Structure and Dynamics of Drug-Carrier Systems as Studied by Parelectric Spectroscopy

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Abstract

In the field of topical application without or with little systemic side-effects to reach anti-inflammatory or anti-androgeneous effects, nanoparticles as carriers for drugs as betamethason-17-valerate, prednicarbate, prednisolone, RU 58841-myristate or cyproterone acetate have proven to enhance the transdermal delivery. This enhancement is closely connected to the interaction of the drug molecules with the lipid carrier systems, i.e. incorporation into the carriers or attachment to their surfaces. Whereas the techniques to measure the penetration profiles in the cutaneous region of the skin are well established in the case of fluorescence microscopy applied to thin slices of epidermis or being established in the case of multiphoton microscopy to monitor this fluorescence, the methods for the investigation of the type of interaction between drugs and carrier systems are relatively new: In the case of electron spin resonance the sample volumes have to be restricted to capillary sizes to avoid parelectric losses in the microwave cavities, in the case of the novel method of parelectric spectroscopy we are free from such restrictions. The application of the latter method will be presented here in detail concerning the underlying theory, the experimental aspects as well as the algorithms to extract the parameters of interest from the measured samples. As samples we restrict ourselves to solid lipid nanoparticles coated with different surfactants as carriers for drug-, dye- or spinlabel molecules.

Key words: Parelectric spectroscopy, Lipid nanoparticles, Drug targeting, Topical application

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1 Introduction

The penetration enhancement of drug-carrier systems depends markedly on the type of interaction between the drug molecules and the surfactant-coated lipid carriers [1; 2; 3; 4]. The large variety of nanoparticular carrier systems, as solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), nanoemulsions (NE) and microparticular systems (MS) is well described in the literature as to their formulation, stability, physical classification and their thermal behavior [5; 6]. To get information about the structure and dynamics of such systems interacting with the drug molecules of interest, with dye molecules attached for studies of skin penetration enhancement using fluorescence microscopy in thin skin slices or with spinlabel molecules for electron spin resonance investigations, the relatively novel method of parelectric spectroscopy (PS) has proven a versatile tool since some years. Although the basis of this method, namely the description of the polarization answer of permanent electric dipole moments to an external radiofrequency electric field, is known since to famous work of P. Debye [7], the experimental methods could not meet the demands of a quick and reliable procedure in pharmacology before the development of frequency analyzers on the synthesizer basis about the year 2000. Many reviews about the possibilities and boundaries of the PS method are available to give insight into the experimental details and, especially, in the function of the open-ended coaxial probes to be used when performing measurements on liquid dispersions or emulsions and even when testing living material for medical diagnostic purposes [8; 9; 10; 11; 12]. In the field of pharmaceutical research the PS method is helpful to distinguish between a possible attachment of the guest molecules to the surface of the carrier system chosen and a possible incorporation of such molecules into the carriers. Moreover, the dependence of the two interesting parelectric parameters, the dipole density $\Delta \varepsilon(c)$ and the dipole mobility frequency $f_0(c)$ on the concentration $c$ of the attached or incorporated molecules gives insight into the maximum possible loading of the carrier systems and yields - as a side-effect - the distribution of the carrier masses in the emulsion or dispersion under test. Finally, a temperature-dependent measurement of both parameters $\Delta \varepsilon(T)$ and $f_0(T)$ can give, via an Arrhenius plot, a good estimate of the activation energies of the drug-carrier systems: The knowledge of the latter behavior can serve as a basis for the development of models for a better understanding of the structure and
dynamics of such systems. We present the experimental set-up consisting of commercially available frequency analyzers and thermo-stabilized open-ended coaxial probes and the algorithms needed to extract in a quick manner the two parameters of interest from the frequency-dependent behavior of the paraelectric dispersion curves $\varepsilon'(f)$ and absorption curves $\varepsilon''(f)$. In all cases presented here, we found as best combination of the frequencies to be applied the bands $(0.01 \,–\, 10)$ MHz, $(0.1 \,–\, 100)$ MHz and $(1 \,–\, 1000)$ MHz depending on the molar masses of the systems under test. Each of this bands can be scanned in 200 logarithmically equidistant steps within a 20 seconds sampling time with resulting signal/noise ratios of $50 \,–\, 200$. The reason why we restrict ourselves mainly to SLN systems as carriers is that such systems have been the main objects of interest in our co-operation between the pharmaceutical and the physics department in our Berlin universities.

2 Theoretical Background

The exposure of a physical ensemble of permanent and induced electric dipole moments to an external radiofrequency electric field $E(\omega t)$ yields a polarization $P(\omega t)$. This answer depends of the frequency $f = \omega / 2\pi$ of the driving field, on the density $\Delta \varepsilon$ of the dipoles and on the temperature of the system. $N$ particles with dipole moment $p$ in the volume $V$ give the polarization $P = (N/V) \langle p \rangle$. If we regard this answer $P$ relative to the driving $E$, we can define the electric permittivity $\varepsilon$,

$$\varepsilon = 1 + \frac{1}{\varepsilon_0} \frac{(P_{\text{induced}} + P_{\text{permanent}})}{E} = \varepsilon_\infty + \frac{1}{\varepsilon_0} \frac{P_{\text{permanent}}}{E},$$  \hspace{1cm} (1)

with $\varepsilon_0$ as constant of permittivity in vacuum. We are allowed to omit the vector character of $E$ and $P$ as long as we are regarding isotropic sample material. The electric field tends to produce the maximum polarization $P = (N/V) p$; the thermal motion of the dipole-carrying particles tends to yield the most probable value $P = 0$. This “competition” leads to the average value $\langle p \rangle << p$ of the permanent dipoles,

$$\langle p \rangle = p \frac{p E}{3kT}$$  \hspace{1cm} (2)

with $k$ =Boltzmann’s constant and $T$ = (absolute) temperature. Thus, we find for the permittivity $\varepsilon$ the relation $\varepsilon = \varepsilon_\infty + \Delta \varepsilon$ with dipole density

$$\Delta \varepsilon = \frac{N}{V} \frac{p^2}{3\varepsilon_0 k T}.$$  \hspace{1cm} (3)

As soon as $E$ is applied as an ac field $E(\omega t) = E_0 \cos(\omega t)$, the polarization answer changes to an ac answer $P'(\omega t) = P'(\omega) \cos(\omega t) + P''(\omega) \sin(\omega t)$. As a consequence, the permittivity consists of two parts, namely the paraelectric dispersion $\varepsilon'(f)$ describing the answer in phase and the absorption $\varepsilon''(f)$ expressing the part shifted in phase by $\pi/2$:
These are the famous Debye equations with \( f_0 = \) dipole mobility frequency. The following figure 1 presents both contributions in dependence of the variable frequency \( f \). Both parameters \( \Delta \varepsilon \) and \( f_0 \) depend on the concentration \( c \) of the guest molecules of mass \( m_D \) in the systems with carriers of mass \( m_C \) and on the temperature \( T \) of the dipole-carrying samples:

\[
\varepsilon' (f) = \varepsilon_{\infty} + \frac{\Delta \varepsilon}{1 + \frac{f}{f_0}}, \\
\varepsilon'' (f) = \frac{\Delta \varepsilon}{1 + \frac{f}{f_0}} f_0.
\]

(4)

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{diagram.png}
\caption{The complex permittivity is shown in dependence on the logarithmic frequency \( x = \ln(f/\text{MHz}) \). As the water molecules in the emulsions or dispersions under test relaxes at 18GHz, we can In any cases add its value \( \varepsilon_{\text{stat}} \) to the limiting value \( \varepsilon_{\infty} \). Thus, the value \( \varepsilon_{\infty} \) can serve to control the water content during long-term measuring series.}
\end{figure}

2.1 Dependence on \( c \)

P. Debye gave an interpretation for the quantity \( f_0 \), now known as the Einstein-Debye relation. He assumed the dipole-carrying molecules as spheres of radius \( r \) which suffer a friction when following the electric ac field, described by the (shear-) viscosity \( \eta \),

\[
f_0 = \frac{kT}{8\pi^2 r^3 \eta} \rightarrow f_0 = \frac{1}{m_C + c100m_D}.
\]

(5)

Here, we have converted the sphere Volume \( V = \frac{4}{3}\pi r^3 \) to the sphere mass using the density \( \rho = m/V \). This is one of the equations necessary for the understanding of the function \( f_0 = f_0(c) \).
2.2 Dependence on $T$

Following the "Theory of Rate Processes" [13] we can express the mobility $f_0(T)$ by the necessity to force neighboring particles to jump over potential barriers of energy height $A$ when the dipole-carrying molecules have to follow the electric field. The Arrhenius law for this process has to be written in the form

$$f_0 = f_0^* e^{\left(\frac{-A}{RT}\right)},$$

with $A =$ activation energy and $R =$ gas constant. The fitting parameter $f_0^*$ is not of interest as we only have to extract the quantity $A$ from the plot $\ln(f_0)$ vs. $1/T$ yielding lines with negative slope $-A/R$.

How can we find the parameters $\Delta \epsilon$ und $f_0$ from the measured values $\epsilon'(f)$ and $\epsilon''(f)$? Not of high relevance for measurements on pharmaceutical samples but as soon as we investigate biological samples in vitro or in vivo is the knowledge of a non-zero electrical conductivity $\sigma$. This quantity has to be taken into account in the absorptive part as an additive term $\ldots + \sigma/\epsilon_0 \omega$. In order to have symmetric functions and in order to be able to calculate integrals over the measured curves as criteria to be discussed later, we convert our frequency abscissa to a logarithmic scale by the substitutions

$$x = \ln\left(\frac{f}{\text{MHz}}\right),$$

$$x_0 = \ln\left(\frac{f_0}{\text{MHz}}\right),$$

$$\frac{\sigma}{\epsilon_0 \omega} = s(\omega)e^{-x}.$$  \hspace{1cm} (7)

Thus, we have to use Debye’s equations in their final form

$$\epsilon'(x) = \epsilon_\infty + \frac{\Delta \epsilon}{1 + e^{2(x-x_0)}},$$

$$\epsilon''(x) = s e^{-x} + \frac{\Delta \epsilon e^{x-x_0}}{1 + e^{2(x-x_0)}}.$$  \hspace{1cm} (8)

To extract the four parameters $\epsilon_\infty$, $s(\sigma)$, $\Delta \epsilon$ and $f_0(x_0)$ we have to find four equations containing these quantities. We find them taking the four integrals $D_1$ for the first 100 values of the dispersion $\epsilon'(x)$ and $D_2$ for the higher 100 values as well as $A_1$ for the first 100 values of the absorption $\epsilon''(x)$ and $A_2$ for the higher 100 values - see fig. 2. As the integrals over the theoretical curves (6) can be solved to give analytically closed forms, we can calculate the denominator $D(x_0, \Delta \epsilon) = D_1 - D_2$ thus eliminating $\epsilon_\infty$ and calculate the numerator $N(x_0, \Delta \epsilon) = 10^{3/2}(A_2 - A_1)$ thus getting eliminating $s(\sigma)$ (the factor $10^{3/2}$ holds only for 3 orders of magnitude of the frequency span used). The quotient $Q(x_0) = N(x_0, \Delta \epsilon)/D(x_0, \Delta \epsilon)$ is free from $\Delta \epsilon$ and the function $Q = Q(x_0)$ can easily be converted into its form $x_0 = x_0(Q)$ which, as an unambiguous relation, yields the desired value for the mobility $x_0$. Going back the above steps gives the values for the density $\Delta \epsilon$ and the parameters $\epsilon_\infty$, $s(\sigma)$. 


For the evaluation of the four parelectric parameters of interest, $\Delta \varepsilon$, $f_0(x_0)$, $\varepsilon_\infty$ and $s(\sigma)$ we have to find four equations: These are given by the four partial integrals $D_1$, $D_2$ under the dispersion curve and $A_1$, $A_2$ under the absorption curve, respectively.

### 3 Experimental set-up

#### 3.1 The principle

A frequency analyzer (= transmitter + receiver) feeds an electromagnetic wave into an open-ended coaxial cable. The areas of the cut inner and outer connector form a condenser the capacity of which depends on the parelectric behavior of the sample in contact with this ‘probe’. The wave reflected at this transition is analyzed as to its amplitude and phase thus giving the imaginary and the real part of the complex reflection co-efficient

$$\rho = \frac{Z(\varepsilon) - Z_0}{Z(\varepsilon) + Z_0},$$

with $Z_0$ = (real) impedance of the coaxial cable. The complex impedance of the condenser filled with the sample of complex permittivity $\varepsilon = \varepsilon' - i\varepsilon''$ is given by the definition

$$Z(\varepsilon) = -\frac{i}{\omega(\varepsilon' - i\varepsilon'')C_0},$$

with $C_0$ = capacity of the empty condenser. After calibration with substances of well-known values for $\varepsilon'$, $s(\sigma)$ and $\Delta \varepsilon$ this set-up is able to scan the pre-chosen frequency bands with the possibility to repeat each run $n$ times, thus giving an improvement of the signal/noise ratio by a factor of $\sqrt{n}$. Two different measuring stations consist of an analyzer Hewlett-Packard type HP 8752 C + notebook Compaq with frequency region (0.3 – 1300) MHz and analyzer Rohde & Schwarz type ZVR + notebook Dell with frequency region (0.01 – 4000) MHz. In both stations the notebooks are responsible for the steering of the pre-chosen frequencies - for most purposes three orders of magnitude scanned in 200 logarithmically equidis-
tant steps - and for the extraction of the parameters of interest as outlined in fig. 2. The block scheme of such a set-up is given in fig. 3: Here, the probe head is well suited to measure liquid samples as emulsions or dispersions of the drug-carrier systems.

**parelectric spectroscopy: experimental set-up**

![Diagram of experimental set-up](image)

Fig. 3. The experimental set-up as given above can guarantee a high long-term stability as to the power level of the analyzer as well as to the thermostat system, both after a warm-up time of at least half an hour.

### 3.2 The probes

The cut inner and outer conductors represent the condenser in contact with the material under test, in the case of a probe with 6mm outer diameter, the capacity of the empty probe has a value of 0.03 pF, approx.. Such probes are necessary when the surface of skin or (using endoscopic methods) of the vocal cord are to be inspected. The calculated distribution of the electric field shows a rather steep decrease of $E(r,z)$ with distance $r$ from the probe axis and with the depth $z$ in the skin - see fig. 4. Although the extremely small capacity causes little changes in the reflection co-efficient $\rho$, the small volume with non-zero electric field yields a high spatial resolution. In the case of liquid samples of relatively low dipole density values $\Delta \varepsilon$ we had to switch to probe heads as depicted in fig. 3: Here, the capacity of the empty condenser is 0.6 pF, approx., and the increase in signal/noise ratio is a factor of 20 compared to the short cut open-ended probes. Moreover, the temperature stabilization to 0.2°C is much easier to handle using the new set-up by forcing the temperature gradient between the crossing point of the coaxial cable with the closed-flow water pipe and the output connector of the analyzer.

A typical experimental result from a formulation of a drug-carrier system with water content using the new set-up is shown in fig. 5. To document the improvement we compare this result to a measurement using the ancient 0.03 pF probe (see fig. 6). Here, we had to use the flat-ended geometry to guarantee the contact with staples of phospholipid bilayers [14]. This example was, by the way, the first case where we
Fig. 4. In the case of an open-ended coaxial line with cut inner and outer conductor we have a far smaller sample volume as compared to the geometry used in fig. 3. The advantage is a high spatial resolution as needed for measurements on skin slices or living skin.

had to use an asymmetric distribution function \([15]\) to understand the distortions in both paraelectric dispersion and absorption - see Section 4.

4 Evaluation of the parameters

The algorithm presented following eq. (8) gives within a seconds time the two parameters of interest, namely the dipole density \(\Delta \varepsilon\) and the dipole mobility \(f_0/\text{MHz}\). As long as the density extracted from the dispersion values \(\varepsilon'(f)\) and from the absorption values \(\varepsilon''(f)\) are equal, we are sure to have one distinct mobility \(f_0\). In this case, a further proof for this assumption is the correct half-width \(\Delta x_F = 2 \ln(2 + \sqrt{3})\) of the normalized function \(F''(x) = (\varepsilon''(x) - \varepsilon_{\infty})/\Delta \varepsilon\) as well as the correct slope \(-1/2\) at the point of inflection of the normalized function \(F'(x) = (\varepsilon''(x) - s e^{-x})/\Delta \varepsilon\). Any deviation from these criteria yield distorted curves as to the maximum and the half-width of \(F''(x)\) and as to the slope at the point of inflection of \(F'(x)\). The cause is a distribution in mass and/or activation energy of the dipole-carrying molecules. This point has thoroughly been treated in the literature: The Cole-Cole formula \([16]\) changes the purely Debye behavior as given in eq. (8) to give the parameter-dependent relation

\[
\varepsilon - \varepsilon_{\infty} = \frac{\Delta \varepsilon}{1 + (i\omega \tau)^{1-\alpha}} \quad \text{with} \quad 0 < \alpha < 1.
\]
Fig. 5. This typical example of a measurement on SLN nanoparticles of approx. 200 nm
diameter with cyproterone acetate as drug is the result of an overall scanning time of 20 sec-
onds. The increase in signal/noise ratio with increasing frequency is caused by the sampling
principle of the analyzer.

Fig. 6. In this example, phospholipid DOPC with hydration water coating the headgroup
electric dipole moment, we consequently have two contributions. Whereas the headgroup
answer at 50 MHz follows a Debyean relation, the hydration water response at 350 MHz
are curves distorted by an asymmetric distribution of the activation energies governing the
mobility of the water molecules.

This relation at least fulfills the demands of a double normalization $M_0 = \pi/2$ and
$M_1 = 0$, where the moments $M_k$ are defined as $M_k = \int_{x=-\infty}^{x=+\infty} x^k F''(x) dx$. To simulate
asymmetric answers of $F'(x)$ and $F''(x)$, The Davidson-Cole equation [17] takes
into account a possible change in activation energies proposing the form

\[ \varepsilon - \varepsilon_\infty = \frac{\Delta \varepsilon}{1 + i\omega \tau}^\beta \]  

with \( 0 < \beta < 1 \).

(12)

This relation is characterized by \( M_0 = \pi / 2 \) but the condition \( M_1 = 0 \) (\( = \) preservation of the center of gravity of \( F''(x) \)) can only be fulfilled by replacing \( \omega \tau \) by \( \omega \tau / \beta^2 \).

The drawback of both proposals is that no conclusions can be drawn from the parameters \( \alpha \) or \( \beta \) to the form of the underlying distributions. We, therefore, entered the field of explanation of such distorted Debyean curves by the assumption of a distribution function \( G(x, x_0, \Delta x_G) \) of half-width \( \Delta x_G \) normalized by \( M_0[G(x_0)] = 1 \) and \( M_1[G(x_0)] = 0 \). In the cases of a distribution of masses of the dipole-carrying molecules (measured in the pharmaceutical analysis as polydispersity value PI) we have to assume symmetric functions, i.e. a rectangular, Gaussian or Pseudo-Debyean distribution. As soon as we have asymmetrical answers \( \varepsilon'(x), \varepsilon''(x) \) we have to use asymmetric distributions, for instance a falling exponential function \( e^{(-x)}, x \geq x* \) [18; 19]. A short outline of the procedure starts from the normalized Debyean functions \( F'(x_0), F''(x_0) \). The weights \( G(x, x_0, \Delta x_G) \) then give the envelop functions \( H'(x), H''(x) \) via the folding integrals

\[ H'(x) = \int_{x_0=-\infty}^{x_0=+\infty} F'(x_0)G(x, x_0, \Delta x_G)dx_0. \]

(13)

Here, \( H'(x), H''(x) \) are the measured functions from which we can calculate the broadened half-width

\[ \Delta x_H = \Delta x_H(\Delta x_G) > \Delta x_F \]  

(14)

, the maximum

\[ H''(x = 0) = H''_{\text{max}}(\Delta x_G) < F''_{\text{max}} \]  

(15)

or the \( \Delta x_G \)-dependent change in the slope of \( H'(x) \) at the point of inflection. The following fig. 6 gives an example, where two contributions had to be separated, caused by the dipoles of phospholipids headgroups leading to a purely Debyean curve and caused by the water dipole in the hydration shell surrounding these heads, the latter being a distorted curve explained by a weighting function \( G(x, x_0, \Delta x_G) \) (= falling exponential) with half-width \( \Delta x_G \approx 0.35 \) [13]. The physical justification for the existence of such an asymmetric distribution was given in the literature as a result of a Monte-Carlo-simulation of the water molecules in such a hydration shell [16].

5 Results

In co-operation with groups of our university working in the field of pharmacology and embedded in common projects we have been measuring emulsions and dispersions, mainly with solid lipid nano-particles as carriers (Compritol®, Precirol®), with different surfactants ( Poloxamer®, Polysorbate® ) and with a whole spectrum of molecules attached to the surface or incorporated into the bulk of the surfactant-clad carriers, such as Nile red for fluorescent measurements to follow, with Spin lables such as Cholestan® to perform ESR studies and with different drug molecules such as BMV, RUM, CPA, PC and PD which are fully given in the
The polarization answer of RU-58841-myristate shows a pronounced deviation from the concentration dependence as proposed by the Einstein-Debye relation. The assumption of an attachment of the drug molecules to the surface of the carrier-surfactant system is verified by a large penetration enhancement in human skin. The values for both $f_0(c)$ and $\Delta \varepsilon(c)$ at $c = 0\%$ and $c = 0.15\%$ are almost identical: This has to be interpreted as a maximum Number of RUM-molecules on the carrier surface is reached at $c = 0.15\%$.

Fig. 7. The polarization answer of RU-58841-myristate shows a pronounced deviation from the concentration dependence as proposed by the Einstein-Debye relation. The assumption of an attachment of the drug molecules to the surface of the carrier-surfactant system is verified by a large penetration enhancement in human skin. The values for both $f_0(c)$ and $\Delta \varepsilon(c)$ at $c = 0\%$ and $c = 0.15\%$ are almost identical: This has to be interpreted as a maximum Number of RUM-molecules on the carrier surface is reached at $c = 0.15\%$.

model to explain why for some data giving the values of $\Delta \varepsilon(c)$ and $f_0(c)$ the dependence on the concentration $c$ of the drugs, dyes or spin labels follow an almost linear dependence in other cases - connected with best penetration enhancement in the skin - show a pronounced parabola-like curve. The most astonishing example for the need of a model for such different results is the concentration-dependent
Fig. 8. Prednicarbate as drug molecules on the SLN Precirol as carrier shows a wide range of the concentration axis for the parabolic behavior for both $f_0(c)$ and $\Delta \varepsilon(c)$. As compared to the behavior of RUM (fig. 7) we have to assume the drug particles to be attached with the maximum number of drug molecules reached at approx. 0.30% concentration.

behavior of a dispersion of poloxamer clad compritol carrier with betamethasone-17-valerate as drug - see fig. 10.
Fig. 9. In the case of prednisolon as drug we have to assume a total incorporation of the guests in the bulk of the SLN coated with the surfactant layer: With its slightly falling curve $f_0(c)$ obeys the Einstein-Debye relation whereas $\Delta \varepsilon(c)$ is slightly increasing caused by the additional dipole moment of the carrier plus concentration-dependent number of the prednisolon molecules. This interpretation is supported by a much smaller skin penetration enhancement of the system.

6 Discussion

As long as the drug- dye- or spinlabel molecules with concentration $c$ just add their masses $m_D$ to the mass $m_C$ of the dipole-carrying SLN particle, the mobility $f_0(c)$ should follow the Debye-Einstein relation eq. (5) resulting in a linear dependence.
Fig. 10. Betamethasone-17-valerate BMV is the drug with the minimum number of molecules to find Free sites on the surface of the carrier-surfactant system. To verify this, measurements have been carried out extending the concentration range beyond the value $c = 0.10\%$: The surplus BMV molecules have been found to form crystallites in the dispersion that can be observed by vis microscopy.

The same holds for the parameter $\Delta \varepsilon(c)$, which after eq. (3) is proportional to the particle density $N/V$ and proportional to $p^2$. Here, the linear dependence can be a line with its slope depending on the guest molecules’ dipole moment and on its direction relative to the carrier dipole - enhancing or reducing it. As soon as the guest molecules are attached to the surface of the carrier, a second effect enters the discussion: The surrounding of the tumbling complex has to obey the theory of rate processes [13], which connects the activation energy needed to the tumbling frequency $f_0$ by an Arrhenius law, eq. (6). This model as described in detail [1] needs a maximum activation energy for zero drug concentration and for its maximum
possible value; in between these limiting cases, the adjacent particles find places in
the wholes between the guest molecules thus needing less activation energy when
forced to jump.

On the basis of this model (for the behavior of $\Delta \varepsilon(c)$ as result of a similar idea) the
attachment of the guest molecules leads to the concentration dependent maximum
of the parameter $f_0(c)$. In the above underlined case as depicted in fig. 10 the max-
imum possible concentration for attached BMV molecules is obviously $c = 0.10\%$
- all additional molecules up to $c = 0.30\%$ are seen as crystallites using a vis mi-
croscopy inspection. The outline of the proposed model is given as fig. 11. This

7 Outlook

The parelectric spectroscopy is well suited to study the structure and dynamics of
dipole-carrying systems in extremely small volumes as found in skin penetration

Fig. 11. This presentation gives the logics of the model taking into account the theory of
rate processes. Whereas the curves $f_0(c)$ obey either the Einstein-Debye relation or pass a
maximum value, the curves $\Delta \varepsilon(c)$ depend - in the case of incorporation as well as in the
case of attachment - on the dipole moment of the drug molecules.

model should explain that in the case of fig. 11 we find the best attachment on the
carrier surface connected to the best penetration and permeation enhancement in
the skin down to the situation as given in fig. 9 pure incorporation in the carrier
bulk and subsequently smaller skin permeation.
experiments or in the medical diagnosis of changes of parts of the outer or inner surfaces of patients. In this case we have to use probes which sense little volumes with worse signal/noise ratios as in the cases of emulsions or dispersions of drug-carrier systems. In the field of skin measurements we can, however, learn from the situation of NMR tomography, that the changes between ‘normal’ and ‘anomal’ amount to a factor of 2...3. The situation is far better when we can, in field of samples of pharmacological interest, use volumes as depicted in the experimental set-up: Here, we have approx. 20 times better relative errors but have to find small changes in both $\Delta \varepsilon(c)$ and $f_0(c)$ in dependence on the concentration $c$ of the drug-, dye- or spin label molecules attached to or incorporated in the SLN carrier systems. The interpretation cannot be restricted to purely physical arguments; the aim of any development in this relatively new field of dermal application with topical instead of systemic effects has to take into account the results of skin penetration measurements as well.

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