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Dissolution kinetics of theophylline in aqueous polymer solutions

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Summary

The effect of polymers on the viscosity of aqueous media has been studied in (bio)pharmaceutics, because of the frequent use of polymers as additives to formulations. A typical feature of the viscosity effect of polymers is their extensive influence on flow viscosity (macroviscosity) and their minor effect on the diffusion of relatively small molecules (microviscosity). Analysis of dissolution kinetics offers the opportunity to study these effects in detail. The rotating disk is the apparatus of choice for this type of studies, as it allows one to discriminate between microviscosity- and macroviscosity-related effects. Theophylline was chosen as a model drug substance, with methylhydroxypropylcellulose (MHPC) and polyvinylpyrrolidone (PVP) as model (pharmaceutical) polymers. The two viscosity effects could readily be discerned. Analysis of the calculated diffusion coefficients indicated a deviation from theoretically expected results in the case of theophylline dissolution in PVP solutions.

Introduction

The bioavailability of drugs can be influenced by the transport kinetics of the drug molecules in the GI tract. Two steps are of interest in this process: dissolution of the drug from the solid dosage form and transport through the lumen and pre-epithelian barrier to the absorbing membrane. Physiological substances like mucous constituents, certain dietary components and pharmaceutical excipients such as cellulose derivates can influence the viscosity of the lumenal contents. Viscosity is one of the parameters affecting the transport kinetics of molecules (both dissolution and transport through the lumen) and therefore the bioavailability of orally taken drugs.

The effect of polymeric substances on viscosity and dissolution rate has been studied since the 1970's (Braun and Parrott, 1972). It was found that the dissolution rate was inversely related to the viscosity; however, the exact nature depended on the experimental conditions. Some authors attempted to relate the dissolution rate (R) to an empirical viscosity function (Florence et al., 1973; Sarisuta and Parrott, 1982):

$$R = \kappa \eta^{-\beta} \quad (1)$$

Several values for κ and β were found. Because of the use of the non-realistic diffusion layer model and experimentally poorly defined hydrodynamics for the interpretation of the dissolution kinetics, no solid theoretical basis could be given

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for the observed phenomena. A concise review of previous work has been published (Nelson and Shah, 1987; Shah and Nelson, 1987). In their studies, Shah and Nelson made attempts to provide a theoretical basis for the observed effect of viscosity on dissolution. They applied the convective diffusion model to the dissolution rate measured in a flow cell under fixed flow rate and under gravitational flow conditions. As a result, the effect of viscosity on the flow rate could be separated from the effect of viscosity on diffusion. These two effects are known in the literature as macroviscosity and microviscosity and can be observed with polymeric solutions. Hydroxypropylcellulose (HPC) was used as a polymer in their work; it gave highly viscous solutions. HPC did not change the dissolution rate in the flow cell compared to water, if the flow rate was kept constant. On the other hand, sucrose and glycerin lowered the dissolution rate under constant flow rate. These small molecules hinder the diffusion of the dissolved molecules by viscosity effects.

The macromolecule in solution causes resistance to flow; this effect can be measured by flow procedures. Viscosity is related to diffusion by the Stokes-Einstein equation:

$$D = kT/6\pi\eta a \tag{2}$$

where D denotes the diffusion coefficient, k is Boltzmann's constant, T represents the temperature, η is the viscosity and a is the radius of the diffusing molecule or particle.

The movement of the solvent and small solute molecules is not necessarily equally hindered by the macromolecules as the (macroscopic) flow change suggests. Therefore, in polymer solutions, the Stokes-Einstein equation, as given in Eqn 2, does not hold. In polymeric solutions, measurement of diffusion coefficients of relatively small solute molecules reveals no decrease or only a minor drop in the presence of polymer macromolecules. In the present study, the above-mentioned aspects of microviscosity and macroviscosity were studied in detail in polyvinylpyrrolidone (PVP) and methylhydroxypropylcellulose (MHPC) buffered aqueous solutions and in the pure solvents methanol and isopropanol with theophylline as a model drug. For the first time a rotating disk apparatus was used to study microviscosity and macroviscosity in polymer solutions. If the convective diffusion model applies, the dissolution rate for the rotating disk is given by (Levich, 1962):

$$R = 1.95 D^{2/3} \nu^{-1/6} \omega^{1/2} \Delta C r^2 \tag{3}$$

where R is the dissolution rate, D denotes the diffusion coefficient, ν is the kinematic viscosity (η/ρ), ρ represents the density of the medium, ω is the speed of rotation, and ΔC corresponds to the concentration at the disk's surface minus the concentration in the bulk; it is equal to the solubility under sink conditions; r is the radius of the dissolving disk. Changes in viscosity influence both D and ν (Eqns 2 and 3). Applying Eqn 2 to a number of solutions with varying viscosities gives:

$$\eta_{rel} = \eta_i/\eta_0 = D_0/D_i \tag{4}$$

where η_{rel} is the relative viscosity, η_i denotes the viscosity at concentration i of the polymer, η_0 is the viscosity without added polymer, D_0 represents the diffusion coefficient without added polymer and D_i is the diffusion coefficient at concentration i of the polymer. From Eqn 4, one can observe that, if microviscosity cannot be discerned from macroviscosity. D_i is inversely related to η_{rel}. In Tables 1 and 2, D_i is presented as $D_{S\text{-}E}$. The effect of polymer concentration and species on dissolution kinetics can be studied by changing the composition of the aqueous medium and experimentally determining ν. As D is the only unknown parameter in Eqn 3 D can be calculated; the results are presented in Tables 1 and 2 as D_L. By comparing D_L and $D_{S\text{-}E}$ the distinction between macroviscosity and microviscosity can be experimentally assessed.

Materials and Methods

Materials

Theophylline monohydrate (Ph. Eur. grade) was stored over a saturated solution of sodium bromide (relative humidity 60%) at 20 °C. Anhy-

drous theophylline (for use in experiments in methanol and isopropanol) was prepared from the monohydrate by heating at 110 °C for 24 h, and cooling the crystals in a desiccator over silica gel. Polyvinylpyrrolidone (PVP, USP grade; Plasdone K29/32) and methylhydroxypropylcellulose (MHPC, Ph. Eur. grade; 4000 mPa s) were used as received. Double-strength buffer solutions were prepared by dissolving glacial acetic acid and sodium hydroxide in the appropriate volume of double glass distilled water. PVP and MHPC were dissolved at 90 °C in half of the final volume of the same type of water. After cooling the two solutions were mixed and kept for at least 24 h. Methanol and isopropanol (2-propanol) (both p.a. grade; Merck, Darmstadt, Germany) were used as received. The kinematic viscosities were determined in Ubbelohde viscometers at 25 °C. The densities were determined in a 25 ml pycnometer at the same temperature.

Solubility and dissolution rate measurements

The solubilities of theophylline monohydrate and anhydrous theophylline in the aqueous solutions or organic solvents were determined by shaking suspensions for 1 week at 25 °C ($n = 3$). After centrifugation the samples were diluted and assayed spectrophotometrically. The dissolution rate was measured in a rotating disk apparatus as described before (De Smidt et al., 1986).

Results and Discussion

Dissolution kinetics and diffusion coefficients

The solubility of theophylline monohydrate in organic solvents and buffer solutions is given in Tables 1 and 2; the viscosity and density of these solvents are presented in separate columns. The solubility does not change upon addition of MHPC to the buffer solution and is influenced only to a small extent by the addition of PVP. The dissolution rate of theophylline (R) in the solutions is also listed in Tables 1 and 2. The values decrease with increasing viscosity of the solutions as expected from Eqn 3.

An indication for a convective-diffusion controlled dissolution process was found in the plot of the dissolution rate as a function of the square root of rotation speed (Eqn 3). Several data sets are shown in Fig. 1. The curves can be properly fitted via linear regression analysis; extrapolation of the speed of rotation to zero revealed no ordinate intercept statistically different from the origin. Values for D_L are given in Tables 1 and 2. The values for the diffusion coefficients of theophylline found in methanol and isopropanol strongly deviate from those in buffer solutions. This is caused by the low viscosity of methanol and the high viscosity of isopropanol. In PVP solutions the diffusion coefficients decrease with increasing PVP concentration. In MHPC solutions the diffusion coefficients D_L are equal to the values found in buffer without MHPC.

The results from application of the Stokes-Einstein equation (Eqn 2; $D_{S\text{-}E}$) are given in the final column of Tables 1 and 2. The diffusion coefficients are inversely related to the viscosity (Eqn 4). In pure solvents like methanol and isopropanol, the values are in excellent agreement with those calculated from dissolution rate measurements by application of Eqn 3. In these sol-

TABLE 1

Viscosity (η) and density (ρ) of solvents, solubility of theophylline (C_S), dissolution rate of theophylline at 520 rpm (R), and calculated diffusion coefficients of theophylline from Eqn 3 (D_L) and Eqn 4 ($D_{S\text{-}E}$) in different solvents at 25 °C

Solvent	η (mPa s)	ρ (g/ml)	C_S (g/l)	$R(\times 10^2)$ (mg/s)	$D_L(\times 10^{10})$ (m^2/s)	$D_{S\text{-}E}(\times 10^{10})$ (m^2/s)
Buffer	1.07	1.0202	5.79	3.84 (0.04)	6.2 (0.2)	6.2 (0.2)
Methanol	0.56	0.7878	5.44 [a]	5.83 [a] (0.06)	11.5 (0.4)	11.8 (0.2)
Isopropanol	1.99	0.7829	2.43 [a]	0.91 [a] (0.01)	3.3 (0.1)	3.3 (0.2)

[a] Values calculated for anhydrous theophylline as used in nonaqueous solvents.

The values for η, ρ, C_S and R are the average of at least five determinations; data for R and D are given with the S.D. in parentheses.

TABLE 2

Viscosity (η) and density (ρ) of buffer solutions containing PVP or MHPC, solubility of theophylline (C_S), dissolution rate of theophylline (R), and calculated diffusion coefficients of theophylline from Eqn 3 (D_L) and Eqn 4 ($D_{S\text{-}E}$) in solutions of PVP and MHPC at 25 °C

Concentration (%)	η (mPa s)	ρ (g/ml)	C_S (g/l)	$R(\times 10^2)$ (mg/s)	$D_L(\times 10^{10})$ (m^2/s)	$D_{S\text{-}E}(\times 10^{10})$ (m^2/s)
PVP						
1	1.19	1.0221	5.79	3.70 (0.04)	6.0 (0.2)	5.5 (0.2)
2	1.37	1.0241	5.87	3.44 (0.03)	5.8 (0.2)	4.8 (0.2)
4	1.70	1.0280	5.93	3.18 (0.03)	5.2 (0.2)	3.9 (0.2)
MHPC						
0.05	1.44	1.0204	5.78	3.65 (0.04)	6.2 (0.2)	4.6 (0.2)
0.1	2.02	1.0206	5.79	3.41 (0.03)	6.0 (0.2)	3.3 (0.2)
0.15	2.87	1.0207	5.78	3.24 (0.03)	6.1 (0.2)	2.3 (0.2)
0.2	3.95	1.0208	5.79	3.07 (0.03)	6.1 (0.2)	1.7 (0.2)
0.25	5.50	1.0209	5.79	2.88 (0.03)	6.0 (0.2)	1.2 (0.2)

The values for η, ρ and C_S and R are the mean of at least five determinations; data for R and D are given with the SD in parentheses.

vents the simple relation between viscosity and diffusion coefficient (as expressed in Eqn 4) holds.

Macro- and microviscosity

The diffusion coefficients in PVP and MHPC solutions calculated with the Stokes-Einstein equation ($D_{S\text{-}E}$; Eqn 4) are very different from the values obtained with the Levich equation (D_L; Eqn 3). Simple application of Eqn 4 does not provide results that agree with the observed phenomena. This discrepancy between observed and calculated results can be explained on the basis of the existence of a microviscosity and macroviscosity under such circumstances. Macroviscosity influences the flow around the dissolving surface and is directly related to ν in the Levich equation (Eqn 3). Microviscosity can be derived from the D_L values in Table 2 if they are compared with D_L for buffer in Table 1. In pure solvents and in solvents containing molecules or ions of the size of the diffusant, these two types of viscosity are identical. In polymeric (macromolecular) solutions microviscosity is the factor influencing diffusion coefficients.

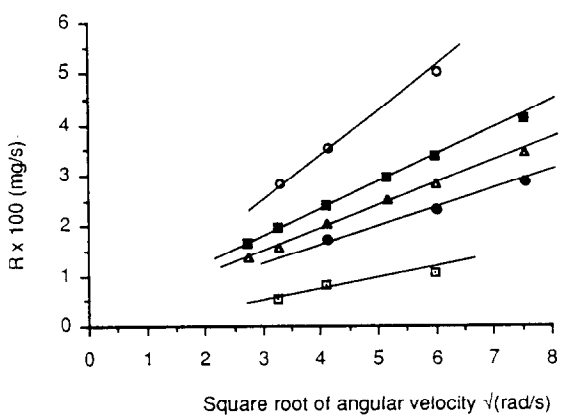

Fig. 1. Dissolution rate of theophylline (R) as a function of the square root of the angular velocity. Buffer solution (■), methanol (○), isopropanol (⊡), 0.25% MHPC (●), and 4% PVP (△). Each point is the mean of at least five determinations; lines were calculated by linear regression analysis.

From Table 2 it can be seen that in PVP solutions the Levich diffusion coefficient is a function of the concentration of PVP. The diffusion coefficient of small solutes in a polymeric solution can be modulated in the presence of large, slowly diffusing macromolecules. This effect is called obstruction and is related to the volume, size and shape of the polymer molecule present. The effect of obstruction by macromolecules is best represented by the Wong equation (Wong, 1954; Farng and Nelson, 1973):

$$D_i = D_0(1 - K_{obst}\phi) \qquad (5)$$

where D_i is the diffusion coefficient at concentra-

tion i of the polymer, D_0 denotes the diffusion coefficient of the solvent or low molecular solute without polymer, K_{obst} is a constant related to size and form of the polymer, and ϕ represents the volume fraction of the polymer. For spherical colloidal particles $K_{obst} = 1.5$, as derived by Wong (1954). At low concentrations of the polymer, e.g. as in the MHPC solutions used in the present study, ϕ is about 0, and consequently $D_i = D_0$. At higher volume fractions of polymer, e.g. in the PVP solutions studied here, some obstruction effect is observed. The values of K_{obst} calculated with Eqn 5 are not constant (at $i = 1$, 2 and 4%, respectively: 2.6, 3.3 and 3.9). The fact that K_{obst} is not constant and exceeds the theoretical value (1.5 for spherical particles) indicates that simple obstruction as discussed above cannot fully explain the drop in D_L. These differences do not fully explain the observed 20% decrease in D_L for the 4% PVP solution compared to the buffer D_L. A second, additional, reason for the drop in D_L for PVP solutions may be an interaction between theophylline and PVP. An indication for such an interaction is the increase in solubility of theophylline for the 2 and 4% PVP solutions. Unfortunately, tools are missing at the present for a further analysis of the data in order to describe this interaction in quantitative terms.

The flow viscosity as measured with viscometers has only a limited predicting value as far as dissolution kinetics in polymeric solutions is concerned. In this study, the rotating disk proved to be a valuable tool in the elucidation of the basis of dissolution processes. With the rotating disk it was possible to discriminate between microviscosity and macroviscosity and to show that the microviscosity for MHPC solutions did not change within the experimental range, while the macroviscosity increased 5-fold.

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