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Viscosity measurement in aqueous polymer solutions by dynamic light scattering

Jan H. de Smidt * and Daan J.A. Crommelin

Department of Pharmaceutics, Faculty of Pharmacy, P.O. Box 80.082, 3508 TB Utrecht (The Netherlands)

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Summary

In this study the effect of polymers was investigated on diffusional transport of model spherical particles (latex) of different size in an aqueous phase. Diffusion was monitored by dynamic light scattering (DLS) measurements. Solutions of carboxymethylcellulose (CMC Na) and polyvinylpyrrolidone (PVP) were used as models for two types of pharmaceutically relevant water-soluble polymers. Microviscosity effects could be observed only for the small sized particles in CMC Na solutions. In PVP solutions no microviscosity effects could be detected under the experimental conditions.

Introduction

In the absorption process of solid drugs in the gastro-intestinal tract, either dissolution or transport of the dissolved drug can be the rate-determining step; these steps can even limit the extent of absorption. Physiological polymers present in mucus and polymeric pharmaceutical excipients influence convective transport and diffusion by increasing the viscosity. In vitro, the effect of viscosity on the dissolution rate is well documented (Florence et al., 1973; Sarisuta and Parrott, 1982, 1983). Controlled release dosage forms have been designed on the basis of the slowing down of diffusional mass transport in viscous media. In the last decade, more insight has been gained into the basic physico-chemical properties of polymers relevant to diffusion and convective transport of drugs (Nelson and Shah, 1987; Shah and Nelson, 1987). Because of the macromolecular nature of the polymers, their effect on macroscopic motion (flow) can differ from their effect on microscopic motion (diffusion). The two 'types' of viscosity resulting from these two effects have been defined in the literature as macroviscosity and microviscosity (Flynn et al., 1974). As will be shown later, data on microviscosity and macroviscosity can differ dramatically. Macroscopic viscosity data cannot be used to analyse properly phenomena based on microviscosity.

Correspondence: D.J.A. Crommelin, Dept of Pharmaceutics, Faculty of Pharmacy, P.O. Box 80.082, 3508 TB Utrecht, The Netherlands.

* *Present address:* KNMP, Alexanderstraat 1, 2514 JL The Hague, The Netherlands.

In dissolution kinetics, both macro- and microviscosity play their role affecting hydrodynamics and diffusion, respectively (De Smidt et al., 1991). To predict dissolution rates in polymer solutions, data on both types of viscosity should be determined separately. For the determination of macroviscosity many instruments are available based on flow measurement (Martin et al., 1983). Microviscosity can be calculated from diffusion data by application of the Stokes-Einstein relation (Hess and Klein, 1984).

$$D = kT/6\pi\eta a \qquad (1)$$

where D is the diffusion coefficient, k represents Boltzmann's constant, T is the temperature, η denotes the (micro)viscosity of the diffusion medium and a is the radius of the diffusant. Factors that determine the microviscosity are: the concentration (volume fraction, ϕ), the shape and size of the polymer and the degree of hydration. Apart from obstruction effects, molecular interactions between the polymer (complexation or 'adsorption') and the diffusant can reduce the rate of diffusion. Diffusion can be measured by dynamic light scattering (DLS) (Derderian and Macrury, 1981). For instance, diffusion coefficients of polystyrene latex spheres (624 nm) in carbopol gels were calculated from DLS data (Al-Khamis et al., 1986). In the present study, DLS was also used as a method to determine diffusion coefficients. The aim was to relate the size of the diffusant to the viscosity effect of the polymers by measuring diffusion coefficients of latex spheres of different size (38, 198 and 624 nm). As model polymers, carboxymethylcellulose sodium (CMC Na) and polyvinylpyrrolidone (PVP) were used, representing two different types of macromolecular pharmaceutical polymers.

Experimental

Materials

Carboxymethylcellulose sodium 'high viscosity' (CMC Na H; Ph. Eur. grade) and polyvinylpyrrolidone (PVP; USP XX-grade; Plasdone 29/32) were used as received. Solutions were made in double glass distilled water by dispersion of the polymers at 90 °C in the required volume of water. After cooling the solutions were stored at 5 °C for 24 h before use. The pH of the CMC Na H solutions was between 7 and 8. The dispersions were checked for physical stability by repeated measurement of the diffusion coefficients of the latex particles over a period of 1 week. Spherical polystyrene ('latex') particles with narrow size distributions (Dow Latex Particles, Duke Scientific, Palo Alto, CA) and of different average sizes (38, 198 and 624 nm) were used at different concentrations. The particles were dispersed in the polymeric solutions and diluted at least 10^4 times.

Methods

The macroscopic viscosity of the polymer solutions was measured in Ubbelohde viscometers (Ph. Eur.) at 25 °C prior to addition of polystyrene spheres. The density of the solutions was determined in a 25 ml pycnometer at the same temperature. DLS experiments were performed in a Malvern PCS system (Malvern Ltd, Malvern, U.K.), equipped with a PCS4700C correlator, PCS8 photomultiplier, and a 25 mW helium/neon laser GLG5700 (NEC Corp., Tokyo, Japan). All experiments were performed at a scattering angle of 90 °; the temperature was maintained at 25 °C; as accompanying software the program automeasure VSN 3.2 was used. New dispersions were made for quadruplicate measurements. Each sample was measured three times on the basis of a 10-fold repetition measurement.

Results and Discussion

The dispersions of latex particles of all sizes used appeared to be stable in the CMC Na H and PVP solutions. Results for the diffusion coefficients of the particles measured in PVP and CMC Na H solutions are given in Tables 1 and 2. Within the experimental range the concentration of the dispersed particles did not affect the results.

TABLE 1

Diffusion coefficients of polystyrene particles of different size in PVP solutions of varying concentration (C_i) measured by DLS

C_i (% m/v)	D_i (m^2/s)($\times 10^{11}$)		
	38 nm [a]	198 nm [a]	624 nm [a]
0	14.7 ± 0.07	3.1 ± 0.1	0.75 ± 0.04
1	9.8 ± 0.05	2.1 ± 0.1	0.49 ± 0.03
2	7.5 ± 0.04	1.5 ± 0.08	0.38 ± 0.02
4	5.9 ± 0.03	1.3 ± 0.07	0.28 ± 0.01
10	2.3 ± 0.01	0.45 ± 0.02	0.093 ± 0.005
20	0.59 ± 0.003	0.11 ± 0.006	0.021 ± 0.004
30	0.17 ± 0.001	0.034 ± 0.002	0.0083 ± 0.002
40	0.046 ± 0.0003	0.0094 ± 0.0005	0.0024 ± 0.0005

[a] Latex sphere diameter; data given ± SD.

For calculation of the relative viscosities (η_{rel}), Eqn 2, based on the Stokes-Einstein equation, was used:

$$\eta_{rel} = D_0/D_i \qquad (2)$$

where D_0 is the diffusion coefficient in pure solvent and D_i is the diffusion coefficient at concentration i of the polymer.

The results for η_{rel} in the CMC Na H and PVP solutions are given in Figs 1 and 2. In PVP solutions particles of all sizes gave similar results; in CMC Na H solutions distinct size dependency was observed. The smallest particles used (38 nm)

TABLE 2

Diffusion coefficients of polystyrene spheres of different size in CMC Na H solutions of varying concentration (C_i) measured by DLS

C_i (% m/v)	D_i (m^2/s)($\times 10^{11}$)		
	38 nm [a]	198 nm [a]	624 nm [a]
0	14.7 ± 0.7	3.1 ± 0.2	0.75 ± 0.03
0.025	8.7 ± 0.5	0.92 ± 0.05	0.25 ± 0.01
0.05	8.3 ± 0.5	0.42 ± 0.02	0.11 ± 0.005
0.1	6.4 ± 0.3	0.36 ± 0.02	0.074 ± 0.004
0.15	5.4 ± 0.3	0.34 ± 0.02	0.054 ± 0.003
0.2	4.1 ± 0.2	0.29 ± 0.01	0.037 ± 0.002
0.25	3.7 ± 0.2	0.16 ± 0.01	0.021 ± 0.001
0.3	3.3 ± 0.2	0.089 ± 0.005	0.015 ± 0.001
0.4	2.3 ± 0.1	0.057 ± 0.003	0.0097 ± 0.0005
0.5	1.4 ± 0.07	0.037 ± 0.002	0.0068 ± 0.0003
0.6	1.1 ± 0.06	0.031 ± 0.002	0.0051 ± 0.0002

[a] Latex sphere diameter; data given ± SD.

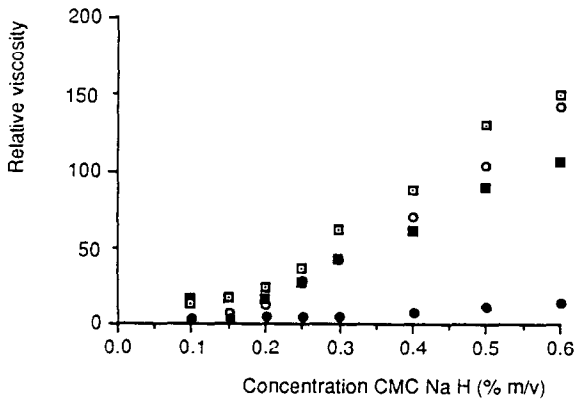

Fig. 1. Relative viscosity (ordinate) as a function of the concentration of CMC Na H in solution, measured by DLS with latex particles of (●) 38 nm, (■) 198 nm and (○) 624 nm diameter and with an Ubbelohde viscometer (⊡).

show only a relatively small increase in relative viscosity with the concentration of CMC Na H.

Relative viscosities were calculated from Ubbelohde viscometer data with Eqn 3:

$$\eta_{rel} = \eta_i/\eta_0 \qquad (3)$$

The results for η_{rel} from Ubbelohde viscometer measurements have been included in Figs 1 and 2.

From these results it can be concluded that, for the particles used, in PVP solutions the microviscosity as calculated from DLS data cannot be separated from the macroviscosity. However, on the basis of theophylline diffusional transport experiments, a microviscosity effect was reported

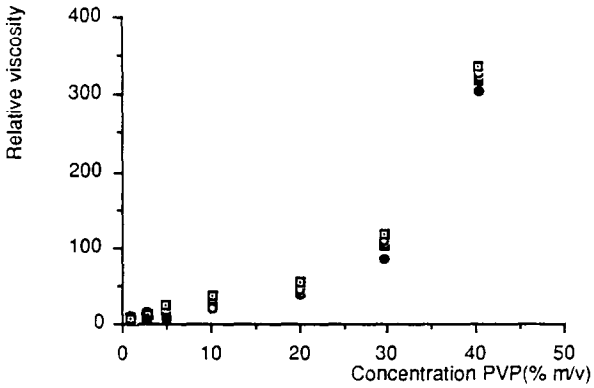

Fig. 2. Relative viscosity (ordinate) as a function of the concentration of PVP in solution, measured by DLS with latex particles of (●) 38 nm, (■) 198 nm and (○) 624 nm diameter and with an Ubbelohde viscometer (⊡).

in the preceding article to exist in PVP solutions (De Smidt et al., 1991). The smallest particles used for DLS measurement in this study were 38 nm. The size of the diffusing molecules of theophylline is over 10-times smaller. As these molecules were not hindered by PVP, the structure of the polymer apparently is porous for this size of solutes, but not for 10-times larger particles.

A completely different situation was encountered in the case of CMC Na H solutions. Here, the 624 nm particles were hindered in their motion and the relative viscosities calculated from DLS data and the Ubbelohde viscometer were similar. However, the 198 nm particles were less sensitive to the presence of polymer and this trend continued for the 38 nm particles. Thus, a clear distinction between micro- and macroviscosity was found. As diffusion of 38 nm particles is influenced only to a limited extent by the polymer, diffusion of 10-times smaller molecules will be even less sensitive to the concentration of polymer. This was indeed reported in the previous paper (De Smidt et al., 1991).

The different behaviour of the two polymers as viscosity increasing agents is also demonstrated by their different potency (on concentration m/v basis) in increasing the viscosity. At 0.6% the macroviscosity of CMC Na H is already higher than at 30% PVP. The study of Al-Khamis et al. (1986) was performed in carbomer gels at concentrations ranging from 0.01 to 1.5%. The macroviscosity was not given; however, because of its gel-like structure, it is likely to be higher than in CMC Na H solutions. If smaller sized particles had been dispersed in the gel, an effect comparable to that of CMC Na H would have been expected; the 624 nm particles used in their study are probably too large to derive conclusions concerning microviscosity and diffusion behaviour of small sized molecules.

Unstable dispersions (flocculation of particles) were observed in methylcellulose (MC) and methylhydroxypropylcellulose (MHPC) solutions. Within 10 min these dispersions showed optically visible aggregates. One can only speculate as to why these polymers tend to destabilise the latex particles.

The determination of the viscosity of polymer solutions by DLS experiments with differently sized latex spheres gives an impression of the structure of the polymer and the viscosity to be expected on a molecular scale (microviscosity). The method can only be applied in physico-chemically stable dispersions. Different sizes of the particles should be used in order to justify extrapolation to diffusion on a molecular scale. Instead of latex particles, other well-characterized, non-aggregating, colloidal particulates available in different sizes (with narrow size distributions) can be utilized.

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