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Investigation into β-cyclodextrin/acetotoluide interactions using low frequency dielectric spectroscopy

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Low-frequency dielectric spectroscopy has been used to characterize samples of β-cyclodextrin and ortho-, meta- and para-acetotoluide, both in aqueous solution and in the solid state. Similarly, β-cyclodextrin/acetotoluide binary systems were studied as aqueous solutions and as freeze-dried solids. The para-acetotoluide binary systems exhibited the highest conductance in aqueous systems and showed anomalous behaviour in the solid state compared to the other two analogues. Previous studies by Jones and Parr have indicated that the para-acetotoluide gave the strongest evidence for complex formation with β-cyclodextrin, hence the studies have demonstrated that the technique may be of use in studying drug interactions with cyclodextrin systems.

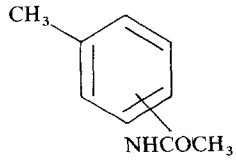
1. Introduction

The cyclodextrins are a series of oligosaccharides containing cyclic α-1,4 linked d-glucopyranose units [1]. The cyclic molecular structure renders cyclodextrins capable of forming inclusion complexes with other substances, notably drug molecules. In solution, the guest molecule is believed to be partially or wholly incorporated in the central cavity of the cyclodextrin, while in the solid state the drug may also fit into the interstitial spaces between the cyclodextrin molecules [2]. Complex formation may confer several advantages on the drug, including increased aqueous solubility, improved stability and improved taste. While a wide variety of cyclodextrins are currently available [3], the molecules on which the majority of research has hitherto been performed have been α-, β- and γ-cyclodextrins, containing 6, 7 and 8 glucopyranose units, respectively.

However, it has frequently proved difficult to determine whether complex formation occurs between the drug and cyclodextrin, both in aqueous solution and in the solid state. Consequently, the factors determining whether complexation will take place are not yet fully understood, although molecular size and polarity are generally accepted as being of primary importance (e.g. [4]). In particular, complex formation in the solid state has proved difficult to study due to a lack of suitable analytical methods. There is, therefore, a need to extend the range of techniques presently used in order to identify not only the presence of inclusion complexes but also the factors which determine whether complexation is possible.

In the present study, a series of model systems have been investigated using low-frequency dielectric spectroscopy. One advantage of this method is that it may be applied to both solid and liquid samples. The technique may therefore be applicable to the study of cyclodextrin systems in aqueous solution and in the solid state. Previous studies [5] have used dielectric spectroscopy in the examination of solid β-cyclodextrin undecahydrate between 77 and 295 K, showing the presence of solid state transitions over this temperature range. In the present study, the use of the technique in examining drug interactions with cyclodextrins has been investigated.

The model systems used were ortho-, meta- and para-acetotoluide (*o*-, *m*-, *p*-ACT) with β-cyclodextrin. The acetotoluides have the general structure I.



(I)

These substances have previously been studied with β-cyclodextrin using conventional techniques such as ultraviolet spectroscopy, solubility, filtration cell studies and thermal analysis [6]. The authors concluded that the strongest evidence for complex formation was found for the *p*-ACT systems.

The results obtained from the dielectric studies will be compared to those obtained using conventional techniques for two reasons. Firstly, to ascertain

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whether the results obtained using this method are in agreement with those obtained by Jones and Parr [6], and secondly to investigate how the dielectric technique may be used to enhance understanding of the factors influencing the formation of cyclodextrin complexes.

2. Theory of dielectric analysis

Dielectric spectroscopy works on the principle that an electric field, when applied to a sample, will polarize that material. In the simplest form, the dipoles within the sample attempt to orientate with the applied field in order to minimize the free energy of the system. At low field strengths, the polarization, P, is given by

$$P = \varepsilon_0 \chi_0 E = \varepsilon_0 \varepsilon E \quad (1)$$

where E is the field strength, χ_0 is the static susceptibility, ε_0 is the permittivity of free space and ε is the relative permittivity of the sample. On applying an alternating field, the dipoles will attempt to reorientate (relax) at the same rate as the changes in field direction. However, as the dipoles will require a finite period of time to reorientate, relaxation is not perfectly efficient. Therefore, a phase lag develops between the applied field and the sample response. In this case the susceptibility becomes vectorial, χ^*, and is hence more conveniently described as a complex number, i.e.

$$\chi^* = \chi' - i\chi'' \quad (2)$$

where χ' and χ'' are the real (energy storage) and imaginary (energy loss) components of the susceptibility respectively and i is $-1^{1/2}$. These two components may be given in terms of the capacitance and dielectric loss, G/ω, where G is the conductance and ω is the frequency, via

$$C(\omega) = \frac{\varepsilon_0 A}{d}[\chi'(\omega) + \varepsilon_\varphi] \quad (3)$$

and

$$\frac{G(\omega)}{\omega} = \frac{\varepsilon_0 A \chi''(\omega)}{d} \quad (4)$$

where A and d are the area and separation distance of the electrodes and ε_φ is the permittivity at infinite frequencies. A d.c. conductivity ($G_{d.c.}$) may also be present in parallel with the a.c. dielectric loss, hence Equation 4 may also be written as

$$\frac{G(\omega)}{\omega} = \frac{\varepsilon_0 A \chi''(\omega)}{d} + \frac{G_{d.c.}}{\omega} \quad (5)$$

C and G/ω are measured over a range of frequencies to yield a characteristic spectrum, the analysis of which may lead to structural information on the sample. The uses of the technique in pharmaceutical analysis have been described by Craig *et al.* [7], while a more detailed description of the theory behind the technique has been given by Dissado and Hill [8].

3. Material and methods

3.1. Materials

β-cyclodextrin and *o*-, *m*- and *p*-ACT were used as received. 0.1% wt/vol aqueous solutions of β-cyclodextrin and equimolar solutions (0.013% wt/vol) ACTs were prepared in double-distilled water, both separately and as binary systems. Solid binary samples were prepared by weighing 50 mg of each ACT isomer into a flask with an equimolar amount of β-cyclodextrin (381 mg). 50 ml 20% vol/vol absolute ethanol/distilled water were added to the flask. The components were dissolved and the solution frozen using liquid nitrogen and freeze dried until all the moisture had been removed.

3.2. Dielectric studies

Approximately 5 ml of each solution were placed in a PTFE container. Two platinum electrodes (approximate area 0.5 cm^2, separation distance 1 mm) were immersed in the sample. An alternating voltage of 0.1 V r.m.s. was generated using a frequency response analyser and applied across the sample via a Chelsea interface. The response was analysed over a frequency range of 10^4–10^{-2} Hz at 303 K. Each point was automatically measured at least three times. All studies were repeated at least once.

Solid samples were prepared by compressing 300 mg of each material (β-cyclodextrin alone, acetotoluide alone and the freeze-dried materials) to a load of 50 kN in a punch and die system to produce a strip of area 4.05 cm^2. The sample thicknesses were 2 mm ($\pm$ 0.1 mm) in all cases except the *o*-ACT/β-cyclodextrin system, whereby the thickness was found to be 1.3 mm. Adhesive copper strips were applied to the samples (area 0.4 cm^2) and a voltage of 1 V applied across the sample. The response was measured at 298 K between 10^4 and 10^{-2} Hz. Each point was automatically measured at least three times, giving a coefficient of variation of approximately 2.5%. All studies were repeated at least once, with excellent reproducibility being found between samples.

4. Results and discussion

4.1. Aqueous solutions studies

A typical spectrum for 0.1% aqueous β-cyclodextrin is given in Fig. 1. The spectral shape suggests a response of the Maxwell–Wagner type [9, 10], whereby the sample can be considered to consist of a conducting bulk layer (seen at high frequencies) in series with a thin barrier layer located at the electrodes which is observed at low frequencies [11]. The slope of the high frequency loss (10^4–10^2 Hz) shown in Fig. 1 was -1.013, indicating that the conductance is effectively independent of frequency in this region. While it is possible to analyse both the shape of the spectra and values of the individual points, it is sufficient for the purposes of the present study to use the conductance values obtained at 10^4 Hz, as this frequency was within the linear loss region for all the aqueous samples, hence facilitating direct comparison. The conductance values are given in Table I.

According to Kohlrausch's law [12], the molar conductivities of the various ionic species in a system at infinite dilution will be directly additive. However,

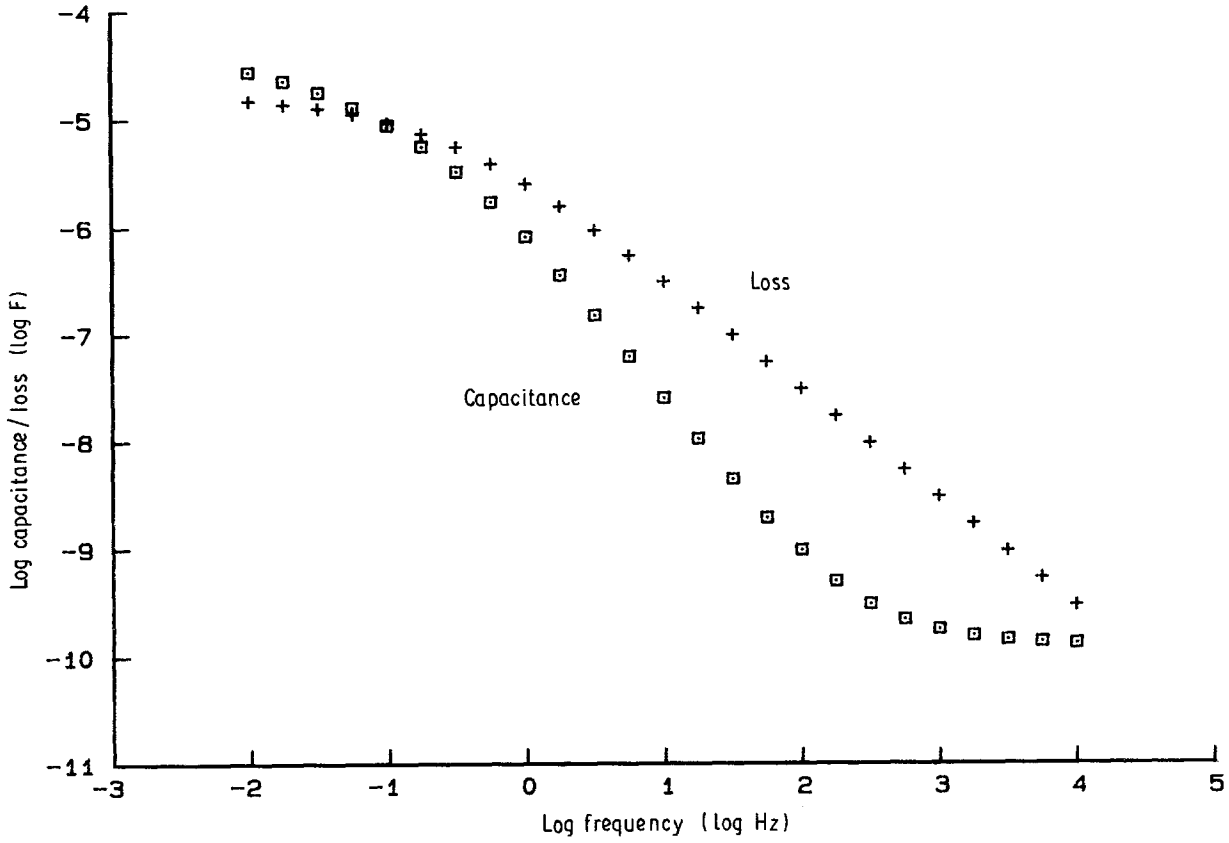

Figure 1 The dielectric response of 0.1% wt/vol β-cyclodextrin in water.

TABLE I Conductance values of aqueous β-cyclodextrin/acetotoluide systems at 10^4 Hz

Sample	Conductance (10^{-5} mho)
Water	1.408
0.1% β-cyclodextrin	1.599
0.013% 2-ACT	1.456
0.013% 2-ACT/0.1% β-cyclodextrin	2.201
0.013% 3-ACT	2.268
0.013% 3-ACT/0.1% β-cyclodextrin	2.169
0.013% 4-ACT	2.162
0.013% 4-ACT/0.1% β-cyclodextrin	3.062

it is necessary to have a knowledge of the ionization behaviour of the system before such values may be ascertained. It is therefore not possible to calculate the theoretical conductivities of the binary cyclodextrin/ACT systems in relation to the experimentally obtained value on the basis of the available data. Nevertheless, it is valuable to observe firstly the rank order of response magnitudes shown by the ACT samples, and secondly to observe the effects of adding an identical quantity of cyclodextrin to each analogue.

The acetotoluides gave conductivities of the rank order $m > p > o$. This ordering may be due to differences in the electron distribution around the benzene ring, or alternatively due to different solvation behaviour between the analogues. On addition of 0.1% β-cyclodextrin, a small decrease in conductance was seen for *m*-ACT, while an increase was seen for *o*-ACT. A larger increase was seen on adding β-cyclodextrin to *p*-ACT. These results, therefore, indicate that the measurement of conductivity may prove to be a useful method of assessing complex formation with cyclodextrins. It is also noted that the analogue showing the greatest change on addition of β-cyclodextrin was the *p*-ACT. This is also the analogue identified by Jones and Parr [6] as providing the most conclusive evidence for complex formation in aqueous solution.

4.2. Solid state behaviour

The response of the β-cyclodextrin is given in Fig. 2. The spectrum shows a peak in the dielectric loss at approximately 1 Hz. Such peaks indicate the dielectric recovery of bound or partially bound species which relax via reorientation, rather than by charge hopping or d.c. conductivity [13]. It is not possible at this stage to state which moiety may be responsible for the reorientation process, although Pathmanathan *et al.* [5] have reported loss peaks due to reorientation of water molecules in solid β-cyclodextrin undecahydrate. It is, therefore, possible that the peak seen in the present case is due to adsorbed water within the sample.

The loss values of the three acetotoluides are given in Fig. 3, omitting the low-frequency response of *o*-ACT due to excessive noise. The solid state response may be expected to be a function of both the configuration of the individual molecules and the crystal form of the sample as a whole. The rank order of conductances seen for the ACT analogues is the same over the majority of the spectra as that observed for

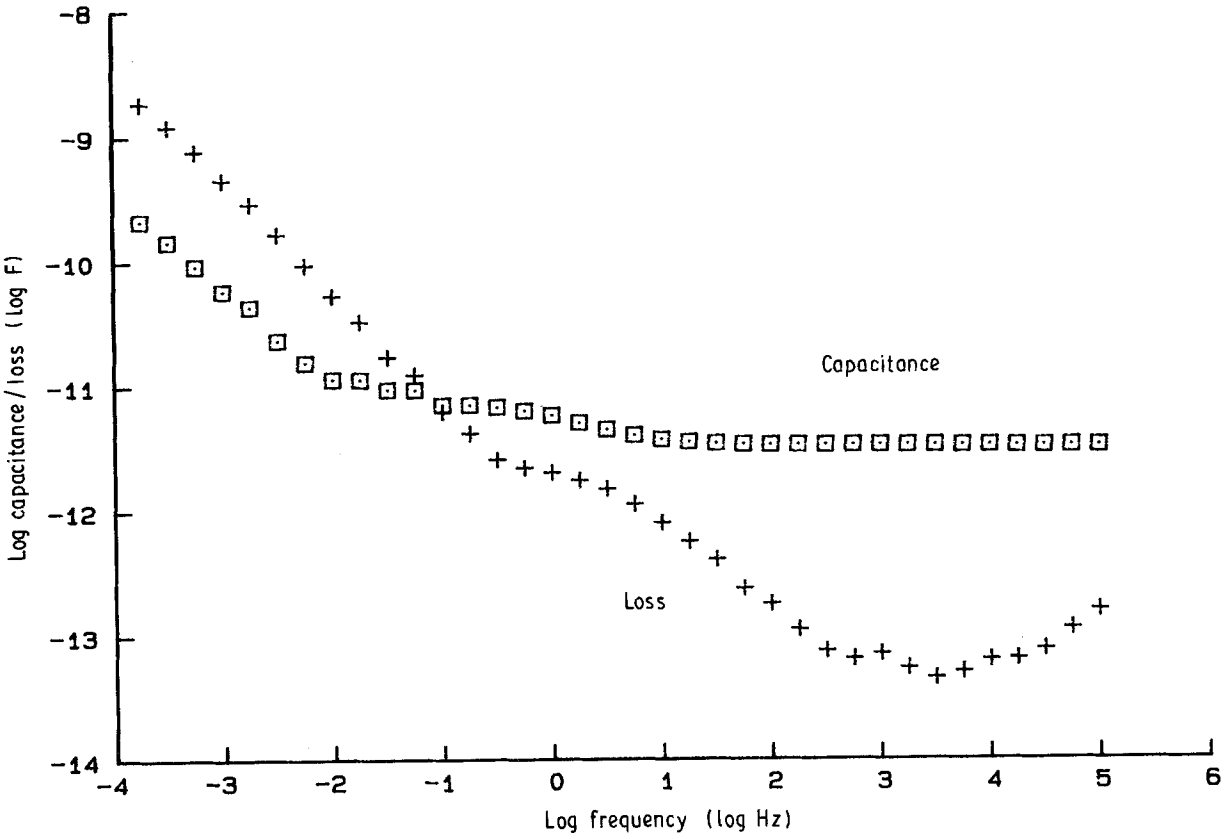

Figure 2 The dielectric response of solid β-cyclodextrin.

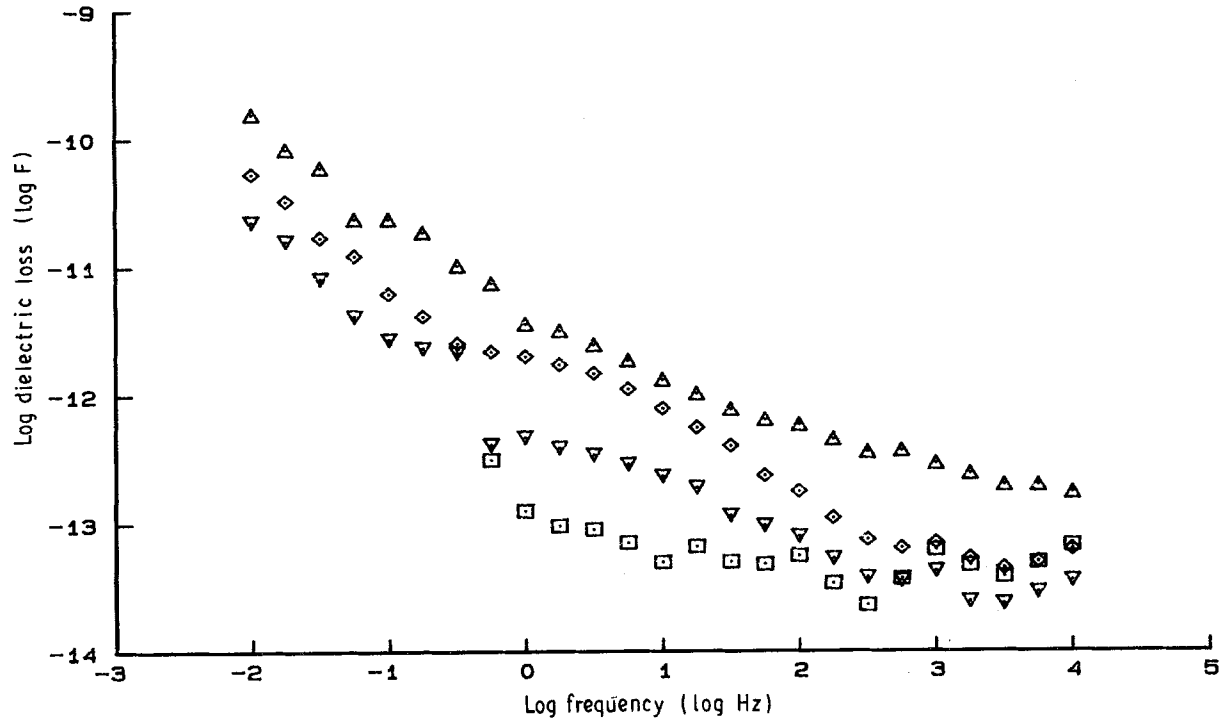

Figure 3 The dielectric response of solid (□) *o*-, (△) *m*- and (▽) *p*-acetotoluide. (◇) Solid β-cyclodextrin response included for comparison.

the aqueous studies, indicating that it is the molecular configuration which predominates in this case.

The loss spectra of the binary solid systems are given in Fig. 4, with the response of β-cyclodextrin alone included for comparison. The *o*-ACT binary system gave a lower response than that of the β-cyclodextrin alone, with no indication of a loss peak. If the components of the binary systems are totally non-interactive, the overall loss spectrum may be dominated by the more responsive constituent. However, this will only occur if this component forms a conduction pathway through the more highly insulating substance. The low response seen in the present case may be due to the β-cyclodextrin existing in isolated regions within the solid, thereby providing no continuous pathway through which charge may travel. The

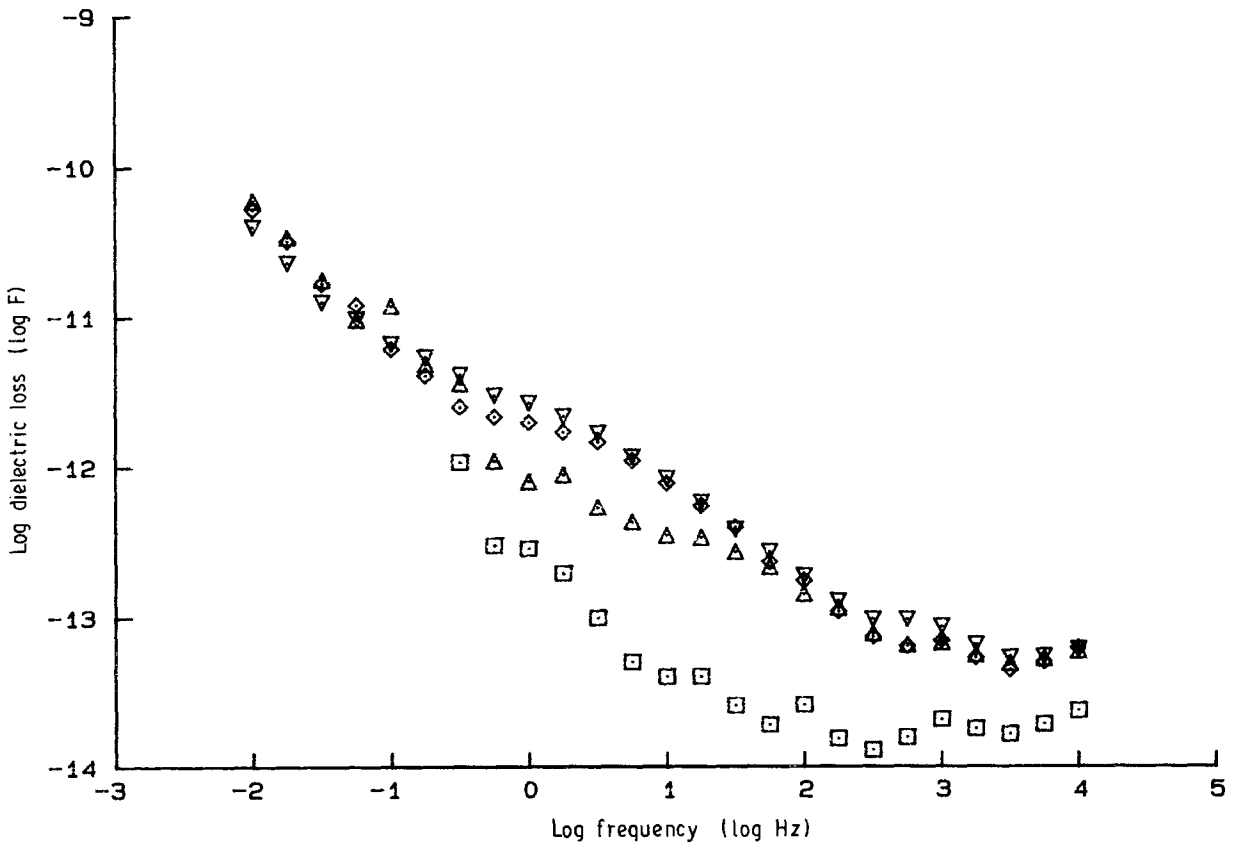

Figure 4 The dielectric response of solid binary systems of (⊡) *o*-, (△) *m*- and (▽) *p*-acetotoluide and (◇) β-cyclodextrin.

converse appears to be the case for the *m*-ACT binary system, as the high-frequency response is dominated by the β-cyclodextrin, despite the greater response seen for the *m*-ACT alone. Furthermore, examination of Fig. 4 indicates that the loss peak is either diminished or is absent altogether in this case. The *p*-ACT spectrum, however, indicates that not only does the β-cyclodextrin dominate the response, but also that the loss peak is retained, and may even be slightly enhanced.

The results have indicated that the three solid ACT analogues show different dielectric behaviour both alone and when present as binary systems with β-cyclodextrin. Moreover, the only binary system in which the loss peak was observed was that of the *p*-ACT. The presence of this peak may, therefore, be an indication of the inclusion complex reported for this analogue by Jones and Parr [6].

5. Conclusions

The investigation has indicated the usefulness of the dielectric technique in characterizing the β-cyclodextrin and ACT analogues, both in aqueous solution and in the solid state. Furthermore, the results obtained for the binary systems are compatible with those obtained using conventional techniques [6]. More specifically, the *p*-ACT solution showed the greatest increase in conductance on addition of β-cyclodextrin, while the solid *p*-ACT binary system yielded a loss peak which was not observed for the ortho and meta analogues. While it is not possible to ascribe all the observed phenomena to specific mechanisms at this stage, the study has shown that the technique could assume an important role in cyclodextrin studies. In particular, dielectric spectroscopy may be of use firstly in identifying and characterizing interactions between drugs and cyclodextrins, and secondly in clarifying the importance of the polarity of the guest molecule in complex formation.

References

1. W. R. G. BAEYENS, B. LIN LING, P. dE MOERLOONE, B. DEL CASTILLO and C. DEJONG, *An. Real. Acad. Pharm.* **54** (1988) 698.
2. S. P. JONES, D. J. W. GRANT, J. HADGRAFT and G. D. PARR, *Acta Pharm. Tech.* **30** (1984) 213.
3. D. DUCHENE and D. WOUESSIDJEWE, *Drug Dev. Ind. Pharm.* **16** (1990) 2487.
4. A. STADLER-SZOKE and J. SZEJTLI, "A forecast for application of cyclodextrin to the pharmaceutical industry", in Proceedings of the International Symposium on Cyclodextrins, Budapest, Hungary (1981) pp. 377–88.
5. K. PATHMANATHAN, G. P. JOHARI and J. A. RIPMEESTER, *J. Phys. Chem.* **93** (1989) 7491.
6. S. P. JONES and G. D. PARR, *Int. J. Pharm.* **36** (1987) 223.
7. D. Q. M. CRAIG, R. M. HILL and J. M. NEWTON, *Int. Pharm. Tech.* **2** (1990) 61.
8. L. A. DISSADO and R. M. HILL, *Nature* **279** (1979) 685.
9. J. C. MAXWELL, "Electricity and Magnetism" (Clarendon Press, Oxford, 1892).
10. K. W. WAGNER, *Arch. Electrochem.* **2** (1914) 371.
11. R. M. HILL and C. PICKUP, *J. Mater. Sci.* **20** (1985) 4431.
12. W. J. MOORE, "Physical Chemistry", 5th Edn (William Cloves, London, 1972).
13. P. DEBYE, "Polar Molecules" (Dover Press, New York, 1945).

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