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

PEDRO C. BRITO,[1] MAGDALENA MECHETTI,[1] CARLOS M. GOTTER,[2] DAVID J. MEREP[3]

[1]Laboratorio de Dieléctricos, Departamento de Física, Facultad de Ciencias Exactas y Tecnología, Universidad Nacional de Tucumán, Tucumán, Argentina

[2]Instituto de Física, Facultad de Bioquímica, Química y Farmacia, Universidad Nacional de Tucumán, Tucumán, Argentina

[3]Cátedra de Farmacotécnia, Facultad de Bioquímica, Química y Farmacia, Universidad Nacional de Tucumán, Tucumán, Argentina

Received 9 April 2008; revised 21 July 2008; accepted 24 July 2008

Published online 9 September 2008 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.21548

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

Correspondence to: Pedro C. Brito (Telephone: +54-381-410 7570; Fax: +54-381-436 5710; E-mail: pbrito@herrera.unt.edu.ar)

Journal of Pharmaceutical Sciences, Vol. 98, 1845–1851 (2009)

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