 2). The impedance data for partially degraded EMAC films could be fitted with the equivalent circuit shown in Fig. 1, although the impedance elements needed to be reassigned. C_g still describes the geometric capacitance of the polymer. Since the formation of pores in the film could be excluded, R_b no longer corresponds to the electrolyte in the pores, but represents a genuine bulk conductivity of the polymer due to the presence of mobile sodium ions. C_{dl} describes the double layer capacitance of the gold/polymer interface. R_{ct} was omitted because there were no redox active species in the solution or in the polymer.

Initially during the breakdown the low frequency region of the spectrum (Fig. 8, curves (b) and (c)) showed a fairly low phase angle, which approached 90 ° as the degradation of the film proceeded (Fig. 8, curves (d)–(f)). This frequency dispersion of the double layer capacitance is also indicated by the low exponent α of the CPE (Table 1), and was probably due to nonhomogeneous ion conductivity in the polymer above the electrode.

The results of the mathematical fit are given in Table 1. The relative swelling (%) of the polymer was estimated from the equation:

$$\text{swelling } (\%) = 100 \times R_b/R_{b,e}$$

where $R_{b,e}$ is the bulk resistance of an EMAC film degraded in 1 M NaOH.

A comparison between the degree of swelling and C_{dl} in Table 1 showed that initially the bulk conductivity increased over several orders of magnitude, while the value of the double layer capacitance only rose by a factor of two. Only in the last stages of the breakdown did the double layer capacitance reach the value for a bare electrode. This indicated that in contrast to the Eudragit S-100 coated electrodes, spreading of electrolyte along the surface of the gold electrode did not occur. Instead, a uniform swelling of the polymer from the surface into the depth of the film occurred without formation of pores.

To investigate whether the breakdown of EMAC was reversible, whether the polymer did not in fact dissolve as in the case of Eudragit S-100, an attempt was made to regenerate the polymer film in 1 M HCl after breakdown (Fig. 9). The Bode plots show that a partial regeneration can be achieved. The bulk resistance of the polymer increased by several orders of

Table 1. Results of mathematical fit of impedance spectra at different stages of breakdown

Spectrum	*Swelling* / %	C_{dl} /μF cm^{-2}	α (*CPE exponent*)
a	0		
b	1.5×10^{-4}	0.019	0.65
c	2.3×10^{-3}	0.026	0.64
d	0.56	0.051	0.69
e	2.4	0.37	0.84
f	100	22	0.91

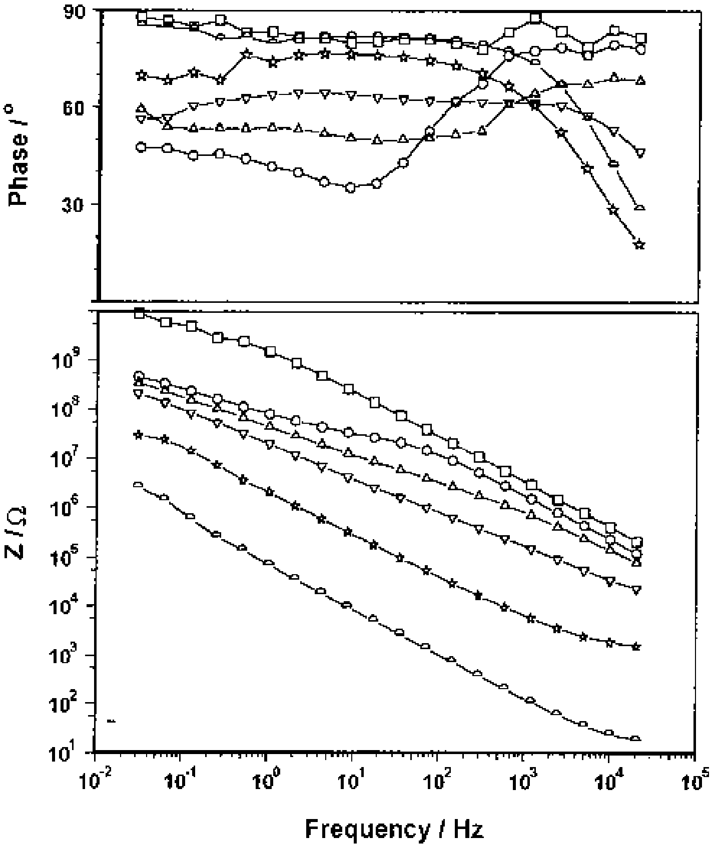

Fig. 8. Bode plots of (a) an EMAC-coated electrode prior to breakdown, (b)–(e) partially degraded EMAC films, and (f) an EMAC coated electrode after breakdown in 1 M NaOH. Key: (a) □, (b) ○, (c) △, (d) ▽, (e) ☆ and (f) ⌓ .

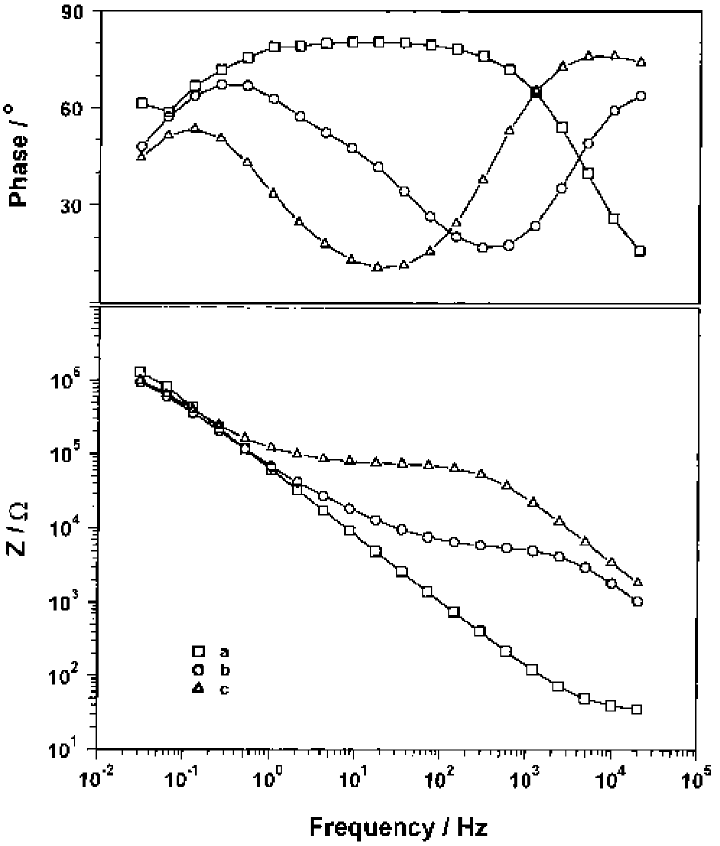

Fig. 9. Bode plots of (a) an EMAC coated electrode after breakdown in 1 M NaOH, (b) of the same electrode after 30 min in 1 M HCl and (c) after 90 min in 1 M HCl. Key: (a) □, (b) ○ and (c) △.

magnitude while the double layer capacitance in the low frequency region remained unchanged. This may have been due to the formation of a hydrophobic layer on the surface of the polymer, which trapped cations in the lower regions of the film.

4. Summary

Two different enteric coatings were characterized as a model system for the degradation of polymer coated electrodes. Although both materials have a similar chemical structure it was shown that they broke down in different ways. Employing impedance spectroscopy and other electrochemical techniques it was found that Eudragit S-100 coatings form pores and that the electrolyte, after penetrating the polymer, spreads underneath the film on the surface of the electrode. This behaviour is similar to the degradation of numerous polymers used as protective coatings.

The EMAC films did not dissolve but swelled and thus showed a much more uniform breakdown than Eudragit S-100. It was shown that only positively charged ions could penetrate the polymer as compensation for the negative charge of carboxylate groups in the bulk of the polymer. For the redox couple $[Ru(NH_3)_6]^{2+/3+}$ a mean diffusion coefficient of $D = 0.7 \times 10^{-8}\,cm^{-2}\,s^{-1}$ in the polymer was determined.

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