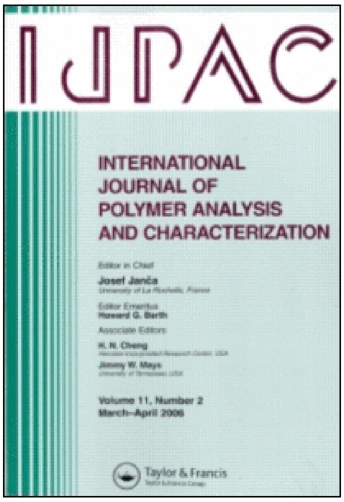

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Molecular Weight Studies on Hydroxypropyl Methylcellulose I. Osmometry

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Molecular Weight Studies on Hydroxypropyl Methylcellulose
I. Osmometry

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Osmometry was employed to measure number-average molecular weight M_n of hydroxypropyl methylcellulose (HPMC) using membranes with different permeability for the solute (polymer or electrolyte) and solvent (water) in such a way that no pretreatment of the polymer solution was required to remove electrolyte impurities, thereby eliminating the risk of sample alteration. A novel osmometric method was developed, based on measurements of the kinetics of the pressure over the membrane, which allows the use of membranes permeable even to the polymer. It was shown that such membranes initially, at time $t = 0$, approaches the physics of a perfectly semipermeable membrane provided that the ratio of the solute/solvent permeability is sufficiently low (*i.e.*, when the molecular weight cut-off, MWCO, of the membrane does not exceed M_n of the polymer). The obtained M_n for a range of viscosity grades of HPMC2910 (3 cP to 10,000 cP) compares favorably with previous estimates, based on analogy with methylcellulose.

Keywords: Hydroxypropyl methylcellulose, molecular weight, osmometry, membrane, transport mechanisms, reflection coefficient

INTRODUCTION

The aim of this work is to develop an absolute method of measuring the number-average molecular weight M_n of hydroxypropyl methylcellulose. Furthermore, in order to avoid possible alteration of the sample composition by any pretreatment such as dialysis, the measurements preferably

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should be performed in the prescence of an electrolyte. Osmometry, using electrolyte-permeable dialysis membranes, was evaluated to fulfill these requirements. Preliminary measurements indicated that the selection of the optimal membrane molecular weight cut-off, MWCO, was related to the relative permeabilities of electrolyte and polymer, and that kinetic experiments were necessary to separate the pressure responses from the electrolyte and the polymer. Development of a kinetic method of osmometric measurements, which allowed the use of membranes impermeable as well as slightly permeable to the polymer, was undertaken.

No literature reports on osmometric measurements on HPMC has been found. However, measurements on methylcellulose have been published,[1] and the relation between viscosity grade and number average degree of polymerization has been regarded to be representative also for HPMC.[2] Previous osmotic pressure methods, and other absolute methods, for measurement of number-average molecular weights, have been reviewed.[3-5]

EXPERIMENTAL

Materials

Commercial HPMC of USP-substitution type 2910 were obtained from the following manufacturers: Dow Chemical, Midland, Michigan (Methocel E3P, E6P, E50P, and E4MP) and Shin-Etsu, Naoetsu, Japan (Metolose 60SH-10000). In addition, a high viscosity grade of HPMC (USP-substitution type 2208), which we determined, using a capillary method, to have a viscosity of around 100,000 cP at 2%w/v and 20°C, was obtained from an other source. Aqueous solutions were prepared by dissolving weighed, untreated HPMC samples with known moisture content.

Instrument

The membrane osmometer used was an Osmomat 090 (Gonotec GmbH, Berlin, Germany). The measurement cell is constructed from stainless steel with a minimum possible cell volume and is separated into two compartments by a membrane, Figure 1. The upper open sample compartment (ca 0.6 mL volume) is filled with the solution to be measured, and the lower reference compartment (μL volume range), closed to the outside, is filled

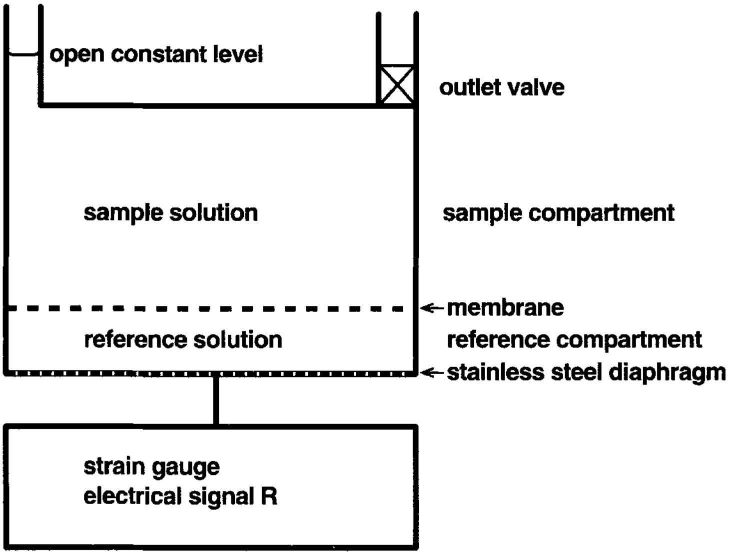

FIGURE 1 Schematic to the measurement cell of the membrane osmometer.

with the solvent (water). A stainless-steel diaphragm fitted to the reference compartment of the measurement cell is used to measure the pressure difference across the two compartments, trough a conversion of its movement into an electrical signal (pressure response *R*). The pressure response *R* is calibrated with an applied known hydrostatic pressure and one "response unit" was determined to be equal to 0.081 mm H_2O (0.83 Pa). The resolution of the pressure measurement system was one response unit. Asymmetric two-layer cellulose triacetate membranes, with a diameter of 40 mm and a molecular weight cut off (MWCO) of 5,000 or 20,000 g/mol (type SM 14549, Sartorius GmbH, Göttigen, Germany), were used.

Measurements

The baseline response, R_b, (*i.e.*, the pressure response corresponding to zero pressure difference over the membrane) is measured with solvent in the measuring cell. In case the previous measurement had contaminated the reference compartment with polymer or electrolyte, the contaminant had to be back-extracted by continous rinsing the sample compartment with pure solvent for up to a day until the baseline was back to normal. The solution was then introduced during a measured time interval, $t = 0$ to $t = t_{stop}$, after which the solution flow was stopped by closing the outlet valve. The pressure response R was recorded as a function of time, $t > t_{stop}$ until this first measurement cycle was either terminated or followed by a consecutive measurement. The pressure at any given time was calculated as the difference $\Delta R = R - R_b$, and all measurements were performed at 21 ± 1°C.

THEORY

The number-average molecular weight M_n is calculable through the well-known van't Hoff relation, which states that the limiting reduced osmotic pressure Π/c, at infinite dilution, equals RT/M_n according to

$$\lim(c = 0)\Pi/c = RT/M_n \qquad (1)$$

where R is the gas constant and T the temperature. If c is given in % w/v (or g/dL) and Π in units of 0.83 Pa as used in this work, then $M_n = 3.00 \times 10^7 \cdot c \cdot \Pi^{-1}$.

The limiting reduced osmotic pressure Π/c is obtained traditionally using the empirical virial expansion,

$$\Pi/c = RT(A_1 + A_2c + ...) \qquad (2)$$

by measurements of Π/c at different concentrations and extrapolation to zero concentration. The first virial coefficient, A_1, equals to $1/M_n$ and the second virial coefficient, A_2, is known as the interaction constant. Higher terms are not anticipated at the low concentrations, less than 0.6%, used in this study.

The measurement of Π/c will depend upon the membrane characteristics. For *semipermeable membranes*, possessing "perfect" semipermeability versus solute and solvent, that is,. being permeable only to the solvent molecules, the pressure measurement will rapidly reach a constant value. However, since there is no possibility of distinguishing between pressure responses from electrolyte or polymer, the use of this type of membranes requires pretreatment of the polymer solution to remove all electrolyte.

In the case of *quasi-semipermeable membranes*, which are permeable to both electrolyte and solvent but not polymer, the measurement is also straightforward, because the pressure response becomes constant after the electrolyte has equilibrated across the membrane; thus, the membrane will be completely specific to the polymer. However, these membranes were not practical (due to slow equilibration) or applicable for low-molecular-weight polymers.

In some cases, membranes which were not only permeable to the solvent and electrolyte, but also slightly permeable to the polymer were used. These membranes may be termed *permeable membranes*. The pressure response has to be back-extrapolated to the initial unperturbed condition, that is immediately after the introduction of the sample solution at $t = 0$, where the concentration drop across the membrane equals c. Back-extrapolation is possible for systems with a finite receiver compartment because the pressure response will decrease proportionally to the decrease in concentration gradient in a predictable way. It can be shown that solute permeation over a membrane, which separates a large donor compartment from a small receiver compartment, leads to a decrease in concentration gradient which is initially proportional to the square root of time. Furthermore, in the present work, one has to consider two different permeation processes, as will be shown below, depending on whether the solution is flowing or stagnant. The initial reduced osmotic pressures, Π/c ($t = 0$), are obtained by kinetic measurements of Π/c (t) with different t_{stop} followed by two separate linear extrapolations vs $time^{1/2}$. In addition, the kinetic measurements should allow for the numerical separation of the pressure responses from several solutes coexisting in the sample solution, that is, electrolyte and polymer, provided that sufficient differences in permeability prevail.

RESULTS AND DISCUSSION

Osmotic measurements were carried out with various combinations of HPMC grades and membrane MWCO, yielding different types of time dependencies of the pressure response (Figs. 2–7). The time dependencies were found to have different mechanisms as discussed below and were the result of different kinetics of various processes: mechanical relaxation, electrolyte permeation, and polymer permeation. After applying the appropriate time dependence for the particular polymer membrane combination, it was possible to derive the pressure response corresponding to the initial polymer sample composition enabling measurement of the limiting reduced osmotic pressure (Fig. 8 and Table I).

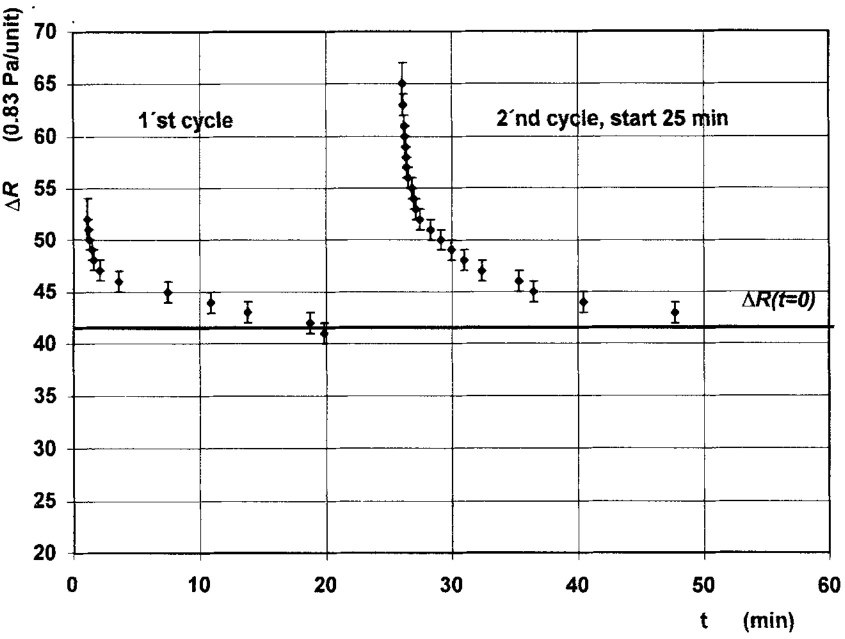

FIGURE 2 Mechanical relaxation of pressure ΔR with time t after forced introduction, using external pressure, of a viscous solution (0.153% w/v HPMC2208, high-viscosity grade). Membrane MWCO = 20,000 g/mol.

Mechanical Relaxation

A typical result obtained with a high-molecular-weight polymer that did not pass through the membrane, is shown in Figure 2, which presents the time dependence for a high-viscosity grade HPMC 2208 using a membrane with MWCO 20,000. The pressure response is initially higher than the equilibrium pressure response, due to mechanical relaxation of the measuring cell, after being subject to an external pressure (up to 9,000 response units) which was used to force the introduction of the viscous solution into the measurement cell in a reasonably short time (1 to 3 min). The mechanical relaxation dominates the time dependence in this case, with such a viscous solution, and takes approximately 20 min at 0.153% w/v, before equilibrium is attained. A second flushing with fresh solution (the second cycle) results in a similar relaxation returning to the same equilibrium pressure response proving that no polymer permeates across the membrane. For

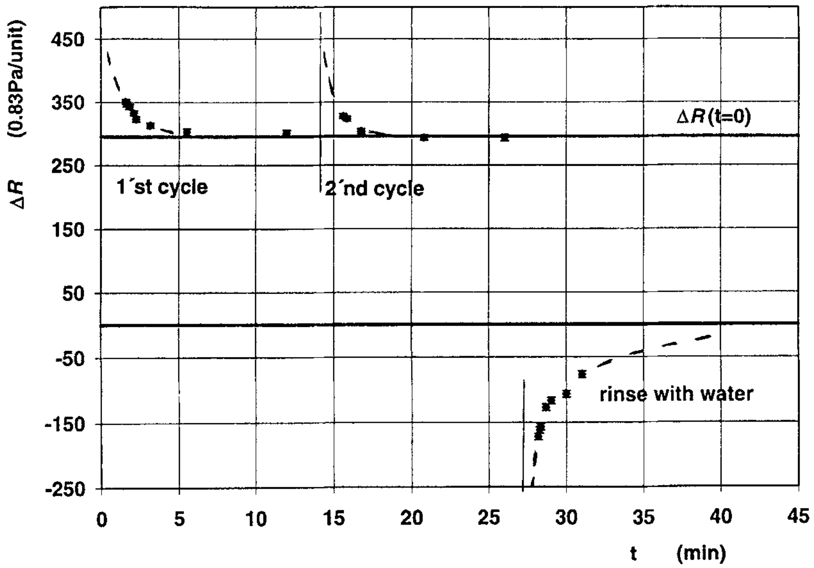

FIGURE 3 Pressure ΔR vs time t, showing declining response due to electrolyte permeation, after flushing the cell twice with 0.26% HPMC-50 cP for 1.47 min (1st cycle) and 1.47 min (2nd cycle start at 14min), and with water 1.00 min (3rd cycle start at 27 min). Membrane MWCO = 5,000 g/mol.

low viscous solutions, near 1 cP, mechanical relaxation was normally much faster and hardly noticeable (a matter of seconds).

Electrolyte Permeation

Another case with a sufficiently high-molecular-weight polymer to prevent permeation through the membrane was observed for HPMC 50 cP using a membrane with MWCO 5,000, as shown in Figure 3. Here, the pressure response declines to an equilibrium value, in approximately 5 min, due the vanishing pressure response from electrolyte impurities. The membrane has in this case sufficiently low permeability for the electrolyte molecules, probably traces of NaCl, to observe a falling pressure response. Yet the permeability is sufficiently high so that electrolyte concentration difference over the membrane is zero within a reasonably short time. The final pressure response appears to be the true equilibrium, as indicated by the 2nd cycle, and may therefore be assumed to

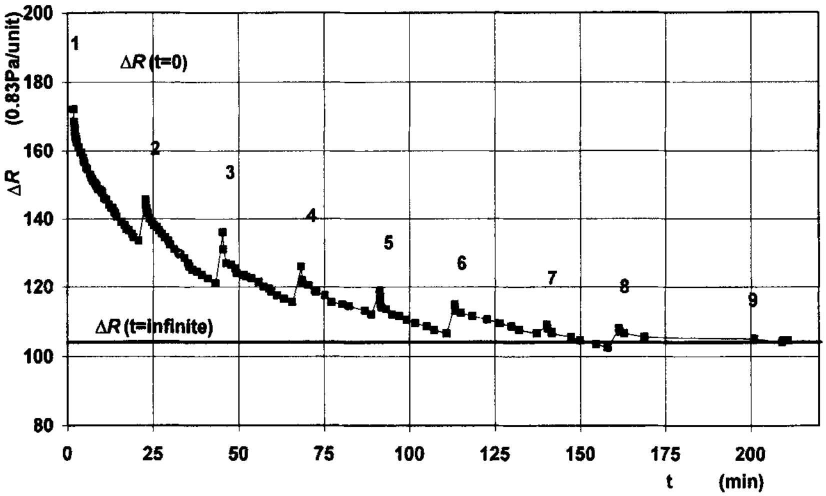

FIGURE 4 Pressure ΔR vs time t for a series of repeated (9 cycles) exchanges of the measured solution, 0.178% w/v HPMC-50 cP, with fresh solution. Membrane MWCO = 20,000 g/mol.

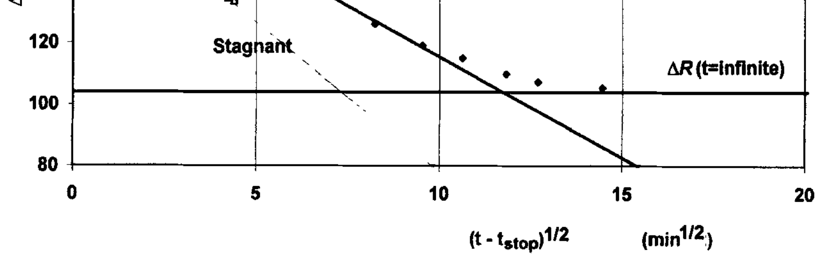

FIGURE 5 Pressure ΔR vs $(t-t_{stop})^{1/2}$ for flowing (t_{stop} = 0 min) and stagnant solution (t_{stop} = 1.50 min), containing 0.178% w/v HPMC-50 cP. Flowing condition was approximated by changing the solution repeatedly (nine times). Membrane MWCO = 20,000 g/mol.

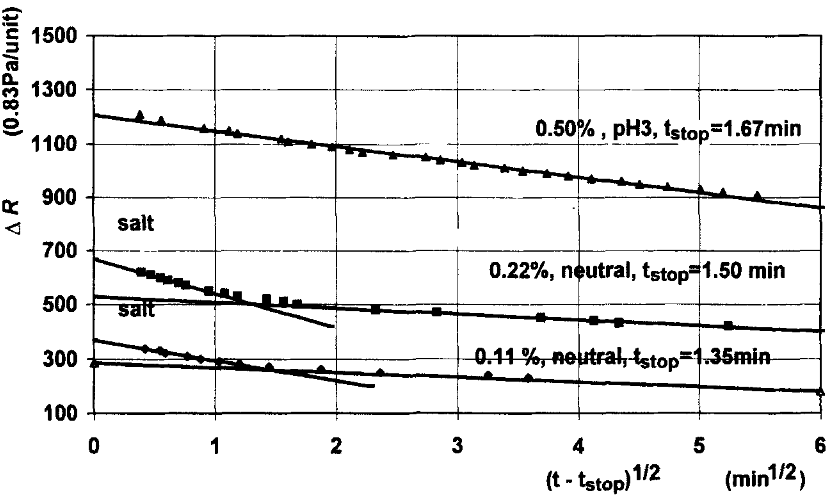

FIGURE 6 Pressure ΔR vs $(t\text{-}t_{stop})^{1/2}$ for solutions of HPMC 6 cP, indicating Fickian diffusion, of both polymer and salt impurity, at different rates. Membrane MWCO = 5,000 g/mol.

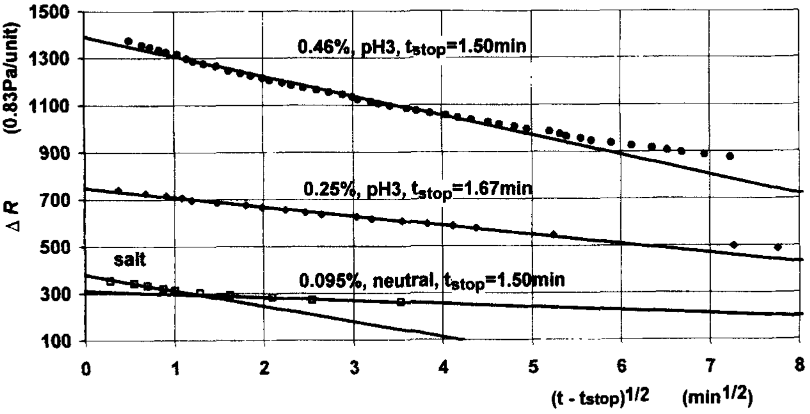

FIGURE 7 Pressure ΔR vs $(t\text{-}t_{stop})^{1/2}$ for solutions of HPMC 3cP. Membrane MWCO = 5,000 g/mol.

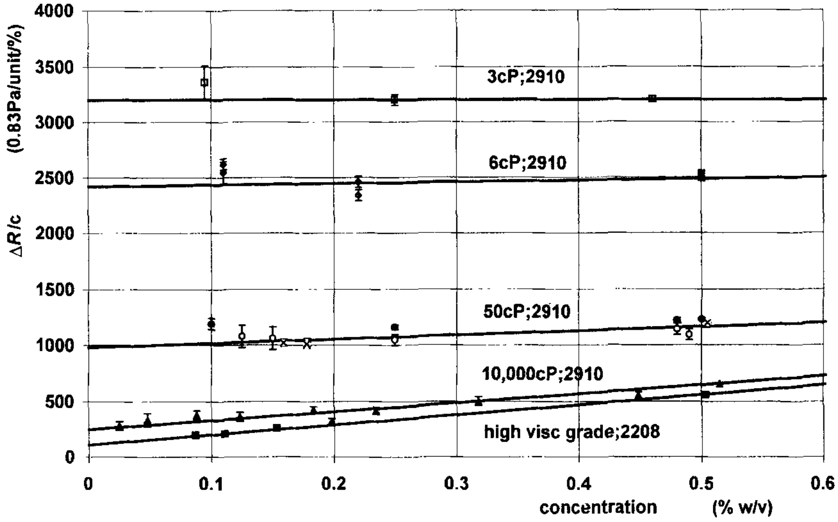

FIGURE 8 Reduced osmotic pressure, Δ*R*/c, vs concentration c for aqueous HPMC at 21°C. Open symbols: pH 3; solid symbols: neutral. Conditions: 3 cP and 6 cP (MWCO = 5,000), 50 cP (MWCO = 5,000 or 20,000 (denoted by solid symbol ×)), 10,000 cP and high-viscosity grade (MWCO = 20,000).

correspond to the osmotic pressure of the intact (*i.e.*, not fractionated) polymer sample.

Separate experiments with dilute electrolyte, NaCl or sodium azide, in the absence of polymer, verified the time dependencies of the vanishing pressure response. Also, the reversed electrolyte response was observed by substituting the test solution, of an equilibrated system, with pure water. Figure 3 shows such a reversed electrolyte response when rinsed with water in the 3rd cycle. The reversed transport process appears to be slower.

TABLE I Number-average molecular weights M_n of various HPMC viscosity grades obtained by osmotic measurements of aqueous solutions, at 27°C

Substitution type USP denotion	*Viscosity grade cP (2% w/v)*	*M_n g/mol*	*Literature [2] g/mol*
2910	3	9,300 (±600)	8,000
2910	6	12,000 (±800)	11,000
2910	50	31,000 (±2500)	25,000
2910	4000	100,000 (±10,000)	92,000
2910	10000	120,000 (±10,000)	120,000
2208	high	270,000 (±20,000)	

Polymer Permeation

Influence of Flow–Development of Depletion Zone. While HPMC 50 cP did not permeate through MWCO 5,000, as described above, it showed a pronounced partial (low-molecular-weight fraction) permeation through MWCO 20,000. Figure 4 depicts the time dependencies of a series of repeated exchange of the measured solution with fresh solution. The nine consecutive cycles all show a decline in pressure response from the start of the cycle, that is, when the solution flow was stopped. After flushing new solution into the cell, that is, the next cycle, the pressure response instantly increased to a higher level, compared to the pressure at the end of the previous cycle, and then the decline commenced. This indicates that the pressure response decreases more rapidly when the solution flow is stopped, a fact that may be explained by assuming that a depletion zone, with lower polymer concentration, develops at the sample solution side of the membrane if the solution is not flowing or stirred. Furthermore, this condition indicates that the mass transport rate through the membrane is controlled by the formation of a diffusion layer of the polymer at the membrane solution surface. This is analogous with the development of a diffusion layer in the mass transportation process of dissolution, in which the layer can be reduced or eliminated by flowing or stirring the solution. The phenomenon may be described as a kind of concentration polarization occurring under diffusional transportation conditions and is apparently opposite to the phenomenon of concentration polarization during forced filtration.[6]

Further information on the influence of flow on the permeation rate is obtained by kinetic analysis of the time dependencies, by plotting the pressure response ΔR against $(t\text{-}t_{stop})^{1/2}$, as shown in Figure 5. In this way, initially linear relations between ΔR and $(t\text{-}t_{stop})^{1/2}$ are observed in agreement with the discussion above. The response decline rate for stagnant solution (represented by cycle 1) is clearly separated from the response decline rate for flowing solution conditions. The flowing conditions are approximated by the conditions at the start of each cycle and are therefore not perfectly representative of a continuous flowing solution, but merely serves as qualitative indicator of the influence of stirring; however, the decline in pressure response is faster at unstirred conditions.

The slope of the initially linear relation between ΔR and $(t\text{-}t_{stop})^{1/2}$ decreases and approaches zero at sufficiently long time. A constant pressure level is obtained, independent of solution flow conditions, after some hours, indicating that a large fraction, roughly 60% of the molecules in the HPMC 50 cP sample, can permeate the membrane. Obviously, the remaining number fraction constitutes molecules that are too large to pass through MWCO 20,000.

Transport Mechanism–Fickian Diffusion. The initial linear relation between ΔR and $(t\text{-}t_{stop})^{1/2}$ observed for HPMC 50 cP and MWCO 20,0000, Figure 5, suggests that the flow of polymer molecules through the membrane is proportial to the concentration difference accross the membrane, that is, consistent with Fickian transportation. Other examples of such linear relations are presented in Figures 6 and 7. Here the results for HPMC 6 cP and HPMC 3 cP show initial linear relations for the polymer at pH 3. In addition, at neutral conditions, one observes a more rapidly penetrating component, correlated to salt impurities, which also appears to obey Fickian transportation.

Coupled Electrolyte and Polymer Permeation. The observation of a salt response in the experiments with HPMC 6 cP or 3 cP with MWCO 5,000, Figures 6 and 7, at neutral conditions but not at pH 3, indicate that the apparent permeation rate of the salt impurity depends on pH. However, since this would be impossible for free salt, it indicates that the migration of salt is coupled to an equilibrium process involving pH. Tentatively this could be the acid dissociation of carboxylate end groups present at low concentrations in HPMC.

Reduced Osmotic Pressure

Concentration Dependence. The influence of concentration on the reduced osmotic pressure π/c was analyzed in order to enable estimation of the limiting reduced pressure at infinite dilution. The values of π/c were derived from the time dependencies of ΔR as outlined above, and extrapolated to the unperturbed condition at $t = 0$. All results for the various HPMC grades are collected in Figure 8 except the values for HPMC 4,000 cP, which nearly overlapped with the values for HPMC 10,000 cP, see Table I, and therefore were omitted to improve the readability of the graph.

All the tested combinations of HPMC-grade, membrane MWCO and pH, demonstrate linear relations in the investigated concentration range, 0.02 to 0.5% v/w. Furthermore, the slopes are nearly the same for all systems, especially considering that the accuracy of the slope is decreasing with decreased viscosity grade.

Linear concentration dependencies are normally observed at sufficiently low concentrations for all solute-solvent systems.[4,5,7–9] For cellulosics this appears to be true for the entire concentration range investigated in dilute systems; the observed slopes are all positive. Aqueous systems studied include: cellulose (<0.4% w/v),[10–11], hydroxyethyl cellulose (<0.5% w/v),[12] sodium carboxymethylcellulose (<0.6% w/v),[13] and ethylhydroxyethylcellulose (<0.3% w/v).[8] Various organic solvents were studied for ethylcellulose (<0.8% w/v),[14] and cellulose acetate was studied in acetone (<0.5% w/v).[11] Deviviation from linearity for aqueous neutral cellulosics appears only to become appreciable at much higher concentrations at least as long as the temperature is not too high, close to the cloud-point, as can be concluded from osmotic measurements of concentrated solutions; hydroxyethyl cellulose (<8%w/v),[15] and hydroxypropyl cellulose (<17% w/v).[16] Interestingly enough an example of linearity up to as high as 10% w/v is given by hydroxypropyl cellulose at 25°C.[16] For low molecular solutes, like glucose or sucrose,[9] linearity is also demonstrated in water, at least up to 10% (w/v). Therefore, the observed linearity for HPMC appears to be consistent with the general behavior of other solute-solvent systems, particularly aqueous cellulosic systems, including monomers as well as polymers.

Solute-Solvent Interaction. The slopes of the linear relations between π/c and c, which equals RTA_2 in Equation (2), is comparable with other polymer-solvent systems.[4–5,7–9,17] It is usually observed that for extended polymers, the molecular weight dependency of A_2 ranges from nearly independent to weakly dependent, as long as the chemical composition is not changed (for example, by a variation in end-group content). A_2 is expected to be proportional to $1/M^a$ where $a = 0$ for rodlike molecules (*i.e.*, fully extended polymers) and $0.05 < a < 0.25$ for incompletely extended polymers.[17] The general picture for cellulosics is that A_2 seems to be invariant with M, especially considering the scatter in the experimental data and the possibility of variations in chemical composition.[8,10–12,14–15] The observations regarding HPMC in this work appears to conform with the other cellulosics.

Number-average Molecular Weights

The number-average molecular weights were calculated from the limiting reduced osmotic pressures, according to Equation (1), and are summarized in Table I. It can be seen that the range of M_n ranged from 9,300 for HPMC

3cP to 270,000 g/mol for the high-viscosity grade HPMC, and that the relative precision was about 8%. The obtained M_n values are similar to literature data of HPMC,[2] which were estimated from osmometric measurements of methylcellulose assuming that the two polymers have approximately the same number-average degree of polymerization for a certain viscosity grade.

CONCLUSION

It appears that the described kinetic method constitutes a novel technique for osmometric measurements which extends the applicability to permeable membranes. The method yields correct results provided that the membrane is not too permeable, that is, the MWCO should not be higher than the true M_n. Since the same Π/c values were obtained independent of the membrane MWCO, as demonstrated for HPMC 50 cP for a polymer-impermeable membrane (MWCO = 5,000) and a polymer-permeable membrane (MWCO = 20,000), the kinetic method developed in this work is valid for the systems used in this study. In addition, this indicates that a permeable membrane, initially (at $t = 0$), approaches the physical behavior of a membrane having perfect semipermeability towards the solute solvent pair, provided that the ratio of the solute/solvent permeability is sufficiently low.

The usefulness of permeable membranes, having the advantage of being fast, has been a controversial question since long.[18] It was pointed out by Staverman[19, 20] that the initial osmotic pressure $\Pi_{t=0}$ obtained with a leaking membrane would always be less than the true osmotic pressure Π_{true}, according to $\Pi_{t=0} = \sigma\Pi_{\text{true}}$, where σ is the refection coefficient. While this is a true statement, it does not indiscriminately prevent usage of all leaking membranes. It only means that a leaking membrane cannot be used for equilibrium studies because the equilibrium osmotic pressure of the permeating solute will ultimately be zero, even if σ is extremely close to unity. However, the membrane may still be well suited for kinetic studies if σ is sufficiently close to unity. The conditions at $t = 0$ approaches that of equilibrium for a perfectly semipermeable membrane when σ approaches unity. Previous theories on the time dependency of non-equilibrium osmotic pressure has been reviewed.[21]

As was also pointed out by Staverman, the use of several membranes with different MWCO may be used for a determination of the molecular weight distribution. While this was not the purpose of this work, the concept was found to hold by a test on HMPC 50 cP using two membranes, one partially permeable and one impermeable, see Figure 5.

The present study confirms the previous assumption[2] that the number-average degree of polymerization for a given viscosity grade is essentially the same for HPMC and methylcellulose; hence it may be concluded that a limited change in hydroxyalkoxylation has no practical effect on the viscosity up to 2% w/v concentration at 20°C.

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