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Reaction kinetics by permeable plate rheometry

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ABSTRACT

A new method has been developed using permeable parallel plates through which a solution (here salt or alkali) can be added to a sample during measurements. The method was validated using stopped flow measurements and applied to a charge responsive gel system aimed to be used in nose spray formulations.

INTRODUCTION

There are currently drugs available for many of the known diseases. These drugs are delivered to the right place in the body using a formulation in which the active medical substance is mixed with other components. The formulation can take the form of a tablet, liquid medicine, nasal spray or eye drops. With the correctly designed formulation the medical substance will reach the right area and will be released under controlled conditions over a specified period of time.

When administering a pharmaceutical substance via the nasal mucose membrane, uptake is rapid and the substance does not need to pass the liver, where it could be destroyed. Bio-availability, however, is low, less than one per cent for protein substances, due to the fact that the nose rapidly and effectively removes particles which stick to the mucosa [1]. It would therefore be desirable to increase the residence time e.g. by administering a gelling formulation which would slow down the transport of the droplet on the mucus membrane.

Carbopols® are commercially available, cross-linked poly (acrylic acid) polymers which swell electrostatically due to their polyelectrolytic nature [2-4]. A pH increase leads to deprotonated carboxylic acid groups and a swelling of the polymer microgels which gives thickening and largely increased viscosity. Similarly, interactions with ions cause deswelling. The application of Carbopols in nose spray formulations would involve administration of a low viscosity solution at low pH. On the mucus membrane H^+ diffusion causes pH to increase, to the physiological pH 7.4, with swelling and thickening as a result. The diffusion of NaCl from the mucus layer into the droplet causes the reverse effect. The knowledge of the relative rates of the pH induced swelling and the salt induced deswelling is therefore crucial to achieve an increased overall residence time.

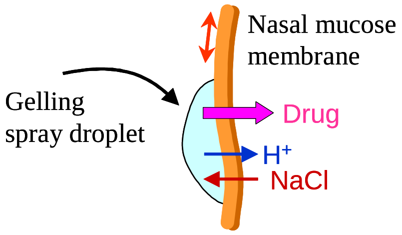

Figure 1. Factors effecting a gelling droplet on the nasal mucose membrane.

A new permeable plate method was tested in the present study and the kinetic results were compared to stopped flow data. The aim of the study was to determine the relative rates of the swelling and deswelling of a Carbopol formulation at physiological conditions and their effect on the rheological properties of the formulation.

MATERIALS AND METHODS

Carbopol 981 NF, (Noveon, Inc. [2]) was kindly provided by Bionord (Stenungsund, Sweden). Carbopol was dissolved in distilled water (0.5% w/w) to a somewhat opaque solution with a pH of 3.0. Transparent gels were formed by adding 0.5M NaOH to the solution and the pH was set to 7.4. The effect of deswelling was studied by adding NaCl to the gel.

A Stresstech HR Rheometer (Reologica Instruments, Lund, Sweden) equipped with a permeable upper plate was used for the swelling and deswelling studies. Oscillating measurements at 1Hz were performed at 20°C with a 1 mm gap. The permeable upper plate was manufactured in house (30 mm diameter) and consisted of a steel filter (Mott Metallurgical Corp., Farmington, USA). A plate made of a stainless steel mesh was also tested obtaining the same results. A lid was used to avoid evaporation.

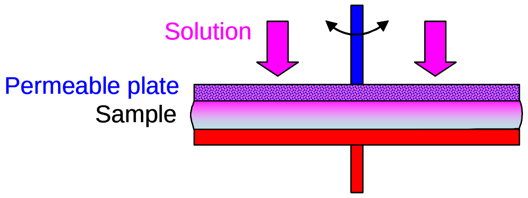

Figure 2. The principle of permeable plate rheometry.

The measurement was started before adding NaOH to the pH 3 solution for the swelling study, or by adding NaCl to the pH 7.4 gel for the deswelling study. Both solutions were added to the sample through the upper permeable plate.

A Stopped-Flow Spectrometer, SX.18Mv-R (Applied Photophysics, Leatherhead, UK) was used for optical determination of reaction kinetics. The two test solutions (Carbopol+NaOH or Carbopol+NaCl) were rapidly mixed from two syringes into a cuvette. A total volume of 100 µl was forced through the 20 µl cuvette in 1 ms. The reaction after mixing was monitored by the transmission of light at 250 nm through the cuvette.

First order reactions were assumed and a double exponential was fitted to the experimental data from the rheological and stopped-flow measurements.

$$response \propto Ae^{-k_1 t} + Be^{-k_2 t} \qquad (1)$$

The data was fitted a by least squares minimization using non-linear regression. The fitted curves are shown in red in the figures.

RESULTS AND DISCUSSION

Rheological effects of kinetics

A Carbopol solution at pH 3 was applied in the permeable plate system and oscillated for 1500 s before addition of NaOH.

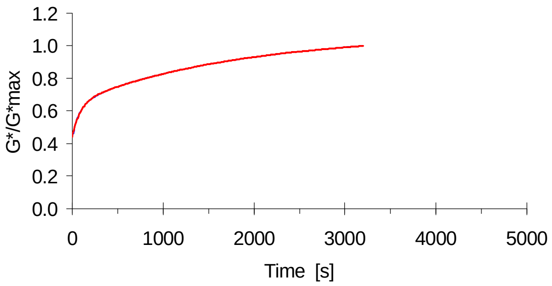

Figure 3. The kinetics of swelling of Carbopol monitored by permeable plate rheometry.

The swelling was monitored by the change in G* and the curve was normalized to the maximum |G*| and shifted to t=0 for the time of NaOH addition. Figure 3 shows the swelling for NaOH addition resulting in a final physiological pH of 7.4.

Another Carbopol sample, a gel at pH 7.4 was applied in the permeable plate system and oscillated for 1500 s before addition of NaCl. The curve in Figure 3 was obtained as described above and shows the deswelling of the gel to a final physiological concentration of 0.15M NaCl.

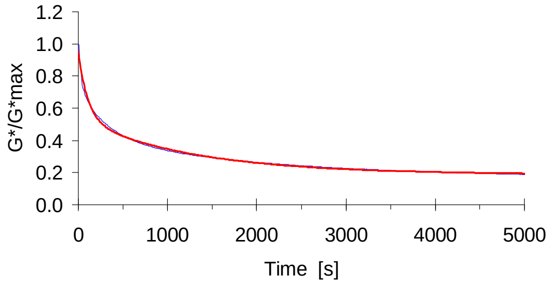

Figure 4. The kinetics of deswelling of Carbopol monitored by permeable plate rheometry.

Validation of the results by stopped flow

The swelling and deswelling behaviour of the Carbopol systems was studied using the stopped flow technique. The UV light transmitted through the samples was scattered by the Carbopol microgels which gave the reaction kinetics shown in Figure 4.

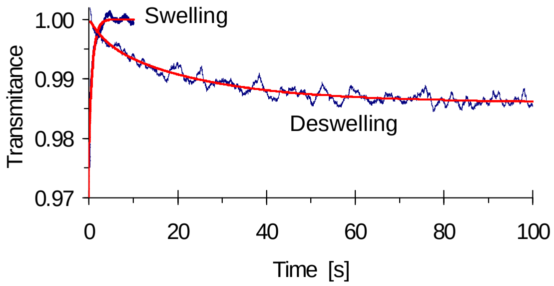

Figure 4. The kinetics of swelling and deswelling of a Carbopol gel monitored by stopped flow.

The stopped flow measurements (Figure 4) clearly showed that the swelling was considerably faster than the deswelling, which was not as evident by rheology (Figure 3). The added solution in the rheological experiment was added through the permeable top plate and had to diffuse throughout the gap whereas the added solution in stopped flow was rapidly mixed with all of the Carbopol. Diffusion will therefore be the limiting step for permeable plate rheometry when it is slower than the studied reaction. Equation 1 was fitted to all results and the rate constant k_1 was always found to be at least $k_1>10k_2$. The rate constant k_1 for the slower reaction, the deswelling, from permeable plate rheometry ($k_{1pp}=0.02$) was in the same range as when measured by stopped flow ($k_{1sf}=0.08$) whereas they differed for the fast reaction, the swelling ($k_{1pp}=0.01$ and $k_{1sf}=2$ respectively). The swelling reaction was therefore too fast to be measured accurately using permeable plate rheometry due to diffusion being slower than the reaction.

The diffusion combined with the parallel plate measurement technique give an underestimation of the slower deswelling reaction rate in permeable plate rheology. In constant stress instruments the deflection of the top plate is measured assuming uniform deformation over the gap. When the NaCl solution was added the viscosity of the sample decreased, first at the top then progressively to the bottom following the diffusion of the added solution. The real deflection was therefore always higher than the registered one for the reaction until the NaCl concentration had equilibrated throughout the gap. This gave an underestimation of the real deflection, an overestimation of the modulus and thus a too low reaction constant, which would explain the discrepancy of the reaction constants compared to stopped flow. Further work is needed to calculate the actual, real deflection in the sample.

CONCLUSIONS

Permeable plate rheometry was shown to be a versatile technique for measuring reaction kinetics of viscoelastic samples after a change of the chemical composition. Diffusion in the sample limits monitoring of fast reactions and the calculation of the modulus needs to be refined to give more accurate reaction constants. For the nose spray formulations studied the swelling was shown to be considerably faster than the deswelling which means that a gelling formulation is possible to accomplish.

ACKNOWLEDGEMENTS

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