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Parelectric spectroscopy of drug-carrier-systems—distribution of carrier masses or activation energies

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Abstract

The answer of a high-frequency electromagnetic wave to a sample as termination of an open-ended coaxial line gives the mobility and the density of permanent electric dipole moments in the substance under test. As long as these dipoles are attached to carrier molecules of well defined masses, both parameters can be extracted from the reflected wave in a quick manner giving unambiguous results. The corresponding algorithm has been applied to solid lipid nanoparticles with glucocorticoid molecules attached to or incorporated in the carrier molecules. The results from measurements in the frequency region (0.1–100) MHz have recently been published. As soon as we have to envisage a distribution in carrier masses and/or in activation energies of the attached molecules, we have to apply a more sophisticated evaluation algorithm. The need for a more generalised algorithm is clear as well, when we have to deal with more than one dipole-carrying constituent in the samples. All these evaluation algorithms shall be presented together with the mathematical basis in a short but exact form.

Keywords: Drug-carrier-systems; Parelectric spectroscopy; Distribution of carrier masses; Evaluation algorithms

1. Introduction

The inner and outer conductor of an open-ended coaxial probe line form a condenser ‘filled’ with the sample under test. The reflection coefficient of such a set-up can be measured using a frequency analyzer that can be swept over at least three orders of magnitude of the frequency. This reflection behaviour can be converted to give the real and imaginary part of the complex parelectric permittivity thus yielding the parelectric dispersion and absorption answers, respectively. As early as 1930 Peter Debye could find the equations describing these frequency-dependent answers [1] and present a microscopic picture for the explanation of the relaxation time of the dipole-carrying molecules which are tumbling in the substance. Since then, the tool of parelectric spectroscopy could find applications in biophysics [2], medicine [3] and in various fields of pharmacology [4,5,6]. If the basis of the underlying theory namely electric dipoles fixed to molecules of a well defined mass is violated, both the frequency-dependent dispersion answer $\varepsilon'(f)$ as well as the absorption $\varepsilon''(f)$ are distorted. Many efforts have been reported [4,5] to fit slightly modified ‘quasi-Debyean’ functions to the measured values, all of them introducing phenomenological parameters. From these parameters, however, no insight can be gained as to the causes of the distortions. We dare present here modified equations on the basis of two a-priori distributions of the Debyean relaxation time τ using an interpretation of the Einstein–Debye-relation and of Arrhenius law [7]. All these interpretations, naturally, are only applicable as long as the signal/noise ratio is sufficiently high. This assumption is as well the basis for the application of the ‘methods of second moments’ as applied to the distorted absorption $\varepsilon''(f)$. There are three reasons from which we present all equations using a logarithmic frequency abscissa. First, the natural logarithm

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of the relaxation frequency f_o as the inverse of the Debyean relaxation time τ is – following Arrhenius law – proportional to the activation energy governing the thermal tumbling of the dipole-carrying molecules; this is a physical reason. Second, only in dependence on the logarithmic frequency the absorption curves $\varepsilon''(f)$ can be integrated to give an analytically closed form of the criteria to be presented; this is mathematical reason. Third, in this presentation the dispersion and absorption curves are symmetrical thus revealing superpositions of two dipole-carrying sub-systems in a striking way; this is a practical reason.

2. Experimental part

The central part of the set-up is a commercial frequency analyzer (Rohde and Schwarz ZVR, Germany) with open-ended probes which were customer-fabricated from rigid copper coaxial lines (Huber and Suhner, Switzerland). The analyzer is programmed via a Dell notebook, with usually 200 logarithmically equidistant frequency steps in the regions (1–1000) MHz or (0.1–100) MHz, depending on the masses of the molecules under test. This notebook can read the analyzer output and convert it to the desired functions $\varepsilon'(f)$ and $\varepsilon''(f)$. The sample-containing head is, naturally, thermostabilized to within ±0.5 °C. The signal/noise ratio, naturally, depends on the number of averages chosen and the bandwidth of the receiver part of the analyzer. For typically 200 frequency steps, 10 averages and a bandwidth of 10 Hz, we need 20 minutes to get a complete set of functions $\varepsilon'(f)$ and $\varepsilon''(f)$ for a fixed drug concentration and a fixed temperature as parameters. In the case of the SLN carriers with glucocorticoid molecules the sample preparation was done by Miss Chié Nakamura, Department of Pharmacy of our university. The results have been published without a mathematical justification of the algorithms applied [6]. Samples which form the basis of the application of the novel algorithms presented here, are polymethacrylate with fluoresceine or with rhodamine to explain a distribution in masses and liposomes+polyethyleneglycole as carriers with peptides of variable concentration to distinguish between the contributions of two dipole-carrying species in the sample: we are grateful for the preparations by Mrs. Ines Sauer and Mrs. Margitta Dathe, Forschungsinstitut für Molekulare Pharmakologie, Berlin and Mr. Bernd-Reiner Paulke, Frauenhofer-Institut für Angewandte Polymerforschung, Golm. The latter results will be published with the due pharmacologic implications and interpretations by these colleagues.

3. Theoretical part

To start with, we present the nomenclature and then write Debye's equations in this notation. We use ε_∞ as the contribution of the induced electric dipole moments and $\Delta\varepsilon$ as the contribution of the permanent electric dipole moments. The Debyean relaxation time τ will be converted to the relaxation frequency $f_o = 1/2\pi\tau$ thus giving the Einstein–Debye-relation and Arrhenius' law in the form

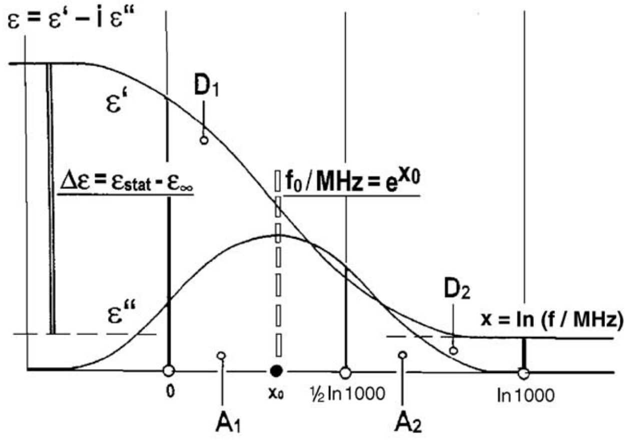

Fig. 1. Calculation of the four integrals $A_1 \ldots D_2$ yields four equations of the four parameters in Debye's equations. As an example we use three orders of magnitude for the scanning frequency f, (1–1000) MHz.

$$f_o = kT/8\pi^2 r^3 \eta, \quad f_o = f_o * e^{-\Delta E/\mathrm{RT}}.$$

We define the logarithmic quantities $x = \ln(f/\mathrm{MHz})$, $x_o = \ln(f_o/\mathrm{MHz})$ and can thus rewrite the expression $\sigma/\varepsilon_o\omega$ as contribution of the electric conductivity σ to the parelectric answer $\varepsilon''(x)$ as $s \cdot e^{-x}$ with $s = 18{,}000 \cdot \sigma/\mathrm{Sm}^{-1}$.

For further applications and discussions we then can write Debye's equations in the form

$$\text{dispersion}: \varepsilon'(x) = \varepsilon_\infty + \Delta\varepsilon \Big/ \left(1 + e^{2(x - x_0)}\right),$$

$$\text{absorption}: \varepsilon''(x) = s \cdot e^{-x} + \Delta\varepsilon \cdot e^{x - x_0} \Big/ \left(1 + e^{2(x - x_0)}\right).$$

In the case of pure Debyean behaviour of the functions $\varepsilon'(x)$, $\varepsilon''(x)$, we have to extract from 201 dispersion values and 201 absorption values the four parameters $s(\sigma)$ and ε_∞ which we are not interested in and the parameters dipole mobility x_o and dipole density $\Delta\varepsilon$ which we need for the interpretation of changes in dependence on the concentration of drug or dye molecules attached to or incorporated in the carrier system or in dependence on the temperature.

We use an integral criterion giving four equations for the four parameters, the integrals sketched in Fig. 1.

For the case of a frequency range chosen between 0.1 MHz and 100 MHz, i.e. $x = -\ln 10$ to $+2 \cdot \ln 10$, we can define the following integrals, namely

$$D_1 = \int_{-ln10}^{+(1/2)\cdot\ln 10} \varepsilon'(x)dx = (3/2)\cdot ln10\cdot\varepsilon_\infty + \Delta\varepsilon\cdot d_1(x_o),$$

$$D_2 = \int_{-ln10}^{+(1/2)\cdot ln10} \varepsilon'(x)dx = (3/2)\cdot ln10\cdot\varepsilon_\infty + \Delta\varepsilon\cdot d_1(x_o)$$

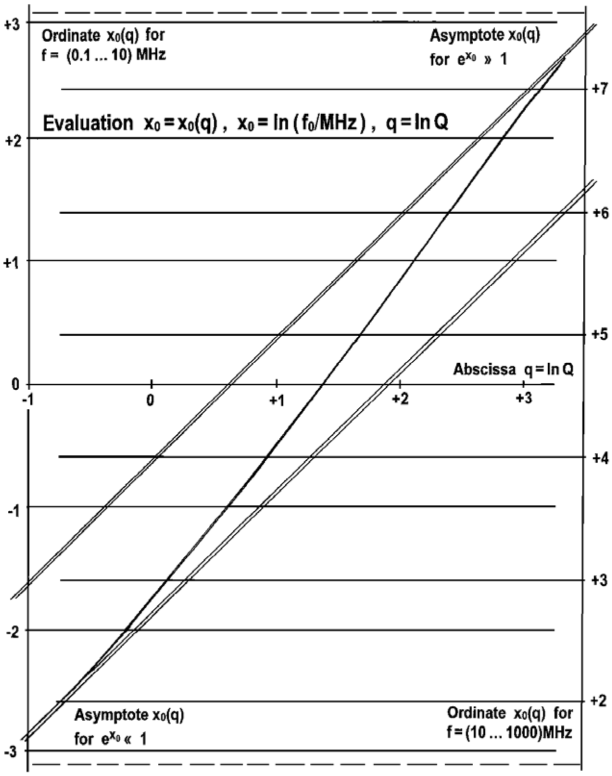

Fig. 2. The evaluation of the parameter ε_∞ and $s(\sigma)$ in a first step and of $\Delta\varepsilon$ in a second step yields a function $x_o = x_o(q)$ which is a monotonous dependence on q. Thus, we can calculate the quantity x_o in an unambiguous way from the 402 values $\varepsilon'(x)$ and $\varepsilon''(x)$.

allowing\ for the difference

$$N = D_1 - D_2$$

$$= \Delta\varepsilon\cdot[d_1(x_o) - d_2(x_0)] \quad \text{free from the parameter } \varepsilon_\infty.$$

Using the absorption part we can define

$$A_1 = \int_{-\ln 10}^{+(1/2)\cdot\ln 10} \varepsilon''(x)dx$$

$$= \left(10 - 10^{-1/2}\right)\cdot s + \Delta\varepsilon\cdot a_1(x_o),$$

$$A_2 = \int_{+(1/2)\cdot\ln 10}^{+(1/2)\cdot\ln 10} \varepsilon''(x)dx$$

$$= 10^{-3/2}\cdot\left(10 - 10^{-1/2}\right) + \Delta\varepsilon\cdot a_2(x_o)$$

allowing for the difference

$$Z = 10^{3/2}\cdot A_2 - A_1$$

$$= \Delta\varepsilon\cdot\left[10^{3/2}\cdot a_2(x_o) - a_1(x_o)\right] \quad \text{free from } s(\sigma).$$

From the quotient $Q=Z/N$ which is free from the third parameter $\Delta\varepsilon$ we can find the fourth parameter x_o in an unambiguous way—see Fig. 2. The logarithmic plot shows that we have a monotonous function $x_o=x_o(q)$, $q=\ln Q$. This function can be programmed as the four integrals $a_1(x_o) \ldots d_2(x_o)$ are of analytically closed forms as given in Appendix A1.

The numerical calculation of the integrals $A_1 \ldots D_2$ via a summation performed in the notebook yield, by the way, a further averaging of the measured values as we have to extract four parameter from 402 values. The second parameter of interest besides x_o, namely $\Delta\varepsilon$, can be found by going back to the last step.

In the cases where the dipole density $\Delta\varepsilon$ as calculated from the maximum of $\varepsilon''(x)$ gives the same value as calculated from the point of inflection of $\varepsilon'(x)$, we are sure to have a pure Debyean relaxation process. A second criterion is the half-width of $\varepsilon''(x)$ which should, in this case, have the value $\Delta x=2\cdot\ln(\sqrt{3}+2)=2.6339\ldots$. The following figure gives results of measured functions $\varepsilon'(x)$,$\varepsilon''(x)$ for polymethacrylate molecules as carriers of fluoresceine and rhodamine dye molecules attached. We see the lesser steep slope of $\varepsilon'(x)$, the lower maximum values of $\varepsilon''(x)$ and a larger half-width Δx in both cases.

To describe such a behaviour, many modifications have been described in the literature [4,5], all of them using phenomenological changes in the Debye equations, for

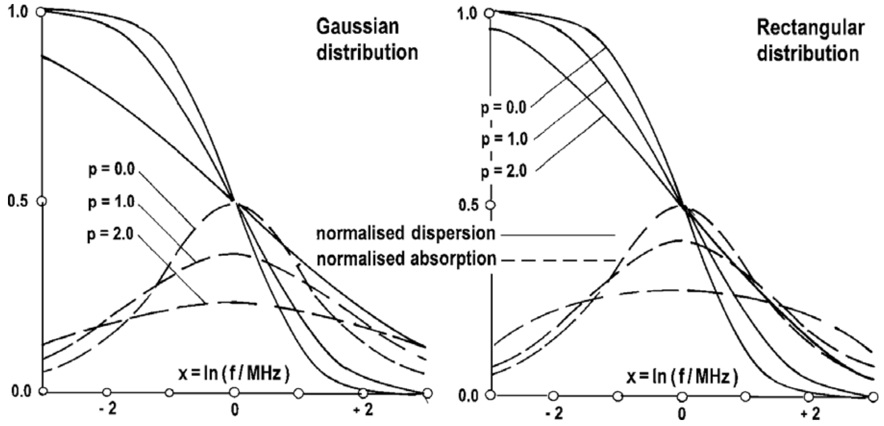

Fig. 3. For the cases of a Gaussian and a Rectangular distribution of the quantity $x_o=\ln(f_o/\text{MHz})$, we can compare the effects on both $\varepsilon(x)$ and $\varepsilon''(x)$. For small values of the distribution parameter $p=\Delta x_G/\Delta x_F$ the differences can obviously only be resolved for very good values of the signal/noise: in the experimental results used here this is possible.

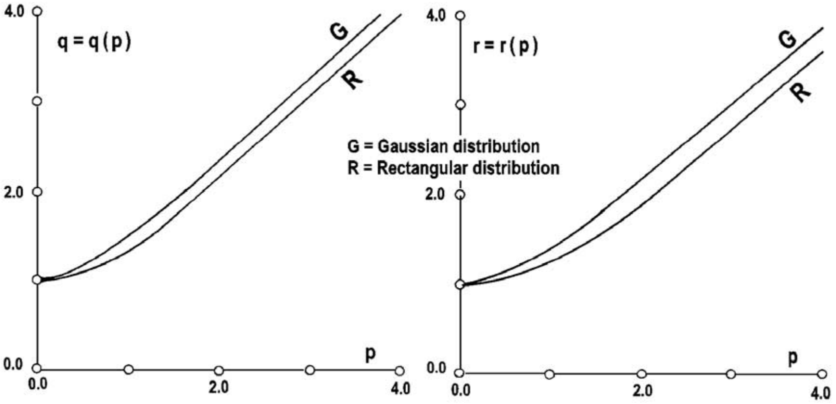

Fig. 4. Here, again, we can see that the differences between the assumptions of a Gaussian and a rectangular distribution of x_o are relatively small. This holds for the relative broadening $q(p)$ of the absorption curve as well as for the normalized decrease $r(p)$ of the maximum value of these curves.

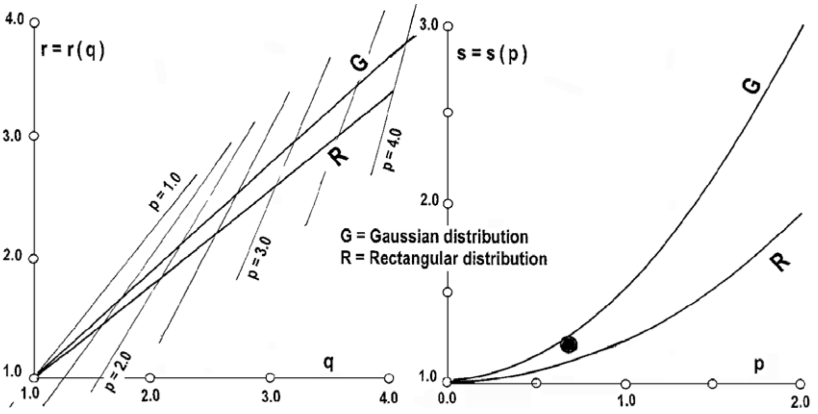

Fig. 5. Left hand side: We can get rid of the parameter p as used in Fig. 4 and are able to plot the relations $r(q)$, both variables being measured values. For small values of q and $r(q)$, a discrimination between the cases R and G can only be possible for very good values of the signal/noise ratio. Right hand side: A relatively sharper criterion is the use of the second moments M_2 for the absorption curves $\varepsilon''(x)$, as long as the frequency range can be extended over a sufficiently large number of orders of magnitude. The fat dot gives the combination of the values from the polymetharcylate+flurosceine/+rhodamine samples. For s=1.215 and p=0.667, we can deduce a distribution of Gaussian character to be much more likely than a rectangular character.

instance an additional parameter $\alpha<1$ leading to the modified equations (in our nomenclature)

$$\text{dispersion}: F'(x_o) = [\varepsilon'(x)-\varepsilon_\infty]/\Delta\varepsilon = 1/\left(1+e^{2\alpha x_o}\right),$$

$$\text{absorption}: F''(x_o) = \varepsilon''(x)/\Delta\varepsilon = \alpha\cdot e^{\alpha x_o}/\left(1+e^{2\alpha x_o}\right).$$

These and similar changes valid for symmetrical behaviour of the measured curves do not change the point of inflection of $F'(x_o=0)=1/2$ and solely change the slope of this curve, give a smaller value $F''(x_o=0)=1/2\alpha<1/2$ and the larger half-width $\Delta x^*=\Delta x/\alpha>\Delta x$. The introduction of such a phenomenological parameter, however, gives no physical insight in the causes of such a deviation from the pure Debyean case.

We propose, therefore, a different way of explanation: whether a distribution in volumes of the dipole-baring molecules gives rise to a distribution of x_o via the Einstein–Debye relation or a distribution in the activation energies gives rise to such a distribution, we assume normalized weighting functions $G(x, x_o, \Delta x_G)$ changing the normalized Debyean functions $F(x_o, \Delta x_F)$ as given above to yield envelope functions $H(x_o, \Delta x_H)$[1] applying the folding process

$$H',''(x) = \int_{x_o=-\infty}^{x_o=+\infty} F','' (x_o)\cdot G(x,x_o)\,dx_o.$$

From these results we can find the changes in $H''_{\max}=H''_{\max}(\Delta x_G)$, $\Delta x_H=\Delta x_H(\Delta x_G)$ and in the second moment $M_2(\Delta x_G)=\int_{x=-\infty}^{x=+\infty} x^2\cdot H''(x)\,dx$. In what follows we restrict ourselves to symmetrical weighting functions, $M_1=\int_{x=-\infty}^{x=+\infty} x\,.\,G(x)\,dx=0$ and use $G(x)$ in the normalized form $M_0=\int_{x=-\infty}^{x=+\infty} G(x)\,dx=1$. As an Appendix A2 we use as such weighting functions $G(x, x_o, \Delta x_G)$ a Gaussian and a rectangular distribution. Although both types have the same half-width Δx_G we can see from Fig. 3 the striking differences on $H'(x)$ and $H''(x)$.

Before we present the different criteria to judge the measured curves $H'(x)$ and $H''(x)$ we will introduce our

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[1] German notations F for Funktion, G for Gewicht and H for Hülle.

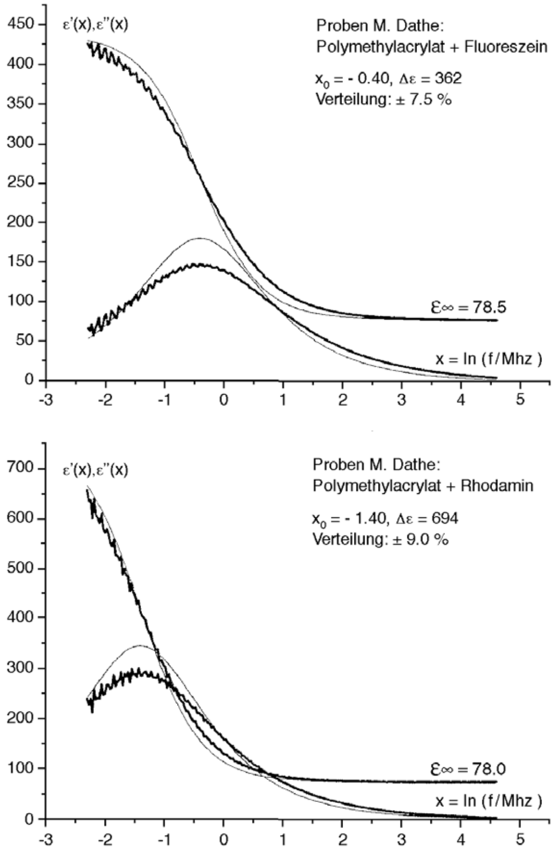

Fig. 6. As an example for distorted curves we have taken the spectra of polymethacrylate as carrier with different dye molecules attached. In this case, the frequency range best suited for the molar masses had to be chosen as (0.1–100) MHz. From the decrease in maximum of $\varepsilon''(x)$ and the increase in half-width $\Delta x_H > \Delta x_F$ we find an average parameter p=0.667 (see text and Fig. 5).

shortest possible notation, in all formulae with R standing for a rectangular and G standing for a Gaussian distribution.

We define the abbreviations

$$p = \Delta x_G / \Delta x_F \geq 0, \quad q(p) = \Delta x_G / \Delta x_F \geq 1,$$

$$r(p) = 1/2 \cdot H''_{\max} \geq 1 \quad \text{and} \quad s(p) = M_2(p)/M_2(0) \geq 1.$$

Although we can give good approximate expressions for these functions (which will be presented as Appendix A3), we give the results as Figs. 4 and 5. Both the expressions $q(p)$ and $r(p)$ still depend on the parameter p governing the distribution. An elimination of p allows for the direct judgement of the character of the possible distribution as they link the two measured quantities q and r.

On the first glance, the criterion s=$s(p)$ seems to be the sharpest criterion, as the difference between a Gaussian and a rectangular distribution is relatively large. A reliable calculation of the second moments depends, however, on a good signal/noise ratio and a sufficiently large region of measuring frequencies—see Results.

In the case of more than one contribution of dipole-carrying constituents, we have to use an iterative procedure to find the contributions $f_{o,1}$, $\Delta\varepsilon_1$ in the lower frequency region and $f_{o,2}$, $\Delta\varepsilon_2$ in the higher frequency region. The contributions of free water always is contained in the term ε_∞, as its relaxation frequency is near 18 GHz. Loosely bounded water molecules can show, however, a contribution in the vicinity of (200 . . . 400) MHz [2] and thus have to be taken into account to explain more than one contribution to $\varepsilon'(x)$ and $\varepsilon''(x)$.

The iterative procedure, in this such cases, applies the A_1 . . . D_2 evaluation algorithm to the lower 100 points thus giving first approximation values $f_{o,1}^{(1)}$, $\Delta_{\varepsilon 1}^{(1)}$. The corresponding function $\varepsilon'_1(x)$, $\varepsilon''_1(x)$ are subtracted from the measured values and the abovementioned algorithm applied to the higher 100 points gives first approximations $f_{o,2}^{(1)}$, $\Delta_{\varepsilon 2}^{(1)}$. Subtraction of the corresponding functions $\varepsilon'_2(x)$, $\varepsilon''_2(x)$ from the measured values yields – in the lower region – better

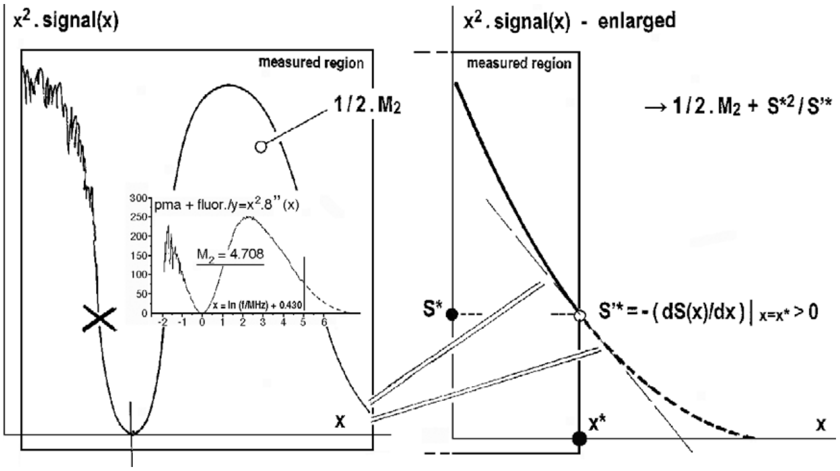

Fig. 7. The principle of calculation of the second moment is shown (left hand side) together with the addition of values missing from too small frequency ranges used during the measurement. The insert gives the example of such a calculation from the pma+fluro sample: With M_2=4.708 and $M_2(0)$=3.876, we find the normalized values of s=1.215.

parameter values $f_{o,1}^{(2)}$, $\Delta_{\varepsilon 1}^{(2)}$, ... This iterative procedure has to be repeated up to the point where the difference in the parameter values f_o, $\Delta\varepsilon$ given by step n to n+1 differs less than the uncertainty caused by the signal/noise ratio.

4. Results

We only selected some few examples to verify the efficiency of the algorithms proposed. The measured curves $\varepsilon'(x)$, $\varepsilon''(x)$ for the two systems as presented in Fig. 6 could be analyzed to have a broadening, most likely caused by a distribution of the masses of the polymethacrylate chains. The evaluation of the corresponding second moments is presented in Fig. 7. We see that we can use only the part for $x \geq 0$ with the better signal/noise ratio, caused by the restriction of the frequency region to values $f \leq 100$ MHz, we have to add a well suited function to be able to extend the calculation of M_2 towards higher frequencies. This procedure only is tolerable as long as this additional contribution is small compared to the M_2 value given by integration over the measured frequency region.

In the case of the system of liposomes+polyethyleneglycole as carriers with peptide molecules of variable concentration added, we had to apply the iterative procedure at low concentration. In this case the peptides added to the carrier

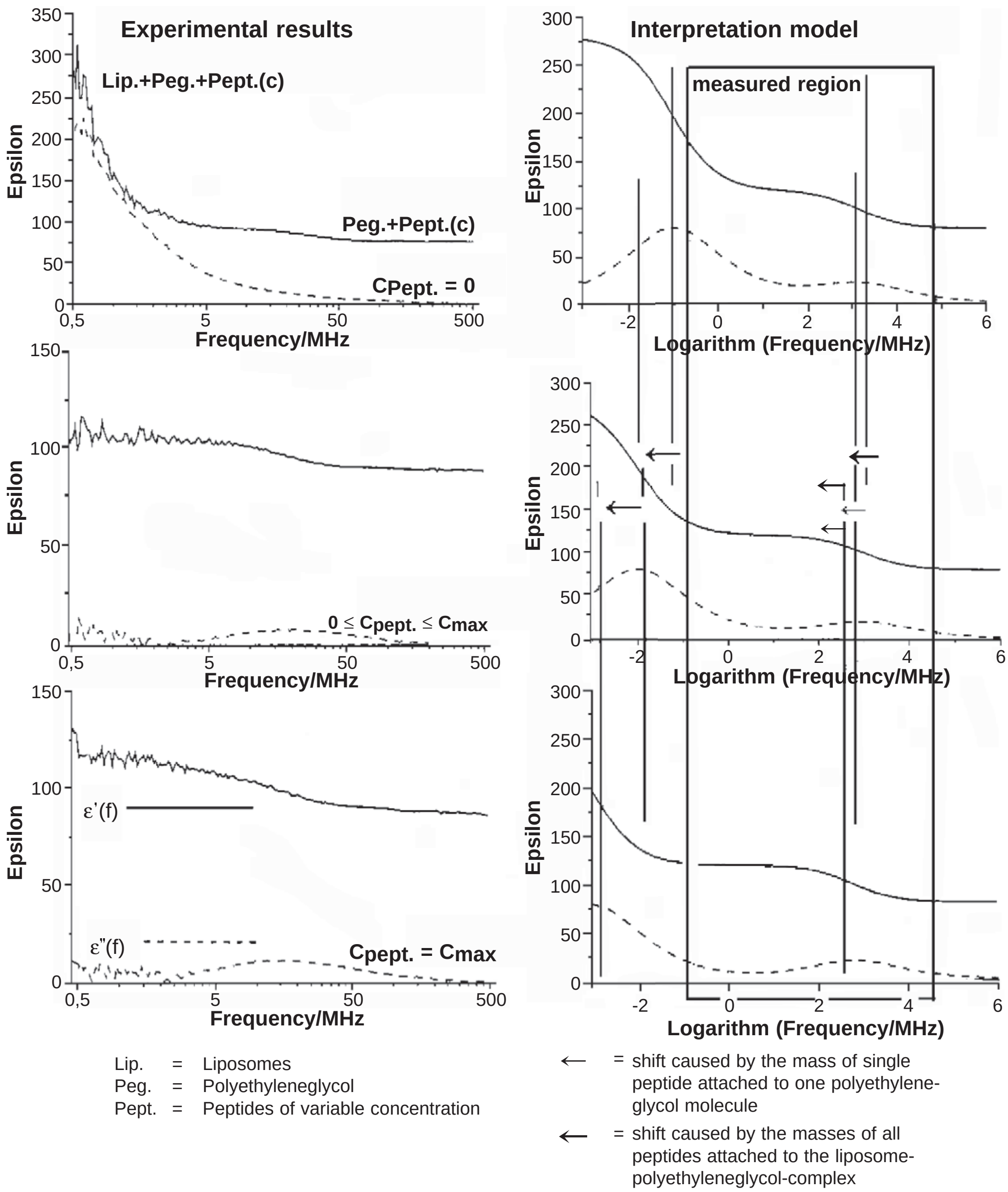

Fig. 8. Here, we present an example of a carrier/peptide system where two components contribute to both the dispersion $\varepsilon(x)$ (full lines) and the absorption $\varepsilon''(x)$ (broken lines). As the systems of liposomes+polyethyleneglycole+peptide move separately from the system polyethyleneglycole+peptide, the separation was laborious for zero concentration of peptide. The underlying model is explained in the figure.

system have two effects. First, they add as a sum to the liposomes+polyethyleneglycole system thus augmenting the whole mass and shift the response in large steps towards lower frequencies. The answer to $\varepsilon'(x)$ and $\varepsilon''(x)$ in the higher frequency region is caused by the sub-system polyethyleneglycole+peptides(c) depending on the concentration c. The shifts connected to an increasing concentration of such single peptide masses to the polyethyleneglycole molecules are, therefore, smaller for this sub-system reacting independently to the external high-frequency electric field. This interpretation is presented together with the measured functions $\varepsilon'(x)$ and $\varepsilon''(x)$ in Fig. 8.

5. Conclusions

The tool of parelectric spectroscopy can give an insight to the physical processes of an attachment of dye or drug molecules to carrier systems well suited to investigate the dermal uptake. The algorithms needed for the evaluation of the parameters–in most cases the dipole mobility f_o/MHz and the dipole density $\Delta\varepsilon$–are easily understandable and can be implanted as a program in the notebook used to scan the frequency analyzer. For a deeper discussion that meets the demands of any pharmacologic interpretation, a close co-operation with the neighbouring groups working in this field is necessary. Here, we only were interested to underline the need for reliable criteria.

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Appendix A

A.1. The integrals $a(x_o)$ and $d(x_o)$

Both types of integrals can be solved to give an analytically closed form, namely

$$\int_{x=a}^{x=b} dx/\left(1+e^{2x}\right) = +b-a-(1/2) \times \ln\left[\left(1+e^{2b}\right)/\left(1+e^{2a}\right)\right],$$

$$\int_{x=a}^{x=b} e^{x}dx/\left(1+e^{2x}\right) = +\arctan\left[\left(e^{b}-e^{a}\right)/\left(1+e^{b+a}\right)\right].$$

A.2. The definition of $G(x,x_o,\Delta x_G)$

In the case R we define $G_R(x,x_o,\Delta x_G)$

$$= (1/\Delta x_G) \text{ for } x-\Delta x_G/2 \le x_o \le x+\Delta x_G/2, \ = 0 \text{ else.}$$

In the case G we define $G_G(x,x_o,\Delta x_G)$

$$= \left(2\cdot\sqrt{\ln 2}/\Delta x_G.\sqrt{\pi}\right)\cdot\exp\left[4\cdot\ln 2(x-x_o)^2/\Delta x_G^2\right].$$

For both definitions we have taken into account the conditions $M_0(x)$=1 and $M_1(x)$=0. The first condition of normalization guarantees the conservation of the normalization of $\varepsilon''(x)$, the second condition restricts ourselves to symmetrical weighting functions.

A.3. Approximations for $q=q(p)$ and $r=r(p)$

From the mathematically exact behaviour of these functions we know the limiting expressions for both $p \ll 1$ and $p \gg 1$. A fitting to the respective values for $p \gg 1$ yields the formulae.

for R:

$$q(p) = \left(1+2.280p^2+1.471p^4+1.000p^6\right)^{1/6},$$

$$r(p) = \left(1+1.734p^2+0.875p^4+0.347p^6\right)^{1/6},$$

for G:

$$q(p) = \left(1+4.968p^2+4.764p^4+1.000p^6\right)^{1/6},$$

$$r(p) = \left(1+3.702p^2+2.736p^4+0.626p^6\right)^{1/6}.$$

A.4. The second moments

We find $M_2(p)$ as

for R:

$$M_2(p) = M_2(0)+0.905750p^2,$$

for G:

$$M_2(p) = M_2(0)+1.965207p^2.$$

With $M_2(0)$=3.875858 we find the functions as given in Fig. 5 as

for R:

$$s(p) = 1+0.233690p^2,$$

for G:

$$s(p) = 1+0.507431p^2.$$

The addition to the integration to give M_2 in cases where the maximum frequency is limiting the functions $x^2\cdot\varepsilon''(x)$ can be found for $x \ge x^*$ using the ansatz $A\cdot e^{-\mathrm{B}x}$ which can easily be integrated between $x=x^*$ and $x=\infty$. Let $S^*=S(x=x^*)$ be the value of the signal to be integrated and

$S'^*=-[dS^*(x)/dx]\,|_{x=x^*}$ be the slope at this point. We, then, have to add the missing part of the integral to give

$$M_2 = 2\left[1/2M_2(0\le x\le x^*) + S^{*2}/S'^*\right] .$$

Glossary of abbreviations

ε_∞	Contribution of induced dipole moments
$\Delta\varepsilon$	Contribution of permanent dipole moments
$\varepsilon'(f)$	Parelectric dispersion
$\varepsilon''(f)$	Parelectric absorption
f	Variable frequency
f_o	Dipole mobility=$1/2\pi\tau$
τ	Debyean relaxation time
x	=ln (f/MHz): logarithmic variable
x_o	=ln (f_o/MHz): logarithmic mobility
c	drug-,dye- or peptide concentration
k	Boltzmann constant
R	Gas constant
T	(Absolute) temperature
η	Shear viscosity
σ	Electric conductivity
ΔE	Activation energy
$F(x_o)$	Normalized Debye function
$G(x,x_o)$	Normalized weighting function
$H(x)$	Envelope function
Δx_F	Natural half-width of $F(x_o)$
Δx_G	Half-width of $G(x,x_o)$
Δx_H	Half-width of $H(x)$
p	Relative half-width of $G(x,x_o)$
$q(p)$	Relative half-width of $H(x)$
$r(p)$	Relative decrease of the $H(x)$ maximum
$M_2(0)$	Second moment of $F(x_o)$
$M_2(p)$	Second moment of $H(x)$
$s(p)$	Normalized second moment of $H(x)$

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