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Short Communication

Influence of ageing process on the low-frequency electrical impedance behaviour of 5% dipirone syrup and 5% sodium picosulphate solution

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ABSTRACT

The influence of the ageing process on the low-frequency behaviour of some electrical parameters of 5 percent dipirone syrup and 5 percent sodium picosulphate solution is studied. The impedance measurements were performed in the range between 0.05 kHz and 1 MHz, using the HP 16452 cell for liquids connected to the HP 4284A impedance analyzer. The electrode separation was changed with spacers of different thickness provided by the manufacturer in order to correct the effect of the electrode polarization on the experimental results. The drug ageing state was artificially generated by dilution or heating processes. The results show that the dielectric technique can be used as a good quality complementary control for evaluation of the ageing.

KEYWORDS: ageing, dipirone syrup, sodium picosulphate solution, impedance spectroscopy, permittivity

INTRODUCTION

Low-frequency impedance spectroscopy is a non-invasive and powerful real-time technique used for characterizing and detecting the properties of a variety of materials, including pharmaceutical drugs and online industrial processes [1, 2, 3, 4]. This technique allows getting a better understanding of the physical properties such as structure, hardness and moisture content of these materials, and changes associated with the ageing phenomenon [5, 6, 7]. Many drugs undergo degradation in time by the action of different agents: ultraviolet radiation, heat, humidity, chemical reactions, etc. [8, 9, 10]. Generally, this degradation process leads to a decrease in the concentration of the active principle. Impedance or dielectric spectroscopy [11, 12] is nowadays considered a good method for determining the structure and properties of drugs, since the electrical polarization of a material produced by an external electric field is very sensitive to variations in molecular structure, surface and/or volume charge density, water content, etc. [13].

In this work the low frequency impedance spectroscopy is applied to detect changes in frequency of the electrical impedance parameters due to the influence of the ageing process. The dielectric behaviour of a material is described by the complex generalized permittivity:

$$\varepsilon(\omega) = \varepsilon'(\omega) - i\,\varepsilon''(\omega) - i\,\sigma_0 / \varepsilon_0\,\omega \qquad (1)$$

or by the complex generalized conductivity:

$$\sigma(\omega) = \sigma_0 + i\,\omega\,\varepsilon_0\,\varepsilon(\omega) \qquad (2)$$

where $\varepsilon'(\omega)$ and $\varepsilon''(\omega)$ are the real and the imaginary components of the complex permittivity,

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σ_0 is the direct current conductivity, $\varepsilon_0 = 8.85 \times 10^{-12}$ C^2/Nm^2 is the free space permittivity, $i = \sqrt{(-1)}$, and $\omega = 2\pi f$ with f the frequency of the applied field. The impedance Z_c of the cell filled with the material can be described by a series combination of the sample impedance, Z_s, the electrodes polarization impedance, Z_e, and the parasitic cell impedance, Z_p. Only the impedance Z_s is directly dependent on the electrodes separation, *d*, whereas all other impedances are frequency dependent [8]. The Z_c impedance is given by the following expression:

$$Z_c = Z_s + Z_e + Z_p = \left[\frac{d}{\sigma(1 + i\omega\varepsilon_0\varepsilon/\sigma)A}\right] + 2[(r_e - i/\omega c_e)A] + Zp \tag{3}$$

where *A* is the electrode area, *d* the spacing between electrodes, r_e is the electrode polarization resistance and c_e is the electrode polarization capacitance, both by unit area [14, 15].

Two processes have been applied to get the ageing state of the pharmaceutical drugs [16, 17]: a) thermal, which may produce a decrease in the water content as well as structural changes and b) dilution, which tends to increase the water content. Both procedures lead to variation of the main drug concentration. Measurements of the electrical impedance parameters in the frequency range from 0.05 kHz up to 1 MHz were performed for detecting the influence of the ageing process on the impedance electrical parameters and hence on the dielectric properties of drugs.

MATERIALS AND METHODS

The 5 percent dipirone syrup is an analgesic, antipyretic and spasmolytic substance and was prepared by dissolving 5 g of dipirone (Saporitti fractionator, batch 510066, origin India), $C_{13}H_{16}N_3O_4SNa$, in 100 ml of simple syrup. The aged syrup has been obtained either by the addition of distilled water in percentages of 10, 25 and 50 of the syrup volume or by heating the original syrup at 56 °C and 90 °C for 4 and 5 hours, respectively.

The 5 percent sodium picosulphate solution is a laxative stimulating bowel mucosa and was prepared by dissolving 5 g of sodium picosulphate (Saporitti fractionator, batch 040707, origin China) and $C_{18}H_{13}NNa_2O_8S_2$, in 100 ml of sterile distilled water. The aged state was achieved by adding distilled water in percentages of 10, 25 and 50 of the volume of the original formula, respectively.

The electrical impedance measurements were performed at room temperature (25 °C) using the Hewlett-Packard cell HP 16452A, with nickel-plated cobalt plane parallel electrodes of 38 ± 0.05 mm diameter, connected to the Hewlett-Packard 4284A impedance analyser. The electrode separation was changed by combining different spacers whose thickness is given with an accuracy of 10 μm. This procedure permits to minimize the influence of the electrode polarization phenomenon on the data processing. Measurements of the following pairs of electrical parameters (Cp, D), (Z, Θ) and (G, B) were performed at electrode separations of 0.5, 1.0 and 2.0 mm, respectively. The short and open correction procedures were done before the cell, filled with the sample, was connected to the analyser [18]. The short impedance and open admittance values led to direct identification of the measured impedance, Z_m, with the cell impedance, Z_c.

The measured values of the electrical parameters were averaged by minimum square fitting from a series of ten measurements for each electrode separation by working with the analyser in the average mode.

RESULTS AND DISCUSSION

Temperatures for aging the dipirone syrup were chosen such that one of them is higher than the normal body temperature and the other is lower than the boiling point of water. A temperature of 56 °C can be reached when the product is stored inadequately. Figures 1 and 2 show, for both substances, the linear dependence of the impedance Z on the electrode separation, *d*, according to equation (3) as well as the slope variations associated to the original and aged states. The electrical resistance R also changes strongly with dilution since the conductivity probably increases due to the contribution of the added water in the whole range of frequency (Figures 3 and 4).

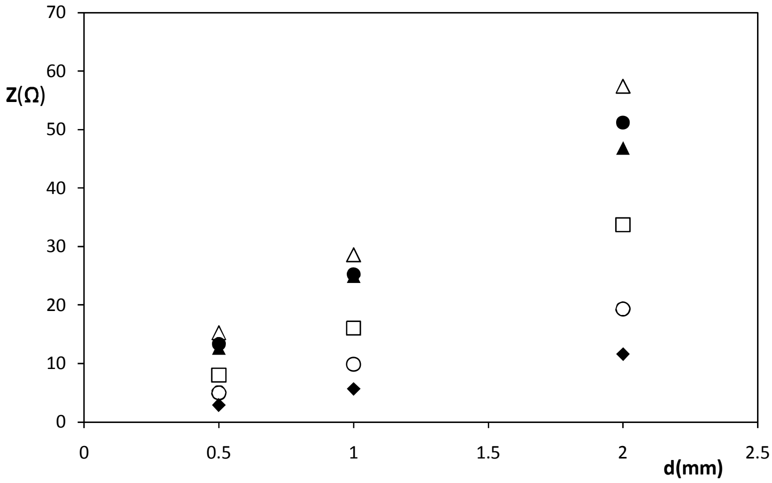

Figure 1. Z(Ω) vs. d(mm) for 5% dipirone syrup at 100 kHz : ▲original, □10%, ○25%, ♦50%, in dilution, ●56 °C and Δ90 °C.

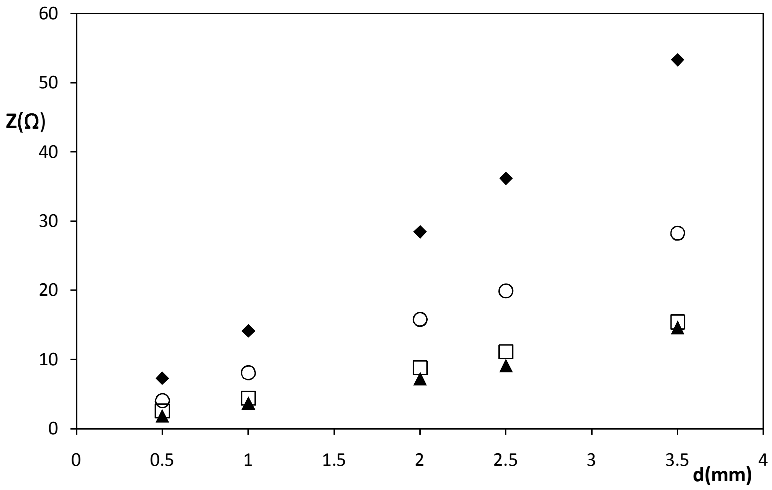

Figure 2. Z(Ω) vs. d(mm) for 5% sodium picosulphate at 100 kHz : ▲original, □10%, ○25%, and ♦50%, in dilution.

Instead, thermal ageing seems to produce a decrease in the conductivity as can also be seen in Figure 3 for the dipirone syrup. Both substances do not show variations of reactance, X, neither by dilution or by heating as shown in Figures 5 and 6. This seems to indicate that non-structural changes are produced by dilution or thermal ageing and consequently changes of the electrical polarization are not observed in the range of frequency studied. It is important to note that despite the fact that Z depends linearly on the volume of both substances, its changes do not depend linearly on the percent of additional distilled water volume (Figures 7 and 8).

Since the values of the real, ε', and imaginary, ε", components of permittivity are very high for low frequencies, a representation of the variation of the decimal logarithm of these values, which are determined by the following expressions, was preferred:

$$\varepsilon' = C/C_o \quad \text{and} \quad D = \varepsilon''/\varepsilon' \qquad (4)$$

where Co is the capacity without medium and D, the loss factor [12]. In Figures 9 to 12 the variation in frequency of these magnitudes for all cases can be seen. The changes of Log(ε') (Figures 9 and 10) are small due to the ageing phenomenon and exhibit the same characteristics of the reactance X in relation to the dilution and thermal effects for both drugs. The Log(ε") changes are more important and seem to indicate the existence of one relaxation process near the 100 Hz without variation due to dilution and a slight displacement due to thermal ageing for the 5% dipirone syrup (Figure 11).

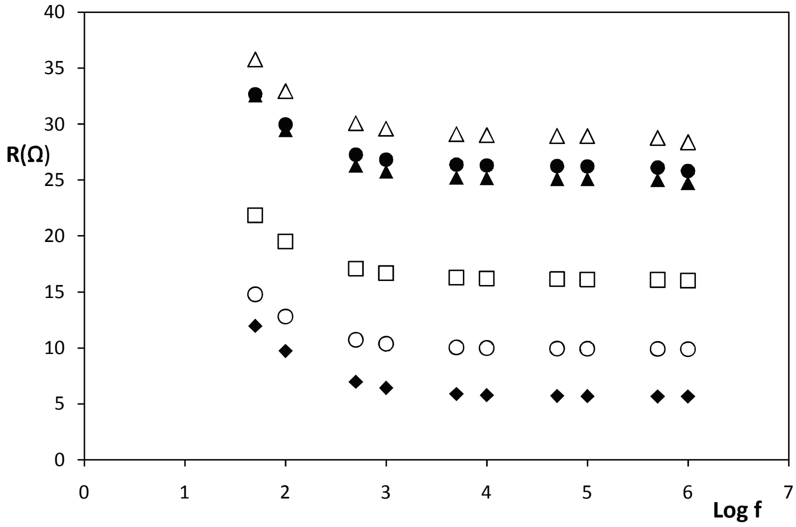

Figure 3. R(Ω) vs. Log f for 5% dipirone syrup at 100 kHz : ▲original, □10%, ○25%, ♦50%, in dilution, ●56 °C and Δ90 °C.

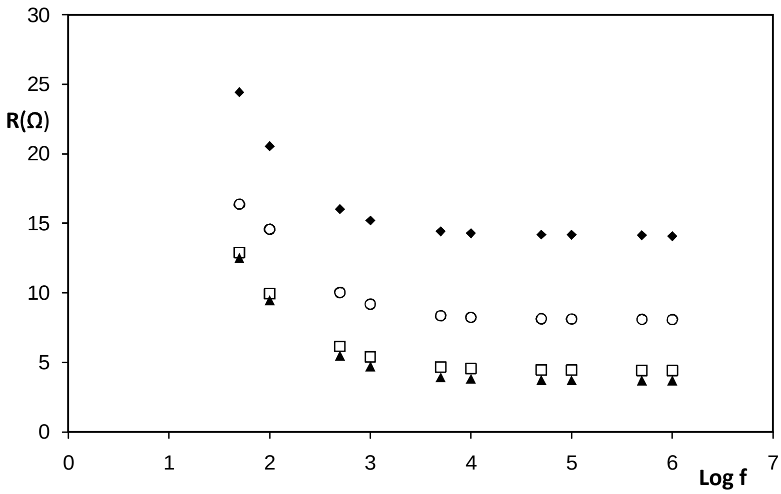

Figure 4. R(Ω) vs. Log f for 5% sodium picosulphate at 100 kHz : ▲original, □10%, ○25%, and ♦50%, in dilution.

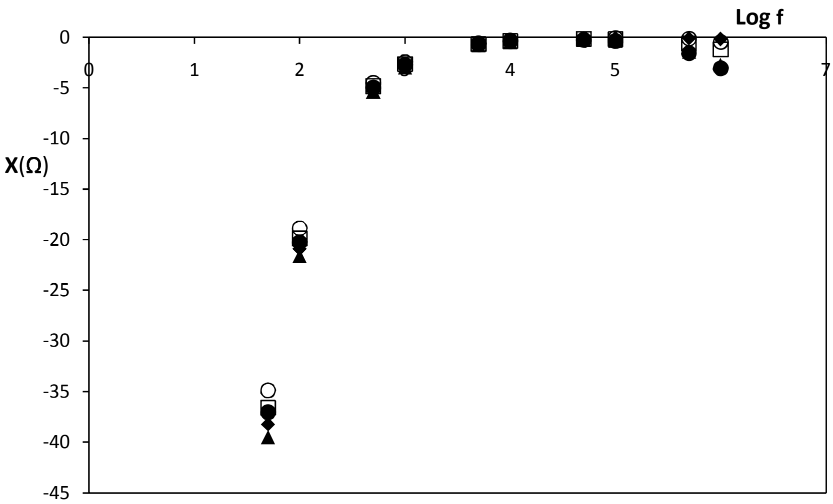

Figure 5. X(Ω) vs. Log f for 5% dipirone syrup at 100 kHz : ▲original, □10%, ○25%, ♦50%, in dilution, ●56 °C and Δ90 °C.

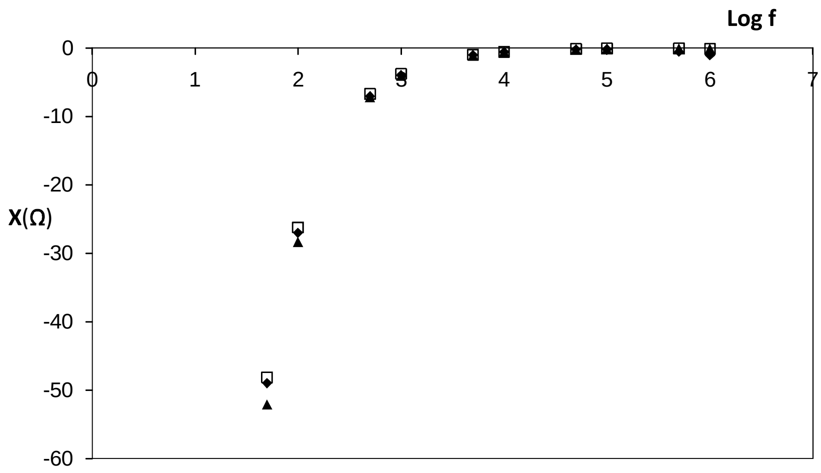

Figure 6. X(Ω) vs. Log f for 5% sodium picosulphate at 100 kHz : ▲original, □10%, ○25%, and ♦50%, in dilution.

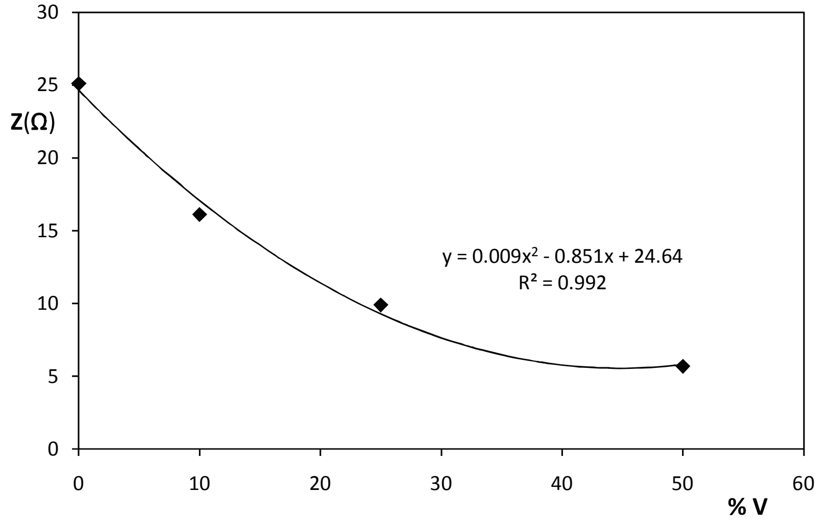

Figure 7. Z(Ω) vs. % V in dilution for 5% dipirone syrup at 100 kHz and *d* = 1 mm.

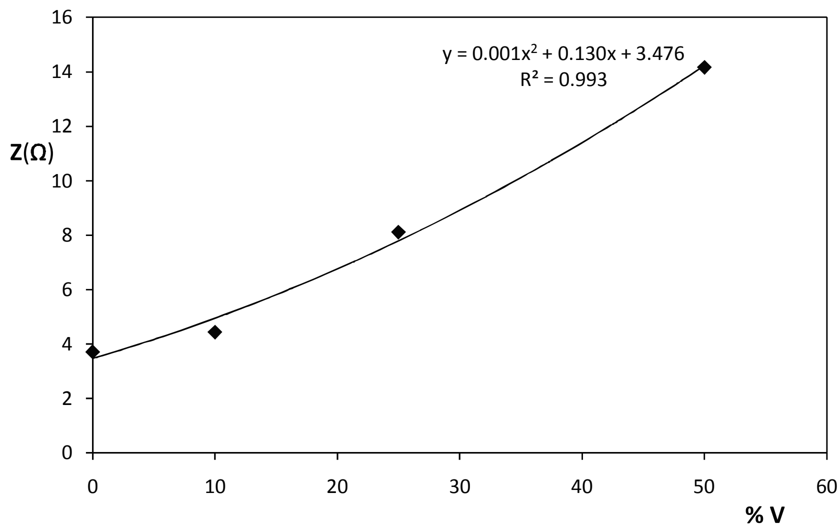

Figure 8. Z(Ω) vs. % V in dilution for 5% sodium picosulphate at 100 kHz and *d* = 1 mm.

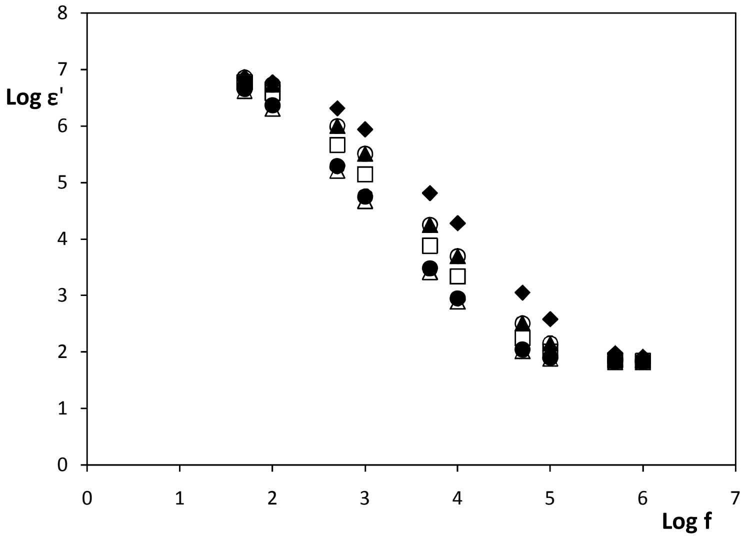

Figure 9. Log ε' vs. Log f for 5% dipirone syrup at d = 1 mm : ▲original, □10%, ○25%, ♦50%, in dilution, ●56 °C and Δ90 °C.

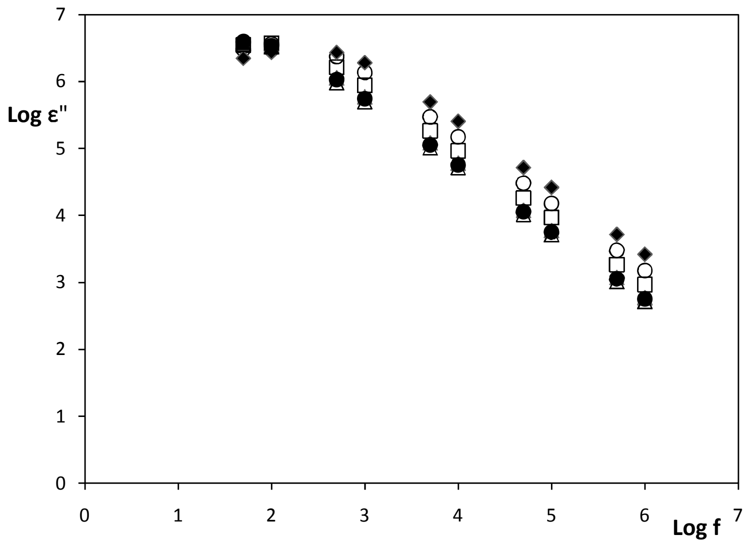

Figure 10. Log ε" vs. Log f for 5% dipirone syrup at d = 1 mm : ▲original, □10%, ○25%, ♦50%, in dilution, ●56 °C and Δ90 °C.

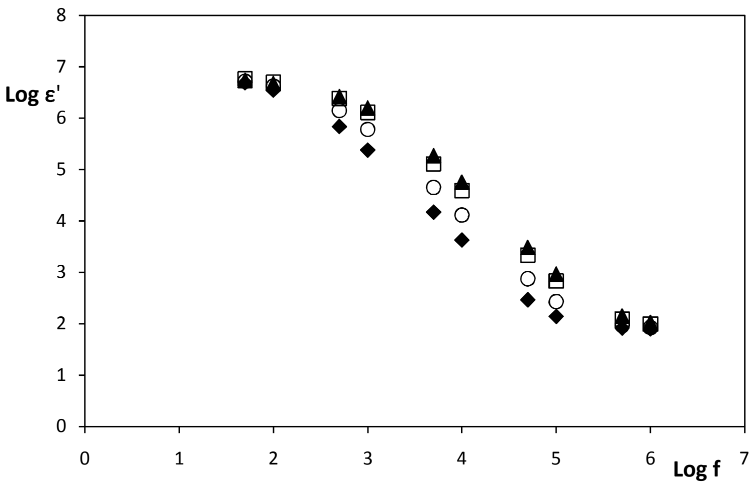

Figure 11. Log ε' vs. Log f for 5% sodium picosulphate solution at d = 1 mm : ▲original, □10%, ○25%, and ♦50%, in dilution.

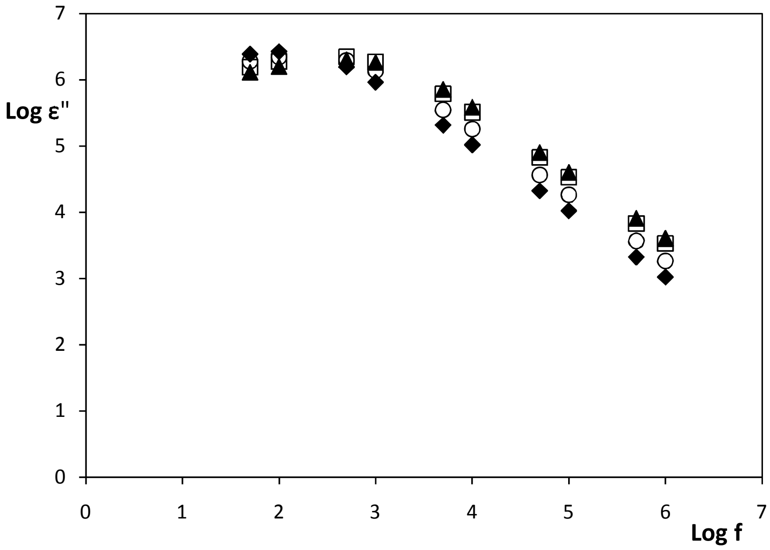

Figure 12. Log ε" vs. Log f for 5% sodium picosulphate solution at d = 1 mm : ▲original, □10%, ○25%, and ♦50%, in dilution.

The same behavior is noted for 5% sodium picosulphate solution, Figure 12, but a small displacement of the loss peak towards a minor frequency due to dilution is observed. Probably, the relaxation process is due to the existence of the electrode barrier in both cases.

CONCLUSION

Although the processes of ageing-simulation applied do not fully describe the aged drug state, it permits to show that the low frequency impedance technique could be used as quality control to analyse and characterize pharmaceutical substances, since the variation of the electrical parameters can be easily detected. Permittivity and conductivity values could also be obtained by combining either impedance and capacitance slopes or resistance and reactance slopes [14].

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CONFLICT OF INTEREST STATEMENT

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript. All the funding sources for this study are mentioned in the acknowledgement section of the paper.

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