# Applicability of Dielectric Measurements to the Adsorption of Beta Blockers onto a Pharmaceutical Grade Ion-Exchange Resin

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## INTRODUCTION

Dielectric measurements have been shown to be useful for the evaluation of the adsorption of chemical species onto powdered minerals (1) and ion-exchange resins (2,3). Dielectric analysis has also been proposed as an interesting analytical technique with considerable applications in pharmaceutical sciences (4).

Ion-exchange resins are increasingly used in pharmaceutical formulations (5), both as drugs (in order to treat hyperkaliemia and hypercholesterolemia) and as excipients (in order to delay the therapeutic effect or to mask bitter taste) (6,7). Consequently, it was of interest to study whether this method could be used to follow the adsorption of drugs onto drug carrier systems such as ion-exchange resins.

In pharmaceutical formulations based on ion-exchange resins, it is necessary to determine the exact amount of drug bound onto the carrier. The usual way is to complete adsorption isotherms, which is relatively time-consuming, since it is necessary to separate the solid and the liquid phases. The second step corresponds to the assay of the drug in the liquid phase. An elegant way to obtain such information is to perform dielectric measurements. This technique has already been proposed for the analysis of poly(isobutylcyanoacrylate) nanoparticles loaded with betaxolol chlorhydrate (8–10), and it was shown that it was possible to determine the amount of drug loaded onto the nanoparticles in this way. The dielectric method has also been developed to monitor the curing of Eudragit RS30D with 20 % acetyltributyl citrate and to investigate the effects of curing on the barrier properties of the film (11).

For this reason, and since dosage forms based on pharmaceutical grade resins are on the market, it was of interest to test the applicability of dielectric measurements to the evaluation of adsorption onto ion-exchange resins.

The test was carried out using Amberlite IRP-69 as an ion-exchange resin (used for the manufacture of dosage forms) and two betablockers (propranolol hydrochloride and timolol maleate) as model drugs. Two dielectric parameters were determined: dielectric loss ($\varepsilon''$) and dielectric permittivity ($\varepsilon'$).

The aims of this report were both to compare the results obtained by the classical adsorption isotherm studies with those of the dielectric method and to propose an alternative technique.

## MATERIALS AND METHODS

### Chemical Reagents

Propranolol hydrochloride was purchased from Cooper (France).Timolol maleate was donated by Merck Sharp and Dohme-Chibret. Under the experimental conditions, betablockers were in their cationic form.

Amberlite IRP-69, a pharmaceutical grade cation-exchange resin, was supplied by Prolabo. It is a sulfonic copolymer of styrene and divinylbenzene. The particle size ranged from 100 to 400 mesh (25–150 μm). This resin is characterised by a total exchange capacity of cations of 4.3 mEq/g.

### Resin Preparation

The resin was supplied in the sodium form, which was transformed into the hydrogen form as follows: Two grams of ion-exchange resin sample in the sodium form were washed with 10 ml of acetone on a sintered glass filter and dried with a vacuum pump. It was then washed with 10 ml of ethanol 95 % (V/V), dried using a vacuum pump, and left in contact with 10 ml of 2 N chlorhydric acid for 3 hours (stirring at 300 rpm, at room temperature). Finally, it was washed with distilled water in order to eliminate all the protons and dried in an oven (40 °C) to constant weight.

### Adsorption Isotherms

A drug concentration ranging from 0 to 100 mmol/l was used to obtain the adsorption isotherms. The ion-exchange resin in the hydrogen form (0.1 g) was added to 2 ml of drug solution. This dispersion mixture was then stirred at 300 rpm at room temperature (20°C ± 2°C) for 3 hours to allow adsorption to occur. Indeed, a preliminary study had shown that this adsorption time was adequate to reach equilibrium.

In order to determine the amount of drug adsorbed onto the particles of resin, the dispersions were filtered with a disposable syringe Norm-ject® and a Millipore® filter GS 0.22 μm. With a view to comparing the results of the tests, the filtration was always carried out 1 minute after the end of stirring. The non adsorption of the drugs on the filter was checked.

The free drug in the filtrate was then quantified by UV spectrophotometry (289 nm for propranolol hydrochloride, 294 nm for timolol maleate) after appropriate dilution in distilled water. All assays were carried out in triplicate. The UV

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spectrophotometry method was specific, reproducible, and linear. The amount of drug adsorbed onto the ion-exchange resin was determined by difference between the initial amount and the amount of drug in the filtrate at equilibrium. Adsorption isotherm curves were obtained by plotting adsorbed drug concentration (mmol/g of resin) versus equilibrium drug concentration in solution (mmol/l).

After transformation of the isotherm according to a method previously described for nanoparticles, two parameters of drug adsorption were determined (12): K (equilibrium constant of adsorption), from the first ascending part of the curve, and $T_{max}$ (maximal bound amount), from the second part of the curve, which displays a plateau demonstrating the saturation of all particle binding sites by the drug.

### Dielectric Measurements

This technique has been previously described for drug carrier systems such as nanoparticles. The complex impedance Z* of a capacitive cell (13) containing the resin, submitted to a high frequency alternative field (5 MHz), was measured with a Hewlett Packard 4193 A Vector Impedance Meter. In these experimental conditions, results were reproducible.

From the complex impedance Z* of the cell, it is possible to deduce the dielectric permittivity $\varepsilon'$ and the dielectric loss $\varepsilon''$ with the help of a physical model (3). The $\varepsilon'$ value reflects the overall polarity of the sample, and the $\varepsilon''$ value the conductivity of the sample.

The coaxial and cylindrical dielectric cell was characterised by an internal diameter of 9 mm into which 2 ml of the sample was introduced. In order to compare the results obtained with the dielectric method and adsorption isotherms, both types of measurement were done at the same time and under the same experimental conditions.

The dielectric assays were carried out in triplicate.

## RESULTS AND DISCUSSION

### Comparison of the Dielectric Results with the Adsorption Isotherm

*Dielectric Loss ($\varepsilon''$)*

Figures 1 and 2 show the variations of the bound concentration and the variations of the dielectric loss $\varepsilon''$ versus the same equilibrium concentrations, for propranolol hydrochloride and timolol maleate, respectively.

Figure 1 shows that the concentration of propranolol hydrochloride bound to the ion-exchange resin increases very quickly with the drug equilibrium concentration up to a saturation plateau. The adsorption isotherm of propranolol hydrochloride is a hyperbola similar to the Langmuir classical isotherm with an asymptote corresponding to the maximal concentration of drug bound: the K and $T_{max}$ values for propranolol hydrochloride were 62.5 l/mmol and 1.5 mmol/g, respectively.

The results obtained with timolol maleate (Figure 2) yielded a profile similar to that obtained with propranolol hydrochloride, although the saturation plateau was reached at higher equilibrium concentrations of the drug (K = 1l/mmol and $T_{max}$ = 1.6 mmol/g).

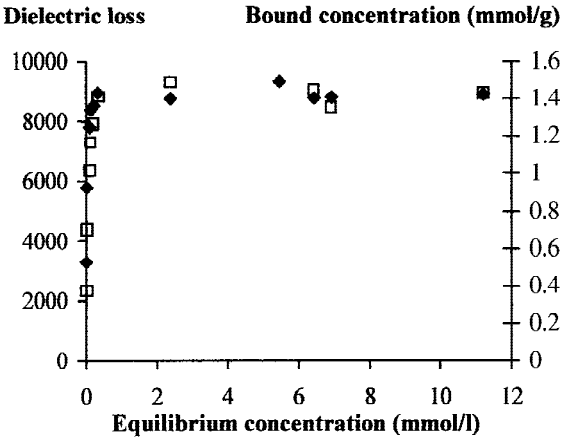


**Fig. 1.** Comparison of the adsorption isotherm (open squares) of propranolol onto Amberlite IRP-69 with the dielectric loss curve (filled diamonds) for the same samples.

Based on the analysis of the two isotherms, $K_{propranolol}$ is larger than $K_{timolol}$ which means that the affinity for the resin is greater for propranolol hydrochloride. On the other hand, the mean $T_{max}$ values for the two drugs, which reflect the binding capacity of the resin, are similar. Figures 1 and 2 show that the isotherm curves matched the plot of $\varepsilon''$ quite closely. However, the adsorption isotherm and the dielectric loss isotherm were better matched in the case of propranolol hydrochloride. Nevertheless, these results show that the variation of the dielectric loss is directly related to the concentration bound for each of the two drugs. Thus, dielectric loss can provide interesting information about the adsorption of drug onto an ion-exchange resin.

*Dielectric Permittivity ($\varepsilon'$)*

Figure 3 shows the adsorption isotherm of propranolol hydrochloride onto Amberlite IRP-69 and the variation of the dielectric permittivity ($\varepsilon'$) at the same equilibrium concentrations. The dielectric permittivity ($\varepsilon'$) does not show the same profile as the isotherm of the concentration bound. Indeed, the dielectric permittivity decreased at low equilibrium drug concentrations (<0.15 mmol/l), and then increased at higher

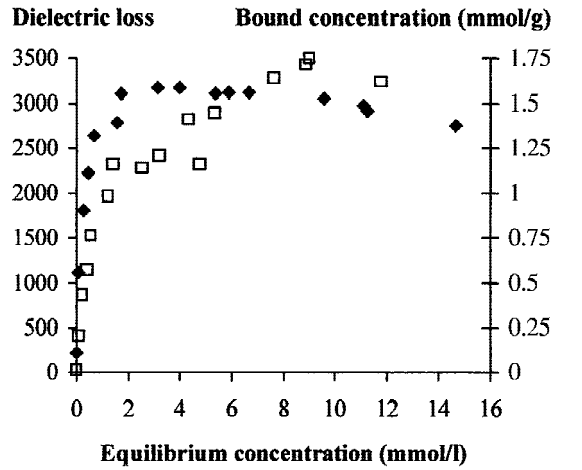


**Fig. 2.** Comparison of the adsorption isotherm (open squares) of timolol onto Amberlite IRP-69 with the dielectric loss curve (filled diamonds) for the same samples.

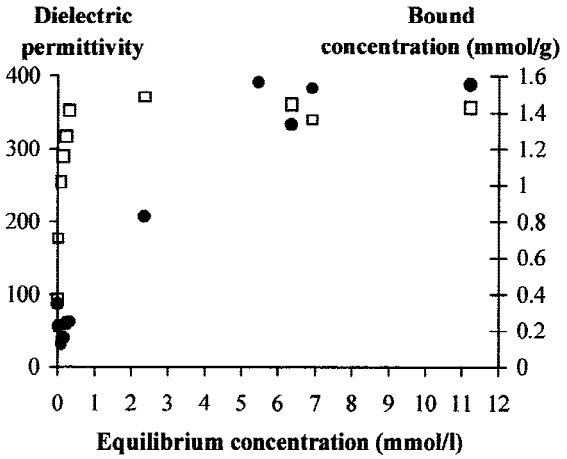


**Fig. 3.** Comparison of the adsorption isotherm (open squares) of propranolol onto Amberlite IRP-69 with the dielectric permittivity curve (filled circles) for the same samples.

equilibrium concentrations, whereas the concentration bound increases progressively.

From the general profile of the isotherm and the saturation plateau, a hypothesis can be proposed in order to explain the binding mechanism of the drug onto the ion-exchange resin. Although the model drugs belong to the same therapeutic and chemical family, they display different adsorption profiles which could be explained by different mechanisms of binding to the resin.

Indeed, in the case of timolol maleate, the dielectric permittivity $\varepsilon'$ decreased in parallel with increased drug binding. This variation can be explained by assuming a single-layer binding mechanism. In this case, the drug interacts through its charged amine group with the sulfonic sites of the ion-exchange resin. Consequently, the drug-resin complex is less polar than the resin in its original protonated form. This decrease in polarity is reflected by the decrease of the dielectric permittivity of the sample.

For propranolol hydrochloride, a decrease of the dielectric permittivity was observed when the equilibrium concentrations were below 0.15 mmol/l. This decrease might reflect the same process as that described above for timolol maleate. However, at higher concentrations, the dielectric permittivity increases. Since the $\varepsilon'$ value is linked to the overall polarity of the system, this increase means that the overall polarity of the complex increases. On the other hand, the shape of the adsorption isotherm shows that the binding of propranolol hydrochloride is a continuous process. Therefore, the polarity of the sample increases at the same time as drug binding to the ion-exchange resin. This could be due to the binding of a second layer of propranolol hydrochloride molecules. The first layer of propranolol hydrochloride molecules would be bound onto the ion-exchange resin via electrostatic bindings, whereas the second layer of molecules would form as a result of hydrophobic interactions between the sidechains of two propranolol hydrochloride molecules (14). In this way, the cationic amine group of propranolol hydrochloride would appear on the external surface of the complex. These positively charged complex would increase the polarity of the sample. This mechanism would explain the increase of the dielectric permittivity ($\varepsilon'$) which was observed when the propranolol hydrochloride concentration was higher than 0.15 mmol/l. The difference between the behaviour of timolol maleate and propranolol hydrochloride can be explained by the greater hydrophobicity of the latter.

### Comparison of the Dielectric Results with the Concentration of Drug Bound as a Function of the Initial Concentration

A comparison of the two curves of the dielectric measurements and the adsorption isotherm indicates that both methods are suitable for determining and characterising the adsorption isotherms of drugs onto a resin. Nevertheless, in order to obtain the curve of $\varepsilon'$ or $\varepsilon''$ versus the equilibrium concentrations, the equilibrium concentrations must first be determined. To do this, it is necessary to separate the continuous from the dispersed phase, and to assay the drug in the continuous phase. This process is equivalent to constructing an adsorption isotherm. Therefore, it would be interesting to adapt the dielectric method to analyse the drug-complex mixture directly without separation.

The values of the dielectric loss and the bound concentration versus the initial propranolol hydrochloride concentration (obtained from the weight of drug introduced in the medium) are therefore plotted in Figure 4. The curves show the same shapes as in Figure 1 except that they are shifted to the right. Similar results were obtained with timolol maleate (data not shown) : in this case the shift to the right was less pronounced. The drug adsorption onto the resin can therefore be characterised by using the dielectric permittivity measurements without determining the equilibration concentrations. This indicates that the drug concentration which is required to saturate all the adsorption sites of the resin particles can be determined by using the dielectric parameters alone. In addition, it should be kept in mind that, in our experiment with 12 concentration points, the dielectric curves were obtained in less than one hour as compared to at least four hours for the classical isotherm method. Indeed, the dielectric measurements are rapid, easy, inexpensive, and require neither filtration nor titration of the drug.

These results show that the dielectric parameters can offer major benefits for the study of the adsorption of drugs onto carriers in pharmaceutical formulations.

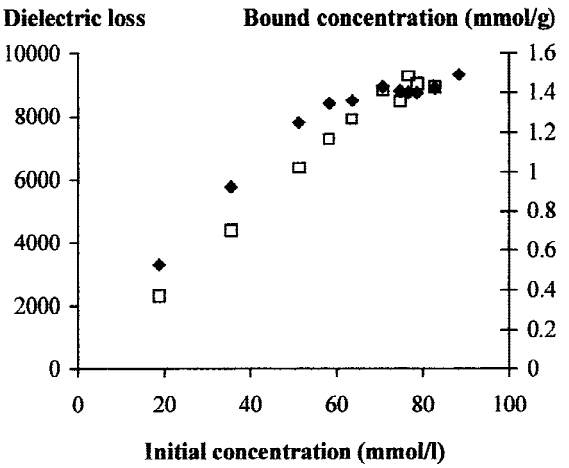


**Fig. 4.** Comparison of the concentration of propranolol bound (open squares) to Amberlite IRP-69 with the dielectric loss curve (filled diamonds) for the same samples as a function of the initial concentration.

## CONCLUSIONS

This report demonstrates that the dielectric method can be applied to following the adsorption of cationic betablockers onto an ion-exchange resin, Amberlite IRP-69. This conclusion was reached by comparing dielectric measurements with classical adsorption isotherms. Similar results would be expected with anionic drugs and cationic exchange resins.

The results show that the dielectric permittivity ($\varepsilon'$) or the dielectric loss ($\varepsilon''$) can be used to follow the modification of ion-exchange resins during the drug adsorption process. The dielectric loss ($\varepsilon''$) seems more useful than the dielectric permittivity ($\varepsilon'$) since it can be used directly without further mathematical transformation. However the use of one or the other parameter should be chosen on a case-by-case basis.

The dielectric method can also be used to determine the quantity of drug required to saturate all the adsorption sites of the particles, i.e., the maximum bound quantity. This could be applied directly in routine quality control of pharmaceutical formulations such as exchange resins currently used in therapeutics.

In addition, a hypothesis about the process of the binding of a drug onto the ion-exchange resin could be proposed, which could help in interpreting release data from specific dosage forms. However, this hypothesis should be confirmed by other appropriate physical methods. Moreover, the dielectric measurements are very easy, rapid and, as mentioned above, require neither filtration nor titration of the drug. If necessary, the whole process can also be automated.

Dielectric analysis seems to be a promising tool in pharmaceutical formulation since it can also be used for solid dispersions, liposomes, cyclodextrins and other relevant systems (4). Due to its simplicity and reproducibility, its increasing use in pharmaceutical sciences can be expected.

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