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Improvements of conductivity measurements of electrolyte solutions using a new conductometric cell design

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Abstract

A new conductometric cell design, for precise conductance measurements has been developed and tested using aqueous lidocaine hydrochloride as a model system. A small portion of a stock solution in the conductivity cell is diluted stepwise by pure solvent. The resistance of the cell is measured by means of a precision conductance bridge. Contrary to conventional technique in precision conductometry, the temperature is allowed to change during the measurements and corrected to the desired standard temperature. The temperature is determined using a thermistor immersed in the cell solution, which is agitated during the entire experiment. Using this new approach, significant improvements over conventional conductivity technique were observed. The time required for the measurements was considerably reduced, by a factor of at least ten. The amounts, especially of costly drugs, required in the measurements are also reduced. The pK_a value obtained, 7.28, is close to the previously reported conductometrically determined average, 7.18. The precision of the single conductivity value is equally high, if not higher, as that obtained using conventional conductivity technique.

Keywords: Conductivity cell design; Drugs; Molar conductivity; Iontophoresis prerequisites

1. Introduction

Iontophoresis is a technique by which charged bioactive molecules are transferred from an electrolytic solution into and through tissue by means of a weak direct electric current. Non-ionic drugs can be transported into the body, provided that a charge can be introduced into the drug molecule or by electroosmosis. Transport properties of charged drug molecules depend on the polarity of the solvent, drug concentration, and pH, to mention just a few important factors. Access to information of this kind is of great importance, for instance, in designing reservoirs for administration of drugs by iontophoresis [1–3].

Electrical precision conductometry has proved to be a most powerful tool to investigate structure and transport properties of electrolytes in liquid

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solution. By determining the concentration dependence of the molar conductivity of an electrolyte and combine such data with transport numbers, the various kinds of aggregates present in the solution may be identified and quantitatively established. Furthermore, individual ionic mobilities may be determined and their interactions with solvent molecules explored. However, though a vast number of investigations of this kind can be found in the literature, only few investigations for ionic drugs have been reported, cf. Karami et al. (2000) [4] and references therein.

Furthermore, many drugs are very costly and it is desirable to use a minimum amount of such substances in exploring their properties. This is one aspect of our motivation to modify the experimental technique used so far. Another aspect is the desire to shorten the time of the measurements which using conventional technique is quite time consuming. In fact, the experimental procedure developed permits at least a ten-fold reduction in measuring time retaining, the same high precision as before or higher.

2. Experimental

The shape of the new conductivity cell, of 550 ml total volume, is shown in Fig. 1(a). Bright platinum electrodes are located near the bottom of the cell, Fig. 1(b). The lower cylindrical part of the cell corresponds to a volume of 25 ml (i.e. this is the volume of stock solution used in an experimental run). Contrary to previous technique ordinarily used, [5–9] the principle of the presented experimental approach is to add portions of pure solvent successively to a small volume of stock solution in the (cylindrical) lower part of the cell. A Dosimat E 535 precision buret connected to the cell is used for this purpose. The solution is continuously stirred at a rate of 60 rpm and the temperature measured by means of a thermistor immersed in the cell solution. The thermistor was calibrated against a certified mercury-in-glass thermometer graduated to 0.01 °C. The entire equipment, kept in an air thermostat box, constitutes a closed system. The cell is connectd to a Leeds and Northrup 4666 high-precision conductivity bridge.

3. Scope of investigation

The present study includes two parts. In the first one, the cell was calibrated using aqueous potassium chloride. The measurements were performed over a broad range of concentrations (0.5–10 mM) to explore any possible concentration dependence of the cell constant. In the second part of this investigation an application of

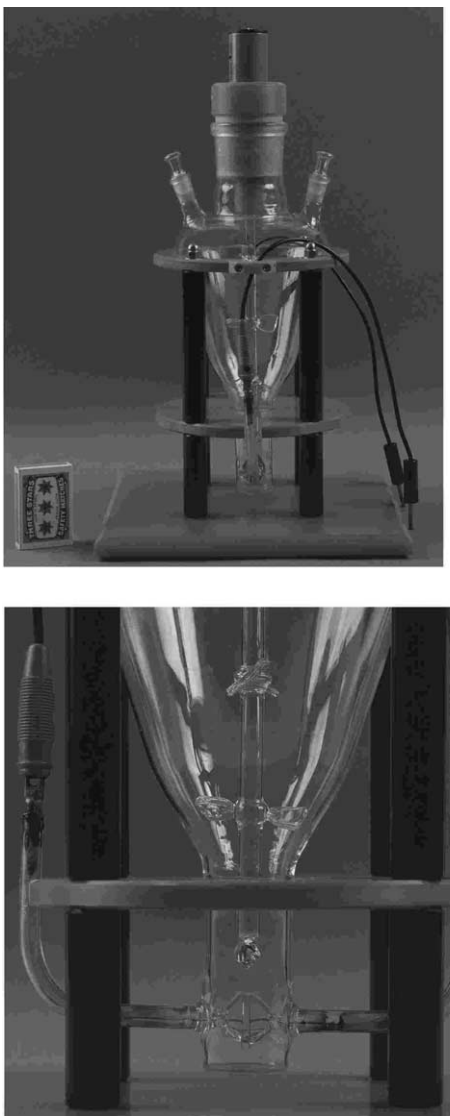

Fig. 1. Shape of the new conductivity cell (a) including an enlargement of the bottom part of the cell (b).

the new cell to a drug solution was studied. Aqueous lidocaine hydrochloride was used as a model system to enable direct comparison with results acquired according to conventional conductivity technique (Sjöberg et al. (1996) [3]).

4. Experimental details

4.1. Reagents

Potassium chloride, suprapur, was purchased from Merck. Lidocaine hydrochloride monohydrate (used in the second part of the study) was purchased from Sigma, USA. The conductivity of the Milipore®water used as solvent was $\kappa = 7.2 \times 10^{-7}\ \Omega^{-1}\ \mathrm{cm}^{-1}$.

Solutions were prepared on weight basis and the weights corrected to vacuo due to the high precision of the techniques used in the experiments. Density measurements of stock solutions were determined by means of DMA O2 C digital precision density meter (Anton Paar K.G., Graz, Austria).

4.2. Prerequisite of new cell design

For short distances between the level of the liquid in the cell and the electrodes, a strong variation of the cell constant on this distance was observed. This is most probably due to a change in the shape of the electric field between the electrodes with the level of solution. The new design of the new cell takes this effect into account. To determine the minimum distance between the level of the solution and the electrodes, a cell of the type shown in Fig. 2 was constructed. It was fitted with bright platinum electrodes. The cell, containing 10 mM aqueous potassium chloride, was placed into the air thermostat box kept at a temperature of 25.00 ± 0.02 °C and the resistance was determined as a function of the level of the liquid. The frequency was kept constant at 3300 Hz. The results of these experiments, shown in Fig. 3, indicate a minimum distance of approximately 5 cm. The volume up to 5 cm was determined to 25 ml. Based on this observation the new cell was constructed accordingly.

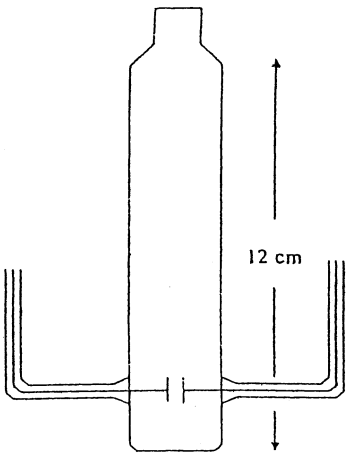

Fig. 2. Conductivity cell used to establish minimum distance between the level of the solution and the electrodes.

4.3. Experimental procedure for the new cell

A stock solution of the electrolyte to be studied was prepared. Approximately 25 ml of the stock was transferred to the cell using a syringe. The exact weight was determined by difference weighing. The cell and buret with pure solvent were placed in the air thermostat box. The thermistor was immersed in the cell solution and stirring

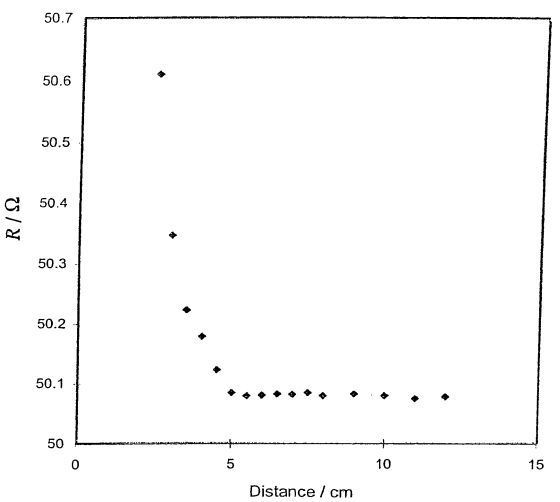

Fig. 3. Dependence of the cell resistance on the distance between the level of the solution and the electrodes for the cell shown in Fig. 2. Electrolyte: 9.98 mM potassium chloride at 25.00 °C.

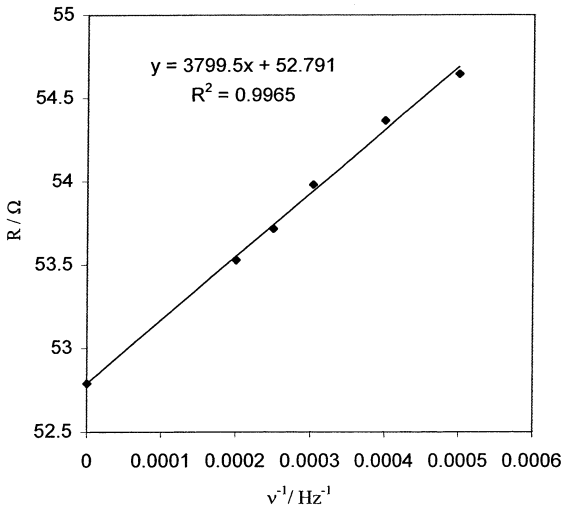

Fig. 4. Typical graph of the dependence of the cell resistance on frequency for 9.98 mM aqueous potassium chloride solution at 25.0 °C. The equation for the curve is shown in the figure. The value obtained for the slope was 3799 with a RSD-value of 5.5%. The value for the intercept was 52.791 with a RSD-value of 0.14%.

commenced. The entire system was left overnight to attain temperature equilibrium. This precaution was taken before starting the measurements to minimize temperature fluctuations. According to observations in preliminary experiments, the cell solution should be continuously stirred during the entire series of measurements. Otherwise, due to the high sensitivity of this method, even minor temperature fluctuations disturb the system markedly.

Resistance measurements were performed at five different frequencies between 2 and 5 kHz. During this procedure the change in temperature varied at most by 0.02 °C. The cell resistance, R, was plotted against the inverse of the frequency, $1/v$. An example of this kind of graph for potassium chloride is shown in Fig. 4. To obtain conductivity data free of relaxation effects, the curve was extrapolated to infinite frequency, i.e. to $1/v = 0$.

To cover the desired concentration range, usually 5–20 ml portions of the solvent were successively added. Following each dilution, it was necessary to wait for no more than 5 min to obtain a stable reading. The densities of the diluted solutions were calculated assuming the density to vary linearly with the electrolyte concentration.

4.4. Temperature correction of resistance readings

In establishing the concentration dependence of the molar conductivity, Λ, the temperature, t, in the cell solution usually increased slowly from about 24.5 to 25.5 °C during each series of conductivity measurements. Recalculation of resistance readings, R, to 25.00 °C was performed as follows:

For aqueous potassium chloride, literature data (Harned and Owen, (1958) [10]) limiting molar conductivities, Λ_0, in the temperature interval 5–55 °C were used. Application of nonlinear regression analysis to these data yielded the following expression for the temperature dependence of Λ_0,

$$\Lambda_0 = 0.008t^2 + 2.550t + 81.133 \quad (1)$$

indicating a temperature coefficient at 25 °C of 1.97% per degree for R (being inversely proportional to Λ).

The corresponding temperature coefficient for aqueous lidocaine hydrochloride was established by measuring the resistance of a 0.4129 mM solution at several different temperatures between 22 and 26 °C. Linear regression analysis yielded the expression:

$$R = -39.807t + 2738.5 \quad (2)$$

for the temperature dependence of R (correlation coefficient, 0.9995). This result indicates a temperature coefficient of the resistance of 2.28% per degree at 25 °C.

In recalculating resistance readings to 25.00 °C, it appears most reasonable to assume that the temperature coefficient is, in practice, concentration independent.

4.5. Calibration of the cell

To determine the cell constant, k, measurements were performed using aqueous potassium chloride over a broad concentration range (0.5–10 mM). In calculating the cell constant the Lind–Zwolenik–Fuoss equation [11]:

Table 1
Molar conductivity of lidocaine hydrochloride in water at 25.00 °C

$10^4 \times c$ (M)	Λ (cm^2 S mol^{-1})	$10^4 \times c$ (M)	Λ (cm^2 S mol^{-1})
4.1290	97.381	27.699	93.566
6.0456	95.993	31.190	93.516
7.5141	95.757	35.687	93.338
9.9250	95.349	38.460	93.157
14.614	94.748	41.700	93.015
19.133	94.378	45.537	92.968
22.633	94.005		

$$\Lambda_{LZF} = 149.93c^{1/2} + 58.74c \log c + 198.4c \quad (3)$$

which is valid up to a concentration, $c \approx 12$ mM, was used. No significant dependence of the cell constant on concentration was observed. As a result of 17 measurements within the concentration interval referred to above, an average value of $k = 0.07095\text{cm}^{-1}$, with a relative standard deviation of 0.30% was obtained. This indicates a high degree of reproducibility of the method.

As a test of the repeatability, eight consecutive measurements of the cell constant were performed using a potassium chloride solution of approximately 10 mM concentration. This series of measurements yielded $k = 0.07034 \pm 0.00067$, where the uncertainty is the standard deviation of the eight k-values.

5. Conductance measurements of aqueous lidocaine hydrochloride

The new procedure to perform conductivity measurements here presented was tested using lidocaine hydrochloride in aqueous solution as a model system. The results are compared with previous data of a similar study [3]. Measurements were performed for several concentrations in the interval, 0.41–4.6 mM. The results are summarized in Table 1.

5.1. Evaluation of conductance parameters

In interpreting the conductance data, it is most reasonable to assume that the only equilibrium which should be taken into account is that between the $LidH^+$ ion, electrically neutral Lid molecules and chloride ions:

$$LidH^+ \overset{K_a}{\Leftrightarrow} Lid + H^+ \quad (4)$$

where K_a is the acid dissociation constant of $LidH^+$. Any disturbing formation of $LidH^+Cl^-$ and H^+Cl^- ion pairs appears most unlikely for water as solvent at the concentrations concerned. Using Kaleida Graph® the conductance equation:

$$\Lambda = m[\lambda_0(LidH^+)(1-\alpha) + \lambda_0(H^+)\alpha + \lambda_0(Cl^-)] \quad (5)$$

was fitted to the experimental conductance data in Table 1 and to the previously reported data by Sjöberg and co-workers [3]. In Eq. (5), Λ is the molar conductivity of LidHCl; m, a concentration dependent ion mobility factor correcting for ion atmosphere effects; α, the degree of dissociation of $LidH^+$ and the λ_0's are the limiting molar conductivities of the species indicated.

Kaleida Graph® allows for a two-parameter fit. By these means the acid dissociation constant, K_a,

Table 2
Comparison of conductance data for lidocaine hydrochloride in aqueous solution at 25.00 °C according to the present study with data of Sjöberg et al. (1996)

Concentration range (mM)	K_a	pK_a	λ_0 ($LidH^+$) cm^2 S mol^{-1}	Reference
0.4–4.6	$5.237 \times 10^{-8} \pm 5.307 \times 10^{-8}$	7.28	17.87 ± 0.09	This study
0.8–3.7	$6.386 \times 10^{-8} \pm 1.186 \times 10^{-8}$	7.20	17.69 ± 0.18	[a]
0.3–6.6	$7.110 \times 10^{-8} \pm 5.065 \times 10^{-8}$	7.15	17.84 ± 0.11	[b]

[a] [3], Series 1 and 2, respectively.
[b] [3], Series 1 and 2, respectively.
The K_a, λ_0 ($LidH^+$) and pK_a values are given in the table.

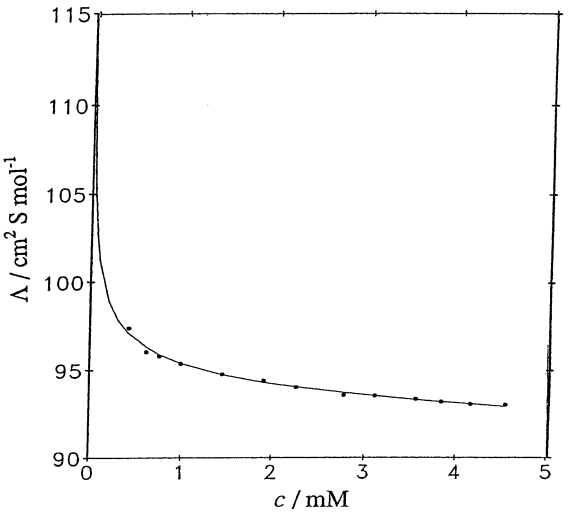

Fig. 5. Dependence of molar conductivity on concentration for aqueous lidocaine hydrochloride at 25.0 °C.

and $\lambda_0(\mathrm{LidH}^+)$ were computed. Furthermore, the standard deviations for these two parameters was calculated. The standard deviations for the single Λ-values were obtained in accordance with the work of Sjöberg et al. [3].

The same values for the dielectric constant and viscosity of the solvent, and of $\lambda_0(\mathrm{H}^+)$ and $\lambda_0(\mathrm{Cl}^-)$ as before [3] were used in the calculations.

6. Results

A graph of the best fit of Eq. (5) to the conductance data in Table 1 is shown in Fig. 5. The computed values of the conductance parameters are: $K_a = 5.237 \times 10^{-8}$ (molarity scale); $pK_a = 7.28$; $\lambda_0(\mathrm{LidH}^+) = 17.78$ cm^2 S mol^{-1}, see Table 2.

For comparison, data according to a previous study by Sjöberg and co-workers [3] are included in Table 2. According to the obtained results, there is no significant difference in pK_a value determined by the proposed and the already existing method. The discrepancy between the values of pK_a according to this study and the previous one is only 0.1 pK_a-unit. For the limiting single ion molar conductivity of the LidH^+ ion there is an almost exact agreement. This indicates a high degree of reproducibility of the conductometric method.

It may be noted that using this new approach in performing conductivity measurements presented here, the precision in the measurements appears to be at least as good, if not better, compared with previous conventional technique; 0.15% standard deviation for the single Λ-value in this study to be compared with 0.14 and 0.21%, respectively, in the two different series according to [3].

7. Conclusions

The experience gained so far in our efforts to develop a more efficient way then before for investigating especially drug solutions by means of precision conductometry will now be summed up.

The time required to perform a given series of conductance measurements is considerably reduced as compared with conventional precision conductance technique. The time reduction corresponds to a factor of at least ten. This is of importance, because previous technique is quite time consuming.

The new technique permits a significant reduction of the amounts of especially costly drugs required in the measurements.

According to the new approach, the temperature in the sample examined must not be kept constant (formerly frequently at 25.00 °C). The temperature is measured directly in the stirred sample by means of a thermistor and the cell resistance reevaluated to the desired standard temperature.

Comparison with previously published data for aqueous lidocaine hydrochloride, used as a model system, indicates a very high degree of reproducibility of the conductometric technique. The precision here arrived at, in determining molar conductivities, is equally high, if not higher compared with the precision obtained by means of conventional precision conductometry.

If desirable, it is possible to reverse the exper-

imental procedure outlined above, i.e. to start with pure solvent in the cell to which portions of a drug stock solution are added.

We believe that inherent in this improvement of conductance measurements there is a potential for further reduction of the size of the conductivity cell and, hence, of the amounts required for investigating drug transport properties.

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