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Applicability of dielectric measurements to the adsorption of drugs onto nanoparticles

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Summary

Measurement of both the dielectric constant and permittivity of a suspension of polyisobutylcyanoacrylate nanoparticles prepared with increasing concentrations of betaxolol chlorhydrate, demonstrates that both methods allow the rapid determination of the adsorption isotherm plateau. These measurements could also provide interesting information about the effect of ageing on such suspensions.

In suspensions of nanoparticles, drugs are either bound to the colloidal carriers or free in the aqueous external medium. Generally, the first objective of studies on nanoparticles is to adsorb large amounts of drugs onto the studied carriers (Couvreur et al., 1990). Therefore, isotherms are constructed in order to determine the maximum quantity of drug that can be adsorbed onto the particles. Usually, the optimal ratio of drug linked to drug in solution is indicated by the beginning of the adsorption plateau.

The construction of such isotherms is relatively time-consuming, since it is necessary first to separate the solid and liquid phases, generally by means of ultracentrifugation and then to determine the free and/or linked drug concentrations by various techniques.

To achieve a more rapid determination of the plateau of the isotherm, we measured the dielectric parameters of suspensions of nanoparticles at high frequencies. This technique has already been proposed for the analysis of adsorption phenomena of ions and floating collectors on minerals (Bessière et al., 1990, 1991), but has thus far not been used to resolve a pharmaceutical problem such as that in the present article. Briefly, the method consists of introducing the nanoparticle suspension into a capacitive cell (Thiebaut et al., 1989). This cell is submitted to a high-frequency field (1–100 MHz) and a measure of Z, the impedance, is obtained. From the complex impedance of the cell, with the help of a physical

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model, Z is converted into a complex permittivity, ε^*, according to the following equation:

$$\varepsilon^* = \varepsilon' - j\varepsilon''$$

where ε' and ε'' are the dielectric constant and dielectric permittivity, respectively. These two parameters, ε' and ε'', are used to monitor the adsorption of components onto surfaces.

Evaluation of the impedance was carried out with a Hewlett Packard 4193 A. The temperature of the cell was maintained at 20 ± 0.1°C. ε' and ε'' were computed from the measured values.

Polyisobutylcyanoacrylate (PIBCA) nanoparticles loaded with betaxolol chlorhydrate were prepared according to a previously reported method (Marchal-Heussler et al., 1990). Briefly, 1 g of isobutylcyanoacrylate was added dropwise to 100 ml of 10^{-2} M HCl containing a solution of dextran 70000 (0.8%, w/v) and dextran sulfate (0.3%, w/v). The polymerisation process was carried out for 2 h and the resulting suspension was filtered and neutralised to pH 7.4 with NaOH (0.1 N). Adsorption was carried out by adding appropriate amounts of betaxolol chlorhydrate to 10 ml of suspension (0.2, 0.4, 0.6, 0.8%, w/v) with stirring for 1 h.

Figs 1 and 2 demonstrate the respective plots of the dielectric constant and permittivity vs the field frequencies.

In Fig. 1, for concentrations of betaxolol chlorhydrate ranging from 0.2 to 0.6%, the value

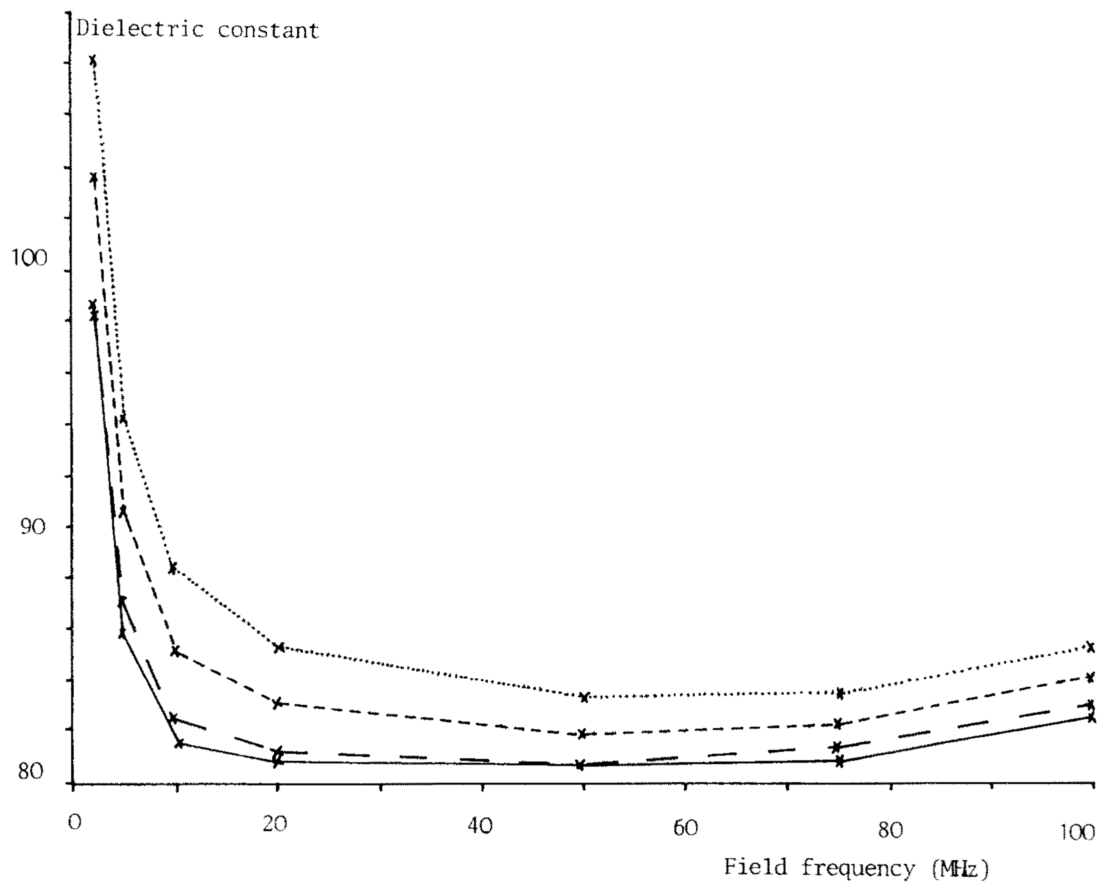

Fig. 1. Dielectric constant vs field frequency (case of increasing concentrations of betaxolol chlorhydrate adsorbed onto cyanoacrylate nanoparticles). Betaxolol chlorhydrate concentration (w/v): 0.2% (– – –), 0.4% (- - - - - -), 0.6% (· · · · · ·), 0.8% (———).

of the dielectric constant increases at every frequency, relative to a probable increase in interfacial polarity on introduction of drug. In Fig. 2, over the same concentration range, the permittivity displays decreasing values. On attaining a drug concentration of 0.8%, a dramatically different pattern of variation in the two parameters becomes evident. In the case of Fig. 1, the dielectric constant falls, reaching its lowest values; contrastingly, in Fig. 2, the permittivity attains its greatest values.

The reversal in the pattern of variation for the two dielectric parameters indicates the onset of the plateau of the adsorption isotherm demonstrated by Marchal-Heussler et al. (1990).

The main advantages of dielectric measurements are firstly the possibility of carrying out the measurement on the overall suspension (separation of the two phases is not necessary) and secondly, the method is rapidly performed (less than 30 min is required in order to obtain the curves). Such procedures can therefore indicate whether or not a maximum exists and provide the value of the concentration at which a maximum appears.

In addition, such dielectric measurements perhaps could provide a useful tool for studying the ageing of nanoparticle suspensions.

On the basis of the present results, the above-described method of determining maxima of the

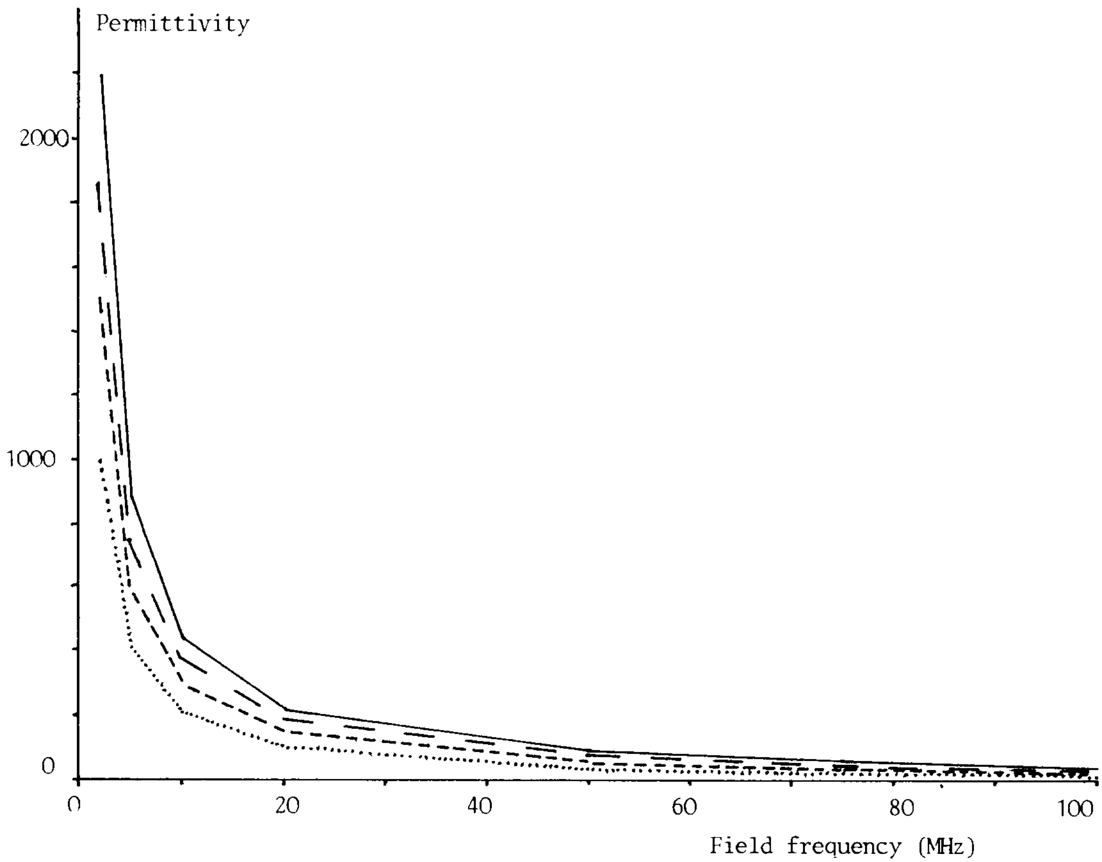

Fig. 2. Permittivity vs field frequency (case of increasing concentrations of betaxolol chlorhydrate adsorbed onto cyanoacrylate nanoparticles). Betaxolol chlorhydrate concentration (w/v): 0.2% (– – –), 0.4% (------), 0.6% (······), 0.8% (———).

adsorption isotherms appears to hold much promise, but should be tested with other polymers and drugs.

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