Permeable Plate Rheometry for Evaluation of Reaction Kinetics of Gels

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ABSTRACT

In nose spray formulations the active drug is administrated by droplets on to the mucosa layer. A swelling system would improve the residence time significantly. To monitor the kinetics of swelling and deswelling a novel permeable plate method was developed. The method was validated using stopped flow measurements.

INTRODUCTION

When administrating drugs using nose spray formulations, the residence time is short due to mucociliary clearance[1]. A gelling formulation would be desired to slow down clearance and hence prolong the time for uptake of the drug.

There are several types of cross-linked acrylic acid polymers, Carbopols®, which swell electrostatically[2-4]. The application of Carbopols in nose spray formulations would involve administration of an opaque low viscosity solution at low pH, ~3, that forms a clear gel when pH is increased to the physiological pH of the mucosa, 7.4. The swelling is however counteracted by the increased NaCl concentration on contact with the nasal mucosa (Figure 1). These relative effects on rheological properties by the reaction kinetics of swelling and deswelling are therefore crucial for a successful spray formulation.
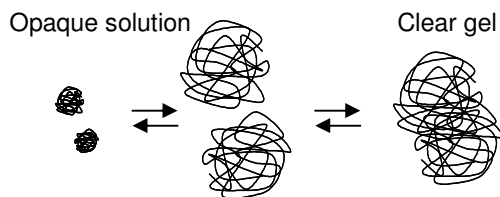

Figure 1. The competitive swelling and deswelling reactions. The top reaction (swelling) is induced by increased pH. The bottom reaction (deswelling) is induced by increased levels of NaCl.

MATERIALS AND METHODS

The reaction kinetics was studied in a parallel plate geometry with a permeable upper plate (Figure 2). NaOH or NaCl solution was added through the permeable plate during the measurement and the complex shear modulus was studied as a function of time.
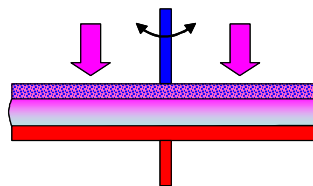

Figure 2. Schematic description of added NaCl or NaOH moving through the Carbopol during oscillatory measurement.

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.

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.

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.

RESULTS AND DISCUSSION
Rheological effects of kinetics

A Carbopol sample was applied in the permeable plate system and oscillated for 1500 s before addition of NaOH or NaCl. The swelling and deswelling 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 and deswelling of Carbopol.
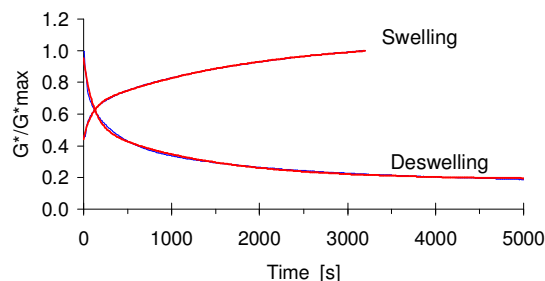

Figure 3. The kinetics of swelling and deswelling in the parallel plate system.

Validation of the results by stopped flow

The stopped flow measurements 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.

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 to the gel 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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