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RESEARCH PAPER

Characterization of Film-Coated Aerosol Canisters Using Electrochemical Impedance Spectroscopy

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ABSTRACT

Drug adhesion to the walls of an aerosol canister can be prevented/reduced by coating the canister with a hydrophobic polymer (e.g., a fluoropolymer). In this study, three batches of fluoropolymer-coated canisters were investigated by electrochemical impedance spectroscopy (EIS) and scanning electron microscopy (SEM). The EIS technique showed that only one of the batches presented as a monolithic, non-porous film. The other two batches were either partially porous or highly porous. Scanning electron micrographs showed evidence of cracks, within the films, but could not alone establish the porous nature of these defects. For the non-porous and partly porous films it was possible to use the EIS data to determine the approximate film thickness. Estimates of 2–4 μm were obtained for the mean film thickness. These values compared favorably with micrometer estimates obtained following acid dissolution of the aluminum canister. It remains to be seen whether the properties of the films (i.e., the porosity and film thickness, determined by EIS) translate to differences in drug adhesion. Nevertheless, the EIS technique was shown to be a powerful, non-destructive method that lends itself to the rapid analysis of batch-to-batch variation in film-coated canisters.

INTRODUCTION

A metered dose inhaler consists of a canister (usually manufactured from aluminum) with a metering valve attached. The drug is contained within the canister, either as a solution or suspension in some propellant or propellant mixture. In some cases the drug adheres to the walls of the canister,

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resulting in dose variability and poor therapeutic control (1). In the case of a suspension, the active ingredient has a small particle size and therefore high free energy. In the case of a solution, the evaporation of the propellant at the surface of the liquid could result in precipitation at the solution–surface interface. Both phenomena can result in the drug adhering to the inner surface of the metal canister. One solution to this problem is to coat the inner surface of the canister with a polymer film (2). However, failure of this coating may occur due to chemical heterogeneity or physical defects (e.g., surface bubbles, pinholes, or cracks) that result from inadequacies in the coating process. Electrochemical impedance spectroscopy (EIS) is a non-destructive in situ method that is suited to the characterization and/or quantification of organic films. For example, it has been shown that the integrity and long-term performance of the film are related to changes in phase angle and coating resistance (3,4).

The method is based on the application of a sinusoidal voltage to the film, over a range of frequencies. At each frequency, the analyzer measures the current passing through the film. The impedance of the film (**Z**) is then determined from the peak voltage (V_0), the peak current (I_0), and the phase difference (α) according to:

$$\mathbf{Z} = V_0/I_0(\cos\alpha + \mathrm{i}\sin\alpha) \tag{1}$$

where i is the imaginary operator. This relationship is usually represented as having a real part $[Z' = (V_0/I_0)\cos\alpha]$ and an imaginary part $[Z'' = (V_0/I_0)\sin\alpha]$. It follows that:

$$\mathbf{Z} = Z' + \mathrm{i}Z'' \tag{2}$$

The ratio V_0/I_0 is known as the magnitude (or modulus) of the impedance and is represented by $|\mathbf{Z}|$. The real and imaginary impedance can therefore be rewritten as $Z' = |\mathbf{Z}|\cos\alpha$ and $Z'' = |\mathbf{Z}|\sin\alpha$, respectively.

An impedance spectrum is generated (i.e., Z', Z'' or $|\mathbf{Z}|$, θ vs. frequency) which is then fitted to an equivalent electrical circuit that characterizes the surface-averaged physical properties of the film.

A perfect film can be defined by a homogenous polymer coating without defects (i.e., cracks, pinholes, bubbles, or under-film deposits). The electrical model for a perfect film is a capacitor (corresponding to the non-conductive or dielectric properties of the film) in parallel with a resistor that models the film resistance. This circuit is in series with a resistor that models the resistance of the solution between the film and measurement electrode. Producing a perfect film is, in practice, difficult to achieve and the outcome of a coating process is usually an uneven film (Fig. 1a). The electrical model for this type of film consists of a constant phase element (CPE) in parallel with a resistor (R1): CPE defines the capacitive properties of the film; R1 characterizes the *average* film resistance. Two values (CPE-T and CPE-P) define the properties of the constant phase element: CPE-P gives the phase angle of CPE (if CPE-P = 1 then CPE is a simple capacitor, the physical significance is that if CPE diverges from 1 then the film is uneven); CPE-T represents the mean capacitance of the film and is proportional to the mean thickness of the film. An imperfect film can also present with defects (e.g., pinholes, cracks, or surface bubbles). The electrical model for an imperfect film consists of a CPE, in parallel with a resistor R1 and a Warberg impedance (W1) (Fig. 1b). The latter element accounts for diffusion processes through the defects in the film. If the coating

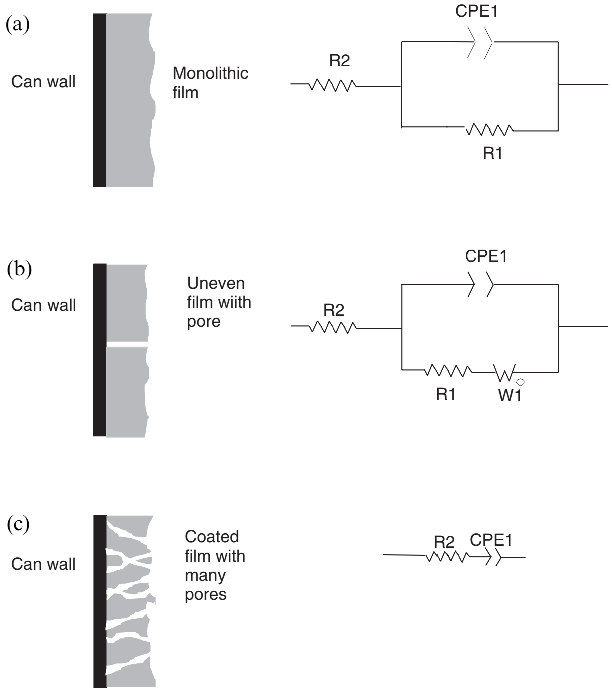

Figure 1. Schematic and electrical model of (a) an uneven coating; (b) an imperfect film (note presence of a defect and surface unevenness); (c) an imperfect film with many defects.

contains many defects then the impedance may be dominated by a diffusion impedance (Fig. 1c).

The aim of this study was to use EIS to determine the quality of three batches of fluoropolymer-coated canisters. The data was compared with scanning electron microscope (SEM) images of regions of film, in order to clarify some of the observations made by EIS, in particular the apparent existence of diffusion pathways through the film.

MATERIALS AND METHODS

Aluminum cans of volume 11.5 mL were coated with a fluoropolymer by spray coating from an aqueous solution, according to a proprietary method. A Solartron 1287/1260 electrochemical impedance analyzer was connected to a three-electrode system (Fig. 2) and used to measure the impedance of the films of three batches of canisters. A 0.1 M potassium chloride solution was used as the fill solution. (The height of the liquid inside the canister defined the surface area measured by EIS.)

Impedance spectra (in the frequency range 0.1–100 kHz) were generated under computer control, using commercial software (Zplot^{TM}). The amplitude of the applied voltage was 100 mV, auto-integration was set to V1-long and the integration cycle set to 50. Three measurements were taken by positioning the RE1 electrode approximately halfway from the base of the canisters, at an angle of 120° to one another. Three cans from each batch were measured. The spectra were displayed as Nyquist plots (imaginary impedance Z'' vs. real impedance Z') and Bode plots (impedance magnitude and phase angle vs. frequency).

Scanning electron micrographs were obtained on sections of wall ($6 \times 6\,\text{mm}^2$) cut from each canister.

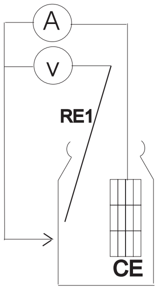

Figure 2. Three-electrode system: CE, WE/RE2 and RE1 are counter electrode (platinum gauze), working electrode, and reference electrode 1 (Ag/AgCl), respectively.

RESULTS AND DISCUSSION

Spectra were analyzed using commercial software (Zview^{TM}). This program is capable of fitting various standard functions to complex impedance data (see Figs. 3–5 for representative spectra from each batch). Three electrical models were sufficient to characterize all data sets. The three models are described in the Introduction and are used to define three film types. Estimates for electrical parameters characterizing the physical properties of the films are given in Table 1.

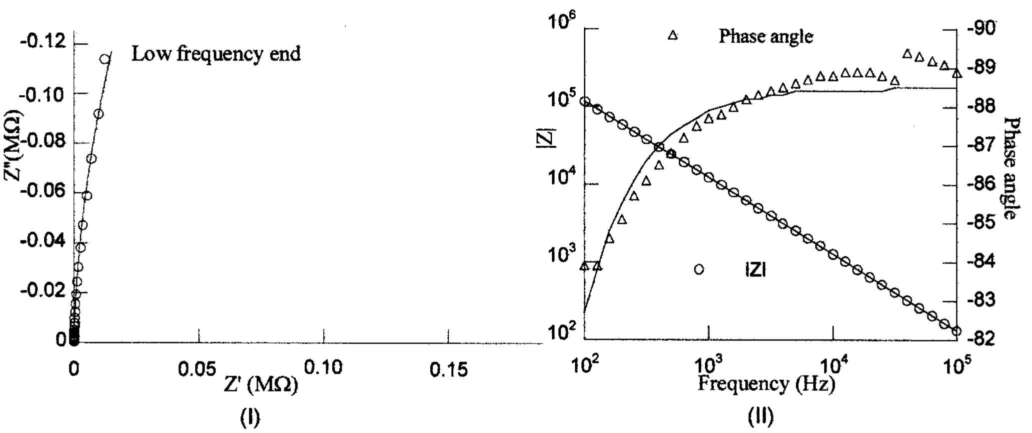

Figure 3. (I) Nyquist plot ($-Z''$ vs. Z') for film type 1. (II) Bode plot showing changes in phase angle and impedance magnitude ($|\mathbf{Z}|$) as a function of frequency.

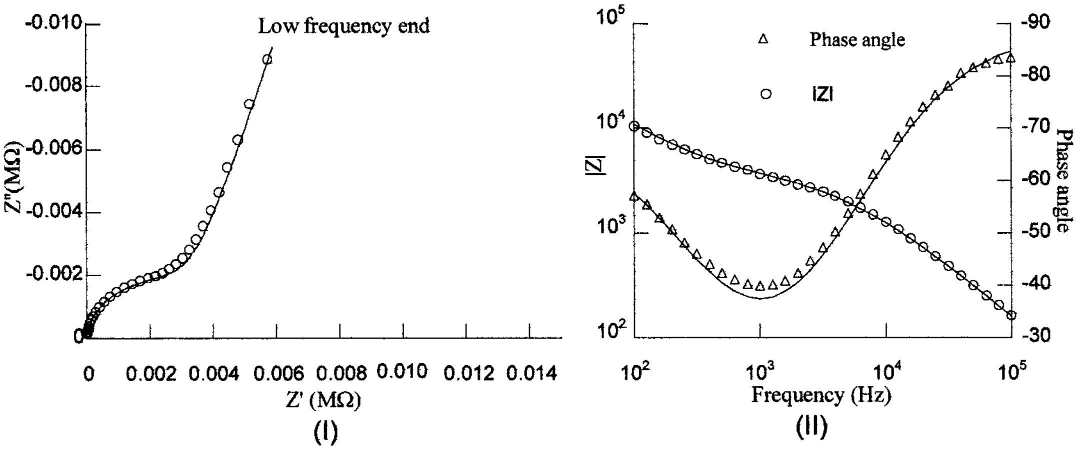

Figure 4. (I) Nyquist plot ($-Z''$ vs. Z') for film type 2. (II) Bode plot showing changes in phase angle and impedance magnitude (|**Z**|) as a function of frequency.

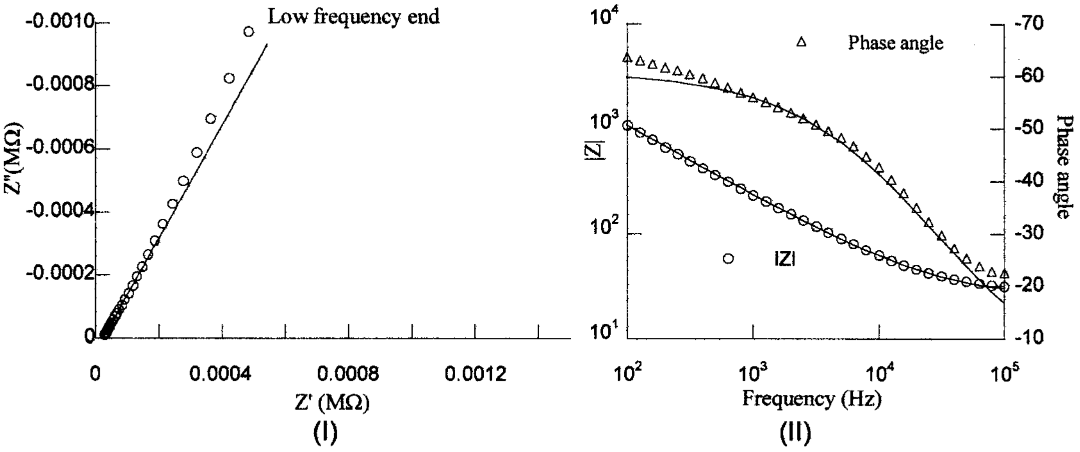

Figure 5. (I) Nyquist plot ($-Z''$ vs. Z') for film type 3. (II) Bode plot showing changes in phase angle and impedance magnitude (|**Z**|) as a function of frequency.

Table 1

*Averaged Values (*n = 9*) for the Impedance Elements Characterizing the Physical Properties of Film Types 1–3. The Parameters CPE-T, CPE-P, R1, and Warberg Are Described in the Text*

Type	CPE1-T (nF)	CPE1-P	R1	Warberg
1	14 ± 1.1	0.99 ± 0.01	1.25 ± 0.88 MΩ	No
2	22 ± 8	0.95 ± 0.02	0.95 ± 0.70 kΩ	Yes
3	4.5 ± 3.6	0.73 ± 0.08	20 ± 7 Ω	Yes

Film type 1 had a consistently high film resistance (1.25 ± 0.88 MΩ) with no evidence of porosity (see Fig. 1a for the model and Fig. 3 for example data). There was a measurable, mean film capacitance (14.0 ± 1.1 nF) and the film was uniform (as evidenced by the high value for CPE-P, i.e. 0.99 ± 0.01). Film type 2 had a much lower resistance and showed evidence of porosity (see Fig. 1b for the model and Fig. 4 for example data). Values for the mean film capacitance were more variable than for type 1. Furthermore, values for CPE-P were lower than those for type 1 (CPE-P = 0.95 ± 0.02).

Together, these data indicate that the film type 2 was thinner and less uniform than type 1, and was partially porous. Film type 3 was different again. The impedance spectra of film type 3 were dominated by diffusion effects, and therefore it was concluded that these films were highly porous (see Fig. 1c for the model and Fig. 5 for example data). This porosity prevented any estimate of the film thickness.

For film types 2 and 3, the impedance models provided estimates for the average film resistance (R1) and average film capacitance (CPE-T). A reasonable estimation of the dielectric constant of the film was available, and therefore it is reasonable to determine the thickness of the film from:

$$d = \frac{\varepsilon \varepsilon_0 A}{C} \tag{3}$$

where: d is the thickness of the film (m); ε_0 is the permittivity of free space ($8.854\,\mathrm{pF\,m^{-1}}$); ε is the film dielectric constant (fluoropolymers commonly have dielectric constants between two and five and therefore in this work the film dielectric constant was assumed to equal three); A is the area of the film, probed by the reference electrode, equal to the area submerged by the potassium chloride solution (in this work $A \cong 2 \times 10^{-3}\,\mathrm{m^2}$); C is the mean capacitance of the film, i.e., CPE-T (F). Film dimensions estimated from Eq. (3) are given in Table 2.

Scanning electron micrographs are shown at two magnifications (Figs. 6–8). The lowest magnification showed the distribution of large deposits of excess fluoropolymer, whereas the higher magnification showed the fine structure of the film itself. At the high magnification (Figs. 6B, 7B, and 8B) each film appeared to show fine cracks. The cracks in film types 2 and 3 appeared to be slightly more pronounced than those observed in film type 1. This data may support the EIS data by indicating that

Table 2

Estimated Film Thickness (n = 9)

	Film Thickness (µm)	
Batch	Mean	Range
Type 1	3.8	3.5–4.1
Type 2	2.8	1.8–3.8
Type 3	Indeterminable	Indeterminable

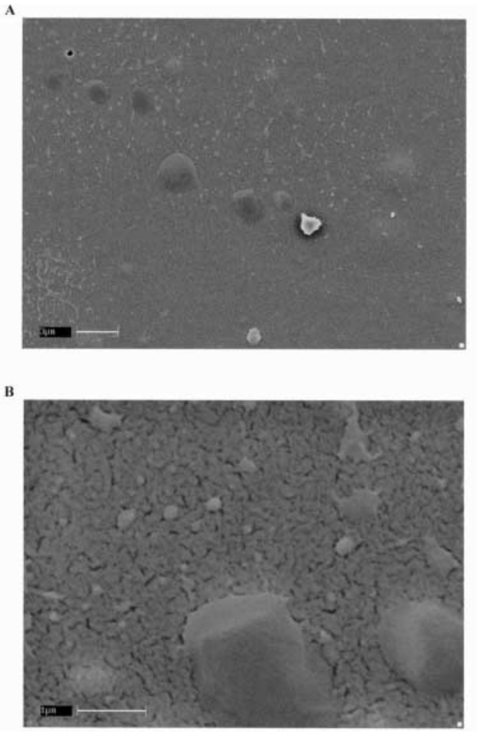

Figure 6. Scanning electron micrographs for film type 1.

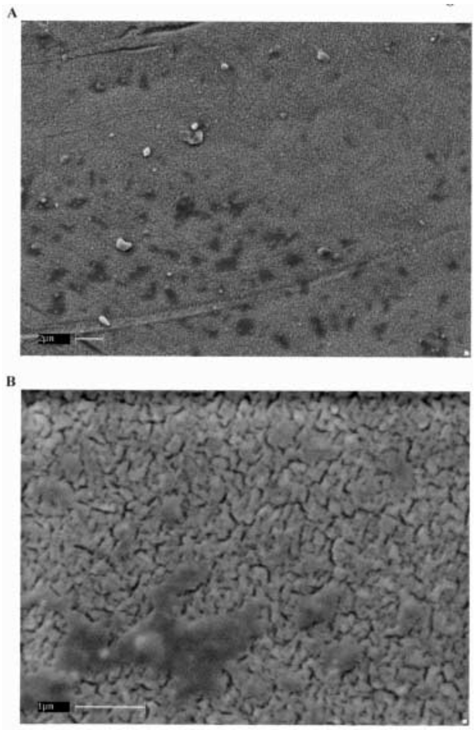

Figure 7. Scanning electron micrographs for film type 2.

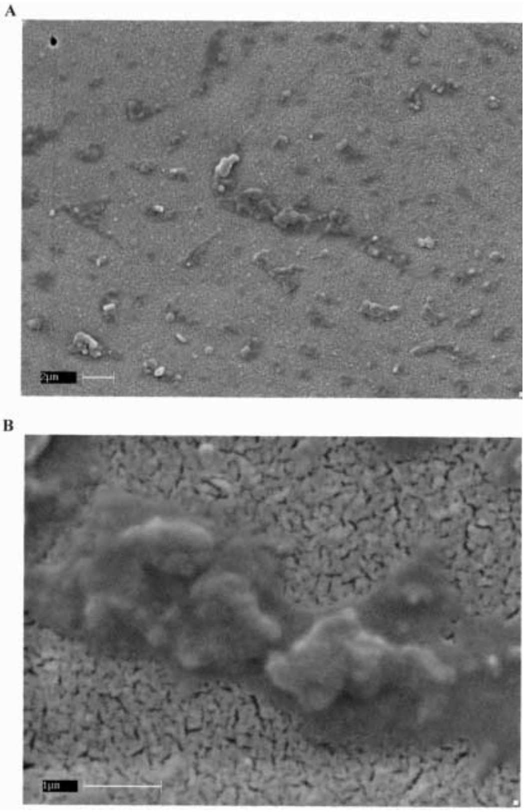

Figure 8. Scanning electron micrographs for film type 3.

the porosity of the films was associated with the fine cracks on the SEM images.

In summary, type 1 presented evidence of a monolithic thin film of high resistance and micrometer dimensions. Type 2 presented evidence of a porous thin film, also of micrometer dimensions. Type 3 presented as a highly porous film. The thickness of this type of film was indeterminable using EIS. If these measurements were to be used to evaluate film quality then a rank order for film integrity would be type 1 > type 2 > type 3.

CONCLUSION

Electrochemical impedance spectroscopy has been shown to be highly discriminating in the differentiation of different batches of film-coated canisters. The technique was capable of measuring film porosity that was thought to be associated with the thin cracks observed in scanning electron micrographs of the films. Three distinct classifications of film were observed that could be ranked into order of film quality. However, it remains to be seen whether any of these features correlate with the performance of the film in preventing drug deposition.

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