Influence of the Ageing Phenomenon on the Low-Frequency Electrical Impedance Behavior of Naphazoline Hydrochloride Solutions and Paracetamol Syrup

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ABSTRACT: The influence of the ageing process on the low frequency behavior of some electrical parameters of naphazoline hydrochloride solutions at 0.5% and 1% in concentration and of 2% paracetamol syrup, is studied. The impedance measurements were performed, in the range between 200 Hz and 1 MHz, using an impedance analyzer and a cell for liquids with plane parallel electrodes whose separation can be changed by using a set of spacers, provided by the manufacturer, in order to get better control of the influence of electrodes polarization effect. The ageing state was artificially generated by dilution and/or heating separated procedures. The results show that this dielectric technique can be used as a good quality complementary control technique. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 98:1845–1851, 2009

Keywords: spectroscopy; drug delivery; suspensions; material science; nasal drug delivery; physical characterization; stability

INTRODUCTION

Low-frequency impedance spectroscopy is a non-invasive and powerful real-time technique used as a method for characterizing and detecting pharmaceutical products and on-lines industrial processes.[1,2] This technique allows to get a better understanding of the physical properties of these materials (structure, hardness, and moist content) as well as of the ageing phenomena. Condition of ageing of a pharmaceutical system can be achieved by (a) thermal process that possible leads to a decrease of the water content, and/or structural changes and (b) dilution procedure which tends to increase the water content. Both procedures lead to a variation of the main drug concentration. In this work, the ageing phenomenon has been artificially produced by both methods. In the case of naphazoline hydrochloride solution it has been reached by adding distilled water and also by heating it for three hours. Ageing of the paracetamol (*p*-acetaminophenol) syrup was produced only by the heating procedure. Measurements of the electrical impedance in the frequency range up to 1 MHz, have been performed in order to determine the usefulness of the impedance technique[3–5] for

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detecting the influence of the ageing process on the dielectric properties of these products due to changes in active principle concentration.

MATERIALS AND METHODS

The naphazoline hydrochloride, $2(CH_6)CH_2N_2H$, is a well-known adrenergic (vasoconstrictor) decongestant substance.[6,7] Solutions were prepared by dissolving 5 and 10 g, respectively, of naphazoline hydrochloride (Roux–Ocefa) in 1000 ml of distilled water. The corresponding aged solutions were obtained by two different procedures: (1) adding distilled water up to 50% in volume and (2) heating the original pharmaceutical solutions up to 56°C during 3 h.

The paracetamol syrup was prepared by dissolving 2 g of paracetamol (Raffo) soluble in water and alcohol, in 100 ml of a viscous solution which contains 85% of sugar dissolved in distilled water. The preservative used was methyl parabens nipagin. In this case, the aged syrup was obtained by heating at 56°C during 3 h.

The electrical measurements were performed using the Hewlett-Packard 4284 A Impedance Analyzer and the Hewlett-Packard cell, HP 16452A, with nickel plane parallel electrodes whose separation can be changed by using the set of spacers provided by the manufacturer. This permits to get a better control of the influence of the electrode polarization phenomenon in the data treatment. The electrode diameter is 38 ± 0.05 mm and the maximum separation between cell electrodes can reach up to 4.5 mm by combining the different spacers which thickness are given with an accuracy of 10 μm. Measurements were performed at electrode separations of 0.5, 1.0, and 2.0 mm, respectively, in the frequency range between 200 Hz and 1 MHz for naphazoline hydrochloride and between 1 kHz and 1 MHz for syrup solutions. All measurements were performed at room temperature (20.5°C). The short and open correction procedures recommended by the manufacturer were done before the cell, filled with the sample, was connected to the analyzer. The correction impedance and admittance values lead to identify the measured impedance, Z, with the cell impedance, Z_c.

The cell impedance Z_c can be represented by a series combination of the sample impedance Z_s, and electrodes polarization impedance Z_e. The first impedance is directly dependent on electrodes distance d, whereas both impedances are frequency dependent. The Z_c impedance is given by the following expression:

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

where ω is the angular frequency, A is the electrode area, d is the distance between electrodes, ε and σ are the permittivity and electrical conductivity of the sample while $\varepsilon_0 = 8.85 \times 10^{-12}\ C^2/N\,m^2$ is the free space permittivity and $j = \sqrt{-1}$. r_e is the electrode polarization resistance and c_e is the electrode polarization capacitance, both by unit area. In order to obtain Eq. (1), the electrical properties of the system have been described by the generalized complex conductivity:[8–10]

$$\sigma(\omega) = \sigma(\omega) + j\omega\varepsilon_0\varepsilon(\omega) \quad (2)$$

On the other hand, the measured capacity, C_p, can be related, in the low frequency limit, with the capacity of the cell filled with the sample, C_s and the electrodes capacity, C_e, by the expression

$$\frac{1}{C_p} = \frac{1}{C_e} + \left[\frac{\omega^2\varepsilon_0\varepsilon(\omega)/\sigma(\omega)}{C_s}\right] \quad (3)$$

The measured values of Z_c and C_p, for each frequency, were averaged by Minimum Square Fitting from a series of 10 measurements for each electrode separation with the analyzer in the average mode. Expression (3) shows the difficulty in obtaining permittivity and conductivity values from C_p measurements in a direct way.

Table 1. Impedance Values Z (Ω) of Original and Aged Naphazoline Hydrochloride Solutions ($d = 2.0$ mm) at Different Frequencies

Frequency (Hz)	Z (Ω) Original		Z (Ω) Heated		Z (Ω) Diluted	
	0.05%	0.1%	0.05%	0.1%	0.05%	0.1%
200	16.38	13.22	9.73	7.29	11.03	10.27
500	8.19	6.22	4.78	4.47	5.94	4.95
800	5.93	4.32	4.28	3.98	4.81	3.64
1000	5.15	3.66	3.19	2.12	4.46	3.22
10000	2.21	1.21	2.05	1.47	3.51	1.92
50000	1.98	1.03	1.96	1.07	3.44	1.83
100000	1.95	1.01	1.96	1.02	3.43	1.81
300000	1.93	0.99	1.95	0.99	3.42	1.80
500000	1.93	0.99	1.94	0.98	3.42	1.79
800000	1.92	0.99	1.94	0.97	3.41	1.79
1000000	1.92	0.99	1.92	0.97	3.41	1.79

Table 2. Impedance Values Z (Ω) of Original and Aged 2% Paracetamol Syrups ($d = 2.0$ mm) at Different Frequencies

Frequency (Hz)	Z (Ω) Original	Z (Ω) Heated
1000	1236	1757.8
5000	1235	1756.3
10000	1235	1755.5
50000	1226	1737.4
100000	1202	1661.8
500000	807	911.3
1000000	492	512.9

RESULTS AND DISCUSSION

Many drugs, among them naphazoline hydrochloride solution and paracetamol syrup, undergo degradation in time by the action of different agents: ultraviolet radiation, heating, humidity, chemical reactions, etc. This degradation process leads to a diminution of concentration of the active principle. When the ageing is produced by warming, it is expecting that it take place accompanied by chemical reactions or breaking molecular structure processes. Then along with the diminution of the concentration of the active principle appears other products of those reactions that must be determined by chromatographic separation, for example. In this work the final ageing temperature has been chosen so that it is major than the normal corporal temperature but minor that the temperature of boiling water. This temperature can easily be reached when the product is stored in not adequate places. The experimental values are given in Tables 1 and 2 for 0.05% and 0.1% naphazoline hydrochloride solutions and paracetamol syrup, respectively. It can be observed the influence of the electrode polarization effect up to 10 kHz in the case of naphazoline solutions being stronger in the original product than in the aged one by heating or dilution. For frequencies greater than 10 kHz, the original and heated solutions show similar qualitatively and quantitatively behavior for both concentrations whereas the diluted solution shows a less diminution of the impedance values in this range of frequency being its values twice that of the original and heated solutions. These behaviors are represented in Figure 1. The impedance values in all cases show a linear dependence with the electrode distance for all frequencies as it is expected from Eq. (1). Figure 2 shows that for 1 MHz The same dependence is observed for the capacitance values but with the inverse of the electrode distance as can be seen in Figure 3 also for 1 MHz. In the whole frequency range, the regression coefficients

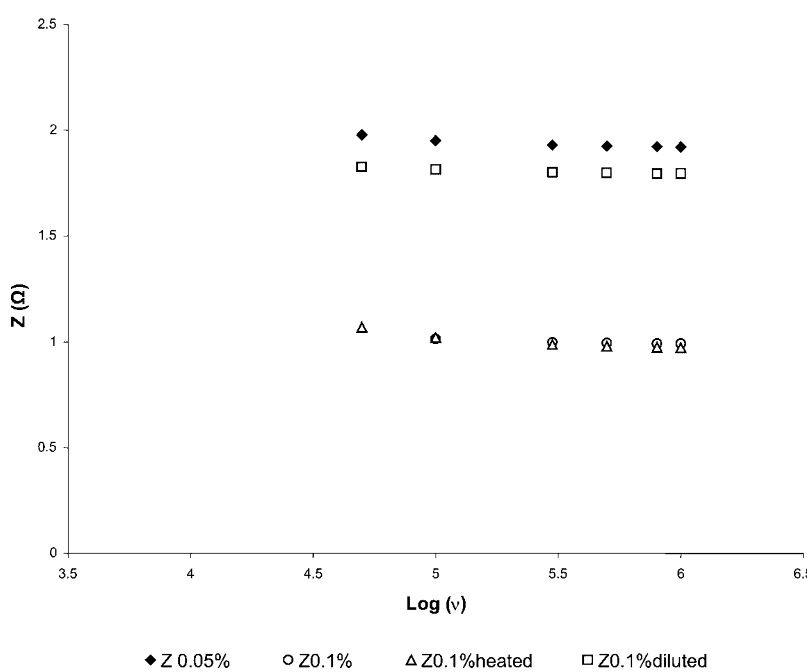

Figure 1. Impedance values, Z (Ω) versus log(ν) of the original and aged 0.1% naphazoline hydrochloride solutions together with 0.05% original solution ($d = 2.0$ mm).

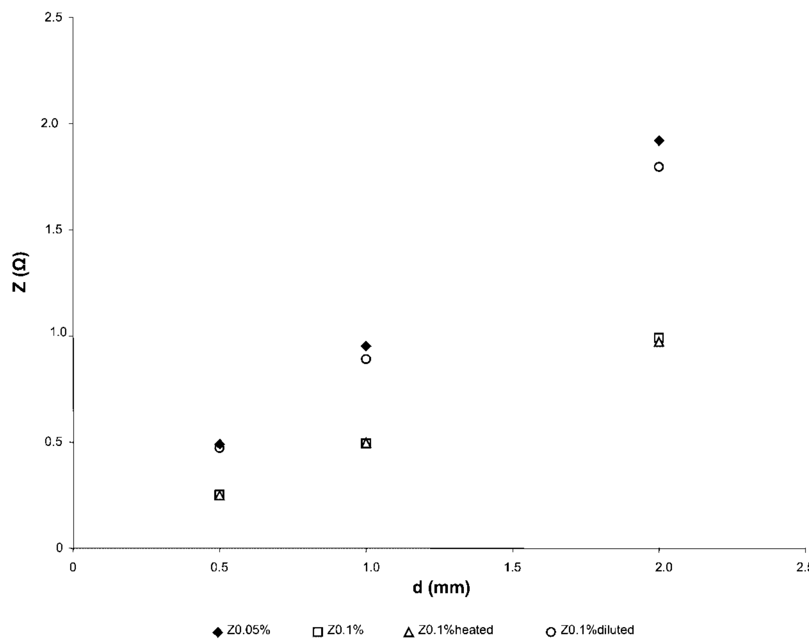

Figure 2. Impedance values, Z (Ω) versus d (mm) of the original and aged 0.1% naphazoline hydrochloride solutions together with 0.05% original solution ($\nu = 1000$ kHz).

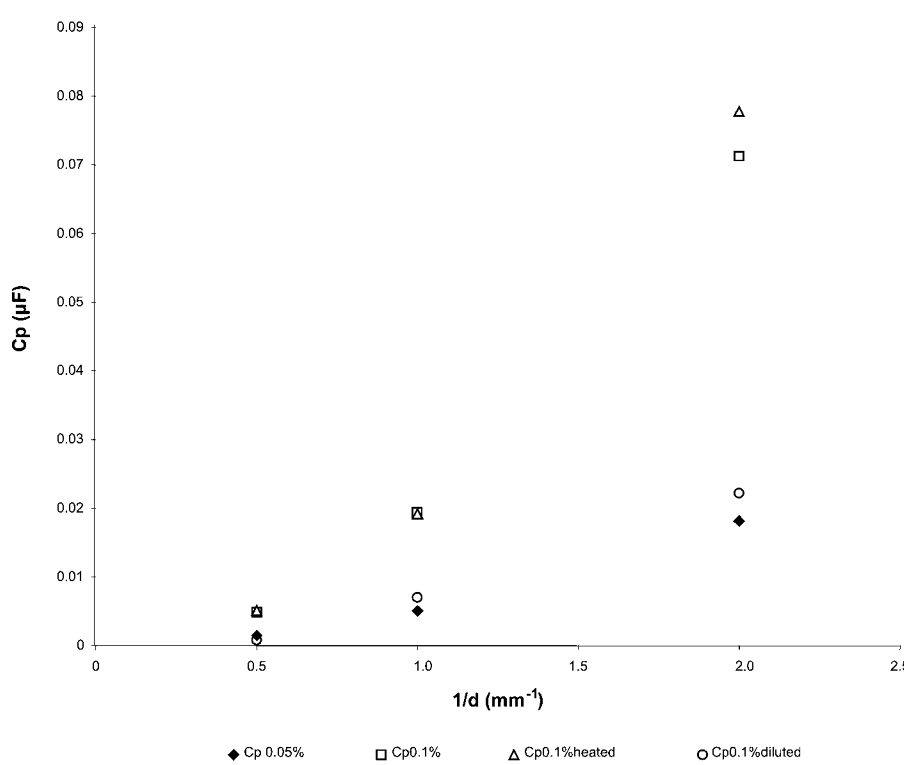

Figure 3. Capacitance values, C_p (µF) versus $1/d$ (mm^{-1}) of the original and aged 0.1% naphazoline hydrochloride solutions together with 0.05% original solution ($\nu = 1000$ kHz).

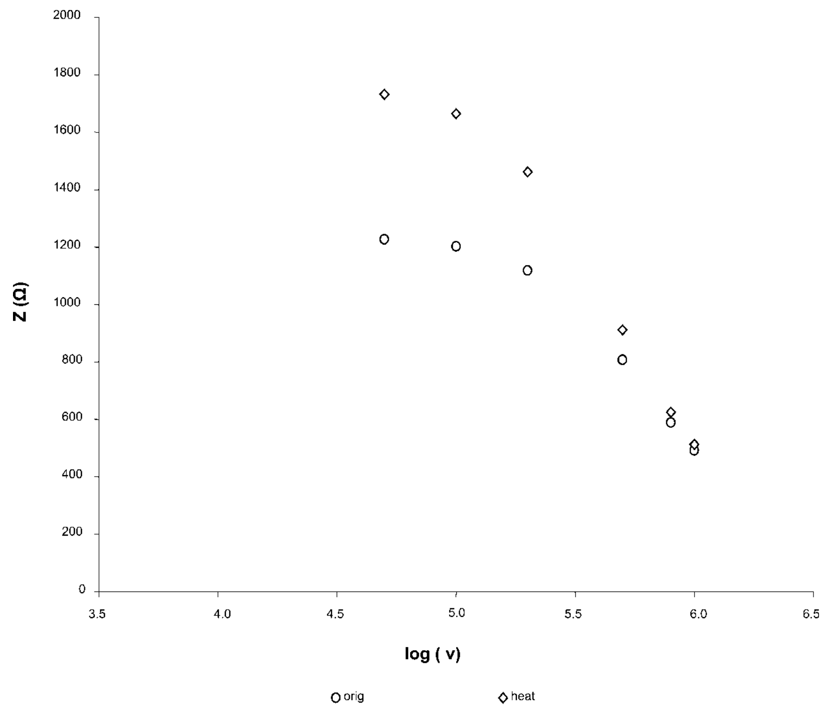

Figure 4. Impedance values, Z (Ω) versus log(ν) of original and aged paracetamol syrups ($d = 2.0$ mm).

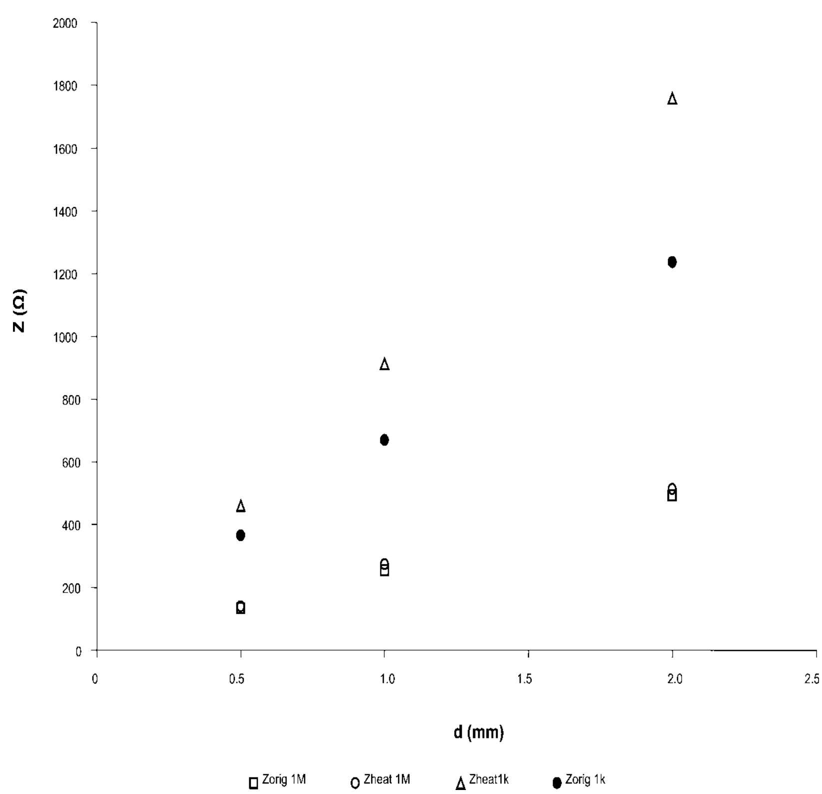

Figure 5. Impedance values, Z (Ω) versus d (mm) of original and aged paracetamol syrups ($\nu = 1$ and 1000 kHz).

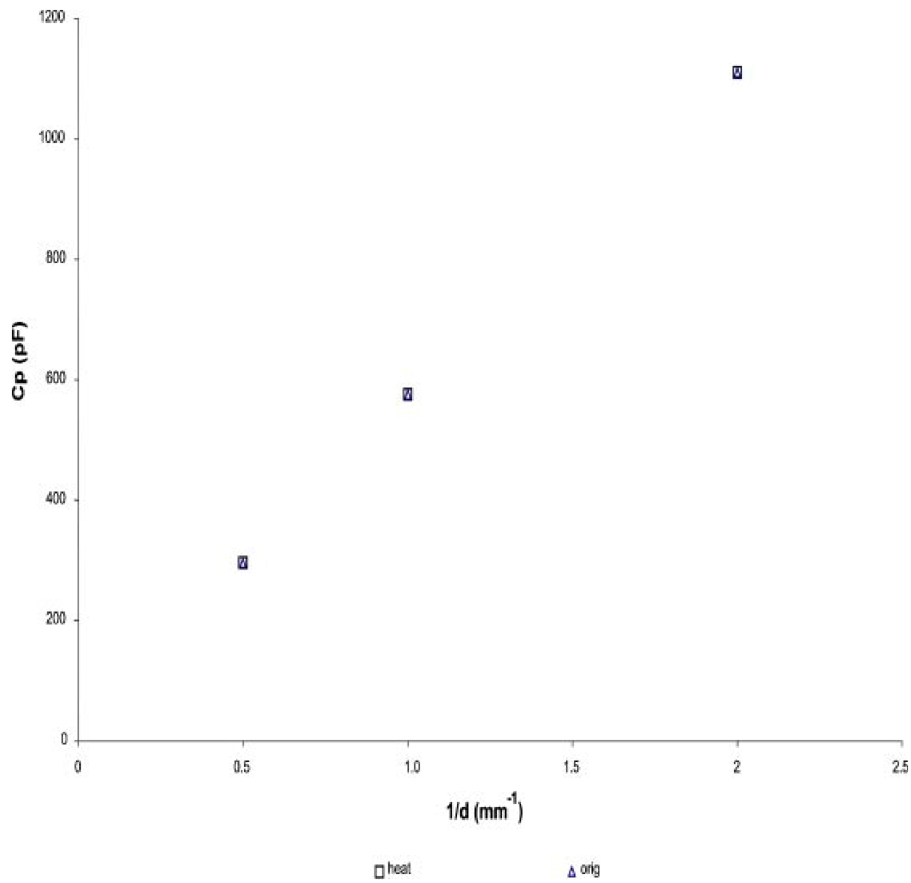

Figure 6. Capacitance values C_p (pF) versus $1/d$ (mm^{-1}) of the original and aged paracetamol syrups ($\nu = 1000$ kHz).

vary between 0.98 and 0.99. For the naphazoline hydrochloride solutions, Figures 1–3 show that the low frequency dielectric spectroscopy technique does not detect practically variation of the electric parameters produced for warming, which can be due to the fact of having chosen a temperature far from the solvent boiling temperature, but a marked differences between the original and diluted solution can be detected probably due to variation of the concentration of the active principle since it is observed that the impedance and capacitance values of 0.1% naphazoline hydrochloride solution diluted by the addition of a volume of distilled water equal to 50% of the original volume, are practically identical to that of the 0.05% solution. By other way, Table 2 shows clear differences between the original and aged syrup impedance values which are greater at low frequency. The behavior of this electric parameters with the frequency for the original and aged paracetamol syrup can be seen in Figure 4. The differences between original and heated syrup can be can be linked to changes on the active principle concentration and also to the known variation of dielectric properties of aqueous sugar solution with temperature. The same linear dependences of the impedance and capacitance values observed for the naphazoline solutions are also noted for the paracetamol syrup, Figure 5 at 1 and 1000 kHz and Figure 6 at 1000 kHz, with linear regression coefficients between 0.98 and 0.99 in the frequency range of measurements. As in the case of impedance values, the differences are not important near to 1000 kHz.

Although of artificial aging process applied do not describe in fullness the aged drug state, it permits to show that the low frequency impedance technique could be used like quality control to analyze and characterize pharmaceutical systems. Permittivity and conductivity values can be obtained by combining impedance and capacitance slopes or resistance and reactance slopes. These last electrical parameters can be calculated from the impedance and phase angle measurements.[8]

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