Acta Farm. Bonaerense **22** (2): 173-6 (2003)
Recibido el 21 de septiembre de 2002
Aceptado el 30 de diciembre de 2002

Influence of the Ageing Phenomenon on the Low-Frequency Electrical Impedance Behaviour of Sodium Dipirone Syrup

Pedro BRITO [1]*, Carlos GOTTER [2] and David MEREP [3]

[1] *Laboratorio de Dieléctricos, Departamento de Física, Facultad de Ciencias Exactas y Tecnología, Av. Independencia 1800 - (4000) Tucumán, Argentina.*

[2] *Instituto de Física and* [3] *Cátedra de Farmacotecnia, Facultad de Bioquímica, Química y Farmacia, Universidad Nacional de Tucumán, Av. Independencia 1800, 4000 Tucumán, Argentina.*

SUMMARY. The impedance behavior of a sodium dipirone syrup is studied in order to analyze the applicability of the low-frequency dielectric spectroscopy for determining the differences between a new and an aged product. The impedance measurements were performed in the frequency range between 20 Hz and 1 MHz, using the Impedance Analyzer Hewlett-Packard HP 4284 A and a non commercial cell for liquids. Different electrodes separations measures were made in order to get a better insight of the electrode polarization phenomenon. The ageing phenomenon has been artificially produced by a dilution procedure. The results show that the dielectric technique can be used as a good quality control procedure for medicines.

RESUMEN. "Influencia del Fenómeno de Envejecimiento en el Comportamiento Impedancimétrico a Baja Frecuencia de un Jarabe a Base de Dipirona Sódica ". El comportamiento de la impedancia eléctrica de un jarabe, cuya droga principal es la dipirona sódica, es estudiado con el fin de analizar la aplicabilidad de la espectroscopía dieléctrica de baja frecuencia para determinar diferencias entre el jarabe original y el producto envejecido. Las mediciones impedancimétricas fueron realizadas en el rango de frecuencias de 20 Hz a 1 MHz utilizando el Analizador de Impedancia HP 4284A y una celda no comercial para líquidos. Se han realizado mediciones a diferentes separaciones de electrodos con el fin de minimizar la infuencia del proceso de polarización de electrodos. El envejecimiento de las muestras se ha producido artificialmente a través de un proceso de dilución. Los resultados obtenidos indican que la técnica de espectroscopía dieléctrica puede ser usada como un buen procedimiento de control de calidad de medicamentos.

INTRODUCTION

Low-frequency dielectric spectroscopy is now used as a new and powerful method of characterizing pharmaceutical products [1]. This technique permits to get a better understanding of properties of these materials such as structure, and phenomena such as ageing process, in both the liquid and solid states. Ageing phenomena of pharmaceutical systems can be produced by a thermal process which lead to decrease the water content of the pharmaceutical products or by a dilution procedure which tends to increase its water content. Both processes lead to a variation of main drug concentration. In this work the ageing phenomenon has been artificially produced by adding distilled water to this particular pharmaceutical system. Measurements of the electrical impedance of a sodium dipirone syrup, in the frequency range between 20 Hz - 1 MHz, have been performed in order to determine the usefulness of the impedance technique [2-4] for detecting the influence of the ageing process on the dielectric properties of this product.

MATERIAL AND METHODS

The sodium dipirone syrup has been prepared with a concentration of 5 mg of sodium dipirone by each 100 ml of the excipient solution using a pure drug of Chinese origin, soluble in water and alcohol. The aged syrup has been obtained by adding distilled water up to

KEYWORDS: Ageing phenomenon, Impedance, Syrup.
PALABRAS CLAVE: Envejecimiento, Impedancia, Jarabe.

* Author to whom correspondence should be addressed. E-mail: pbrito@herrera.unt.edu.ar

50% of the excipient volume. The electrical measurements were made using a Hewlett-Packard 4284 A Impedance Analyzer with a frequency range between 20 Hz and 1 MHz and a non commercial cylindrical cell with stainless steel plane electrodes of variable separation between them in order to get a better control of the electrode polarization phenomenon. The diameter of the stainless steel electrodes was 54,8 mm and the maximum separation between electrodes reached 15 mm. The measurements were made at electrode separations of 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 mm, respectively. The distance between electrodes has been determined with a precision of 0.05 mm. All measurements have been done at 20 °C.

The impedance Z_c of the measuring cell is a series combination of the impedance of the sample Z_s, the polarization impedance of the electrodes Z_e, and the parasitic cell impedance, Z_p. The first impedance is directly dependent of the electrode separation d, whereas all impedance are frequency dependent. The Z_c impedance is given by the following expression:

$$Z_c = Z_s + Z_e + Z_p = [d \ / \ \sigma \ (\ 1 + i \ \omega\varepsilon_0 \ \varepsilon \ / \ \sigma \ )A] + 2 \ [\ (\ r_e - i \ / \ \omega \, c_e \ )A] + Zp \qquad (1)$$

where ω is the angular frequency, A is the electrode area, d the spacing between them, ε and σ are the permittivity and electrical conductivity of the sample, respectively, while r_e is the electrode polarization resistance and c_e is the electrode polarization capacitance, both by unit area. In order to obtain equation (1), the electrical properties of the system have been described by the generalised complex conductivity equation [5,6] :

$$\sigma^* \ (\omega) = \sigma \ (\omega) + i \ \omega \ \varepsilon_0 \varepsilon(\omega) \qquad (2)$$

The short and open corrections procedures recommended by the manufacturer has been done before the electrical impedance measurements of the cell filled with the sample were made and their values permit to identify the measured impedance Z_m with the cell impedance Z_c.

RESULTS

The experimental values obtained for the electrical impedance versus the electrode spacing d working with the original and of the aged sodium dipirone syrup, for the frequencies of 1, 10, 100 and 1000 kHz, are given in Table 1 and showed in Figure 1.

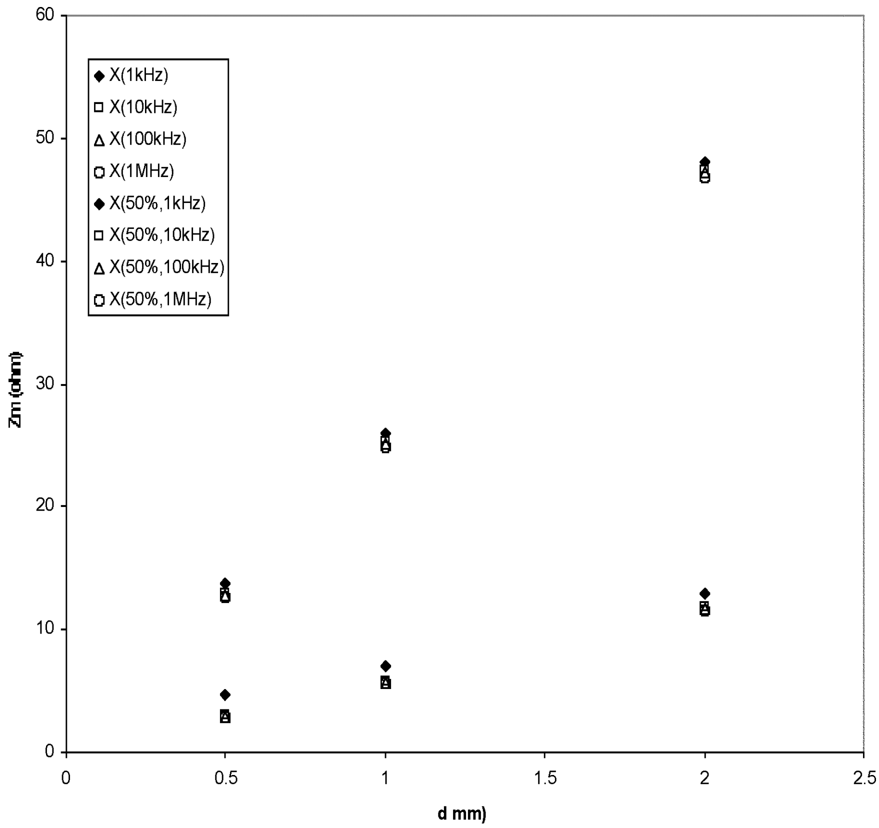

Figure 1. Electrical Impedance values, Z_m, of the original (upper points) and aged (diluted at 50%) sodium dipirone syrups as a function of the electrode separation d . The represented values were measured at the frequencies of 1, 10, 100 and 1000 kHz.

d	**original**	**aged 50%**
0.5	12.65	2.89
1.0	24.91	5.67
2.0	46.81	11,60

Table 1. Impedance values Zm [Ω] of original and aged syrups *vs.* electrode separation d[mm] at the frequency of 1 MHz.

As can be seen, a lineal relation between Z_m and the spacing d given by expression (1) is recovered for all frequency being its slope K_z closely related with the permittivity and conductivity at each frequencies through the following expression:

$$K_z^2 = 1 \ / \ [\ \sigma^2 + (\omega \varepsilon\, \varepsilon_0)^2\ ]\ A^2 \qquad (3)$$

were ε_0 = 8.85 10^{-12} coul²/ N m² is the vacuum permittivity. From Fig. 1 it can also be seen that the impedance values of the original and aged syrups are very different between them, being for each system practically superposed in the frequency range considered.

Freq.(Hz)	**original**	**aged 50%**
50	43.10	39.92
100	27.20	22.31
500	14.96	6.78
1000	13.78	4.71
5000	12.96	3.20
10000	12.86	3.05
50000	12.78	2.93
100000	12.76	2.91
500000	12.72	2.89
1000000	12.65	2.89

Table 2. Impedance values Z_m [Ω] of original and aged syrups *vs.* log (freq.) for 0.5 mm of electrodes separation.

The measured values of the impedance *Zm* in the whole range of frequency is given in Table 2.

The differences on the impedance behaviour of the original and aged syrups, can be observed in Figure 2 .

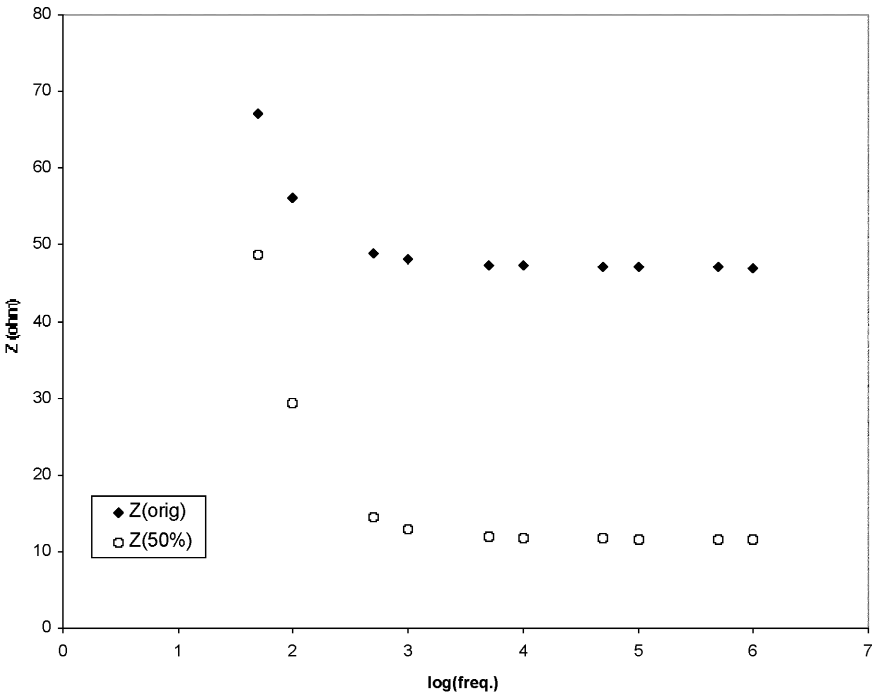

Figure 2. Electrical Impedance values, Z_m, of the original (upper points) and aged sodium dipirone syrup as a function of log (freq.) for an electrode separation of 0,5 mm .

DISCUSSION

The results given in this paper show that there is a clear difference between the electrical impedance values of the original and the aged sodium dipirone syrups probably due to changes on the permittivity and conductivity parameters which are associated with structural and/or ionic density changes of the excipient. The differences between impedance values are greater enough to conclude that low frequency impedance technique is a good quality control method to be used in the analysis and characterisation of pharmaceutical systems.

Measurements of impedance and loss angle also permit to determine the permittivity and the conductivity of the sample [7] and perform further studies related with molecular structure interactions.

REFERENCES

1. Craig, D.Q.M. & J.M. Newton (1994) *"Dielectric Analysis of pharmaceutical systems"*, Ellis Horwood Ltd., Chichester.
2. P.J. Riu, J. Rosell, R. Bragós & O. Casas (edits.) (1999) *Electrical Bioimpedance Methods: Applications to Medicine and Biotechnology,* Ann. N.Y. Acad. Sci., V. 873.
3. N. Hill, W.E. Vaughan, A.H. Price & M. Davies (1969) "Dielectric Properties and Molecular Behaviour", Van Nostrand, London,.
4. Macdonald, J.R. (1987) *"Impedance Spectroscopy"*, Wiley- Interscience, New York.
5. Grosse, C. & M.C. Tirado (1996) *Mat. Res. Soc. Symp. Proc.* **430**: 287-93
6. Böchtter, J.C. & P. Bordewijk (1973) *"Theory of electric polarization"*, Vol. I and II, Elsevier, Amsterdand.
7. Tirado, M., F.J. Arroyo, A.V. Delgado & C. Grosse (2000) *J. Colloid Interface Sci.* **227**: 141-6.