ANNUAL TRANSACTIONS OF THE NORDIC RHEOLOGY SOCIETY, VOL. 19, 2011

Investigation of HPMC behaviour in a buffer solution using rheology and UV imaging

Stefania Baldursdottir, Jari Pajander, Jukka Rantanen, Jesper Østergaard

Department of Pharmaceutics and Analytical Chemistry,
Faculty of Pharmaceutical Sciences, University of Copenhagen

ABSTRACT

Hydroxypropyl methylcellulose (HPMC) was used as the model polymer and UV images were obtained of a polymer surface from immersion into phosphate buffer saline (PBS) and for the following 90 min. Both oscillatory shear and steady shear measurements were conducted on 6 different concentrations of the HPMC. As expected the matrix tablet swelled in the presence of the buffer solution and a gel layer was observed. With time erosion of the polymer takes place which could be correlated to rheological parameters such as yield stress and gel point.

INTRODUCTION

Oral drug delivery can be considered as the main route for systemic delivery. In order to improve the pharmacological activity, diminish toxic effects and reduce the number of daily doses, prolonged release pharmaceutical dosage forms have been introduced, which are able to release their contents slowly in the gastrointestinal tract. Among the most widely studied of these systems are matrix tablets, in which the active pharmaceutical ingredient (API) is either dissolved molecularly or suspended physically into the surrounding excipient, e.g. a swelling polymer. The physico-chemical properties of the polymer used in such systems control the release of the API. The release rate limiting factors are swelling, gelling and erosion of the polymer in the gastrointestinal tract. There are many excipients available for these systems, but one of the most used is hydroxypropyl methylcellulose (HPMC). HPMC is a biocompatible polysaccharide that is widely used in the food industry and approved by the European Pharmacopoeia (Ph.Eur.) and the Food and Drug Administration (FDA) as an excipient for pharmaceutical products.

The performance and, thus, the functionality and safety of the preparation have to be tested. Traditionally, the performance has been studied by the utilization of an *in vitro* dissolution test, which provides information on API release rate and kinetics. However, these tests give little or no information on factors determining the API release, such as swelling, gelling and erosion. Therefore, the current trend is chemical imaging, which can provide spatial information on the distribution of the different components in the tablet[1]. There are many imaging techniques available and one of them is UV imaging that is able to generate space- and time-resolved images from the absorbance of UV light[2,3]. In this system, the intensity of light in the UV range passing through an area of a quartz tube is measured as a function of position and time[2]. Therefore, together with other physico-chemical characterization tools, it may be regarded as an attractive choice for HPMC behaviour determination and, consequently, the functionality and safety assessment of a prolonged release system.

The aim of this work was to investigate the performance, i.e. swelling, gelling and erosion, of HPMC by UV imaging and relate them to rheological properties.

MATERIALS AND METHODS

Materials

Hydroxpropyl methylcellulose (Metolose 60SH-50, Shin Etsu Chemical Co., Ltd., Tokyo, Japan) was used as a model polymer. Potassium dihydrogen phosphate (Merck, Darmstadt, Germany), sodium hydroxide (VWR International S.A.S., Fontenay-sous-Bois, France) and purified water (Milli-Q plus, Millipore, Molsheim, France) were used for the phosphate buffer preparation.

UV imaging

Approximately 10 mg of HPMC was poured into a die with a diameter of 2 mm and compressed with a torque 75 cNm. The die, which contained the sample, was placed into a sample holder inside the quartz cuvette (7.5×3.0×63 mm^3 (height × width × length)). A syringe pump was used for the infusion of the dissolution medium (phosphate buffer solution (USP), pH 6.8, 37 °C) into the cuvette and thus exposing the sample surface to it.

UV imaging was performed using an Actipix SDI300 dissolution imaging system (Paraytec Ltd., York. United Kingdom) with an Actipix flow through type dissolution cartridge. The detection area of the UV imager was 9×7 mm^2 (1280×1024 pixels) and the pixels (7×7 μm^2) were binned 4×4. The light source was a pulsed Xe lamp, and imaging was performed at 214 nm. Images were recorded with a frame time of 2.054 s for 90 min and analysed using Actipix D100 software version 1.4 (Paraytec Ltd. York, United Kingdom). Pixel intensities were converted into absorbance using the Actipix software. The concentration of HPMC as a function of distance from the centre of the die into surrounding solution phase (Fig. 1) and time was consequently determined by utilization of a calibration curve (0.5-11.5% (w/w)).

Rheology measurements

Samples of 6 different concentrations, 0.5, 1.0, 3.0, 5.0, 7.0 and 9.0% (w/w), of HPMC were prepared by dissolving appropriate amounts of HPMC in phosphate buffer. Oscillatory shear measurements were conducted with a TA AR-G2 rheometer (TA Instruments) using a cone and plate geometry, diameter of 60 mm and 1° cone angle. Stress sweeps from 0.1 to 1000 µNm oscillation torque, frequency of 1 Hz, and frequency sweeps from 0.1 to 100 Hz, oscillation torque of 1 µNm, were conducted, at a fixed temperature of 37°C. All samples were allowed to stand for minimum four days at room temperature to ensure complete dissolution of the polymer.

Light microscope measurements

The behaviour of HPMC in the buffer solution was also observed by light microscope (Carl Zeiss, Inc., Göttingen, Germany). A die containing polymer was attached to a petri dish and a buffer solution (≈37 °C) was poured on to it and the development was followed for 90 min.

RESULTS AND DISCUSSIONS

The UV imaging can be used to visualize HPMC immediate swelling into surrounding medium (Fig. 1). Fig. 2 shows the behaviour of the HPMC presented as a function of distance from the centre of the die (Fig. 1). Swelling and gelling proceed rapidly up to 20 min, after which the rate starts to stabilize and even decrease when the time point of 50 min is reached. In addition to this, an increase of the concentration very close to the sample holder can be observed throughout the measurements.

The behaviour of HPMC in a buffer solution is highly complex, since there are parallel events taking place and even affecting each other. Therefore, the data is dealt with in more detail by dividing the measurements into phases of 0 - 15 (Fig. 3), 20 - 50 (Fig. 6) and 55 - 90 min (Fig. 7).

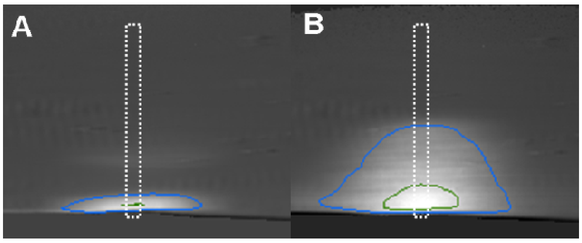

Figure 1: UV images of the sample after A) 0 min and B) 45 min. The outer and inner contour correspond absorbance thresholds of 2 and 7 % (w/w) HPMC, respectively. The rectangle designates the area, in which the analysis was performed.

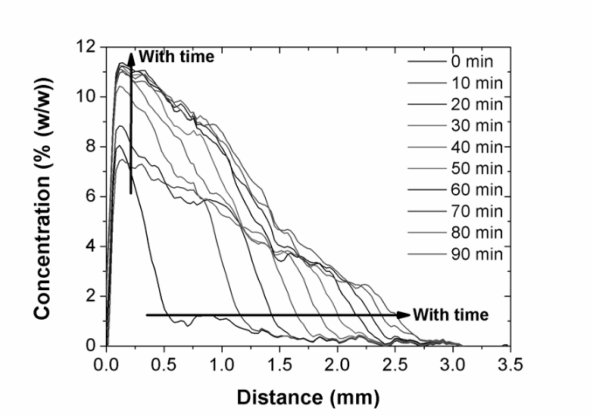

Figure 2: Swelling, gelling and erosion of the HPMC over 90 min depicted as the apparent concentration of HPMC versus the distance from the sample holder.

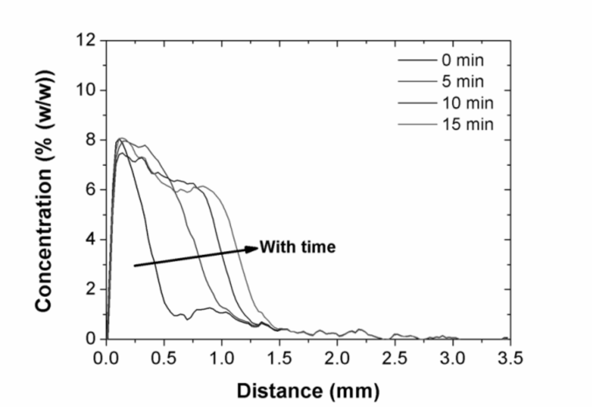

Figure 3: The swelling of HPMC during the first 15 min of exposure to PBS depicted as the apparent concentration of HPMC as a function of distance to the sample holder.

In the beginning of the measurement the water molecules are penetrating into the sample and swelling occurs (Fig. 3). After 15 min the swelling layer has reached the thickness of 1.3 mm. High concentrations are observed as little dilution of the polymer has yet occurred and a plateau is reached at a concentration of approximately 7% (w/w).

When looking into the yield stress measurements of the HPMC system, both the storage modulus (G’) and the yield strength increased with increasing concentration of the polymer (see Fig. 4), where approximately 20-fold increase in the G’ is detected from the lowest concentration of 0.5% (w/w) to the highest concentration of 9% (w/w).

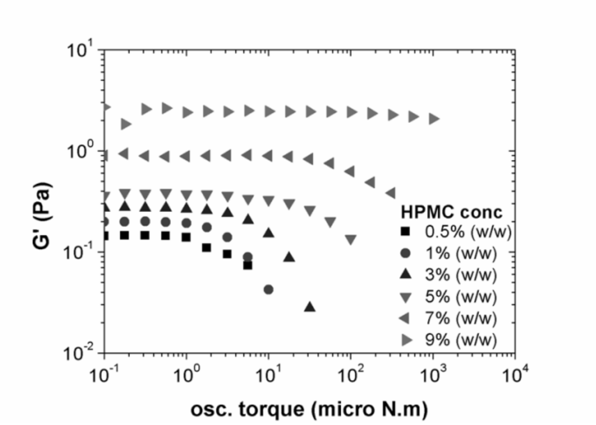

Figure 4: Storage modulus as a function of oscillation torque for the different concentrations of HPMC measured.

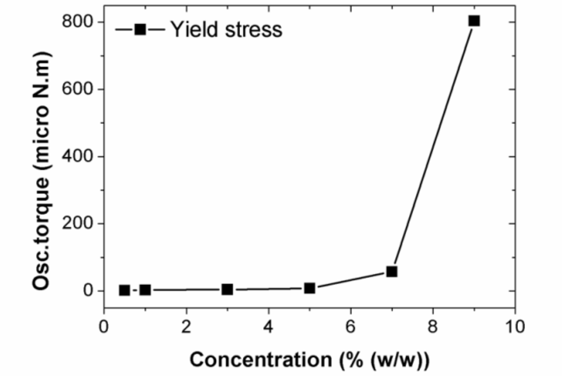

Figure 5: Concentration dependency of the yield strength for the HPMC samples.

The increase in the yield stress can be seen in detail in Fig. 5. Drastic increase in the yield strength of the system can be seen around 7% (w/w), which correlates well with the plateau detected in Fig. 3. This indicates that a minimum yield strength is necessary for the system to resist the erosion into the buffer solution in the beginning of the measurement.

Two folded fall in the concentration is observed after 20 min (Fig. 6). The first is close to the sample holder where un-dissolved or partially dissolved HPMC particles lead to distinct increase in the UV absorbance due to light scattering and therefore the concentrations calculated are not real. However, this can be used as an indication of the movement of the particles further into the swelling layer as it expands, which was confirmed by light microscope (data not shown). After the first fall in the concentration, there seems to be a short plateau and then a second fall in the concentration where another front is observed. This is the erosion front, which is also moving further out from the sample holder indicating the ongoing swelling of the polymer. The plateau concentration, at approximately 4% (w/w) in Fig. 6, also decreases indicating the dilution of the polymer due to the diffusion of the water molecules into the swollen layer.

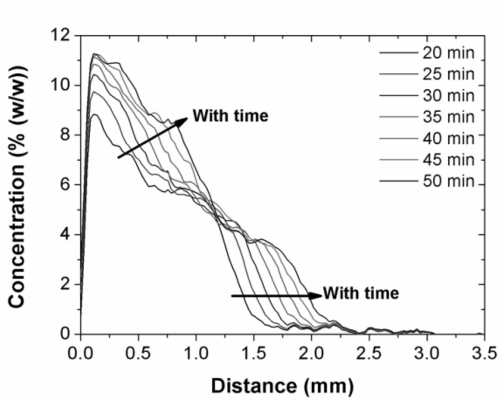

Figure 6: The swelling of HPMC between 20 and 50 min of exposure to PBS depicted as the concentration of HPMC versus the distance to the sample holder.

In the long-time-range the diffusion of water is still ongoing with expansion of the gel layer, although at a much reduced rate (Fig. 7). After 60 min the concentration of the last front seems to reach a steady state at approximately 2.3% (w/w) and below that only erosion of the polymer is observed. Thus, the polymer is able to resist erosion above the concentration of ~2.3% (w/w).

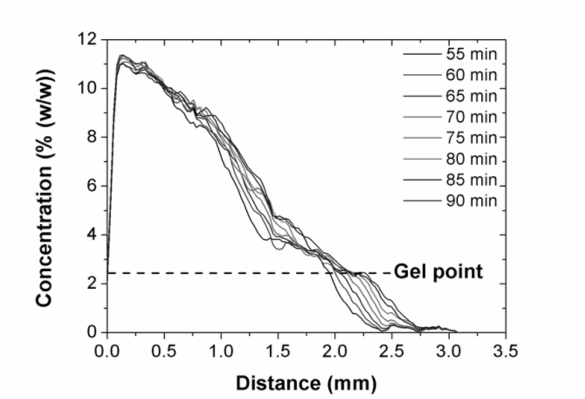

Figure 7: The swelling of HPMC between 55 and 90 min of exposure to PBS depicted as the concentration of HPMC as a function of distance to the sample holder.

The gel point was determined to ~2.3% (w/w) by finding the frequency independence of the loss tangent in a multi-frequency plot (Fig. 8). Furthermore, at this specific concentration the apparent viscoelastic power law exponents, n’ and n’’, were equal (Fig. 9) and thus by this method a similar result was obtained with respect to the previously found gel point.

This correlates well with the long-time-range erosion front of the system that seems to reach steady state after 60 min at the concentration of ~2.3% (w/w). This result indicates that the swollen polymer layer is not able to resist erosion below the gel point concentration. The entanglements at lower concentrations are insufficient and the polymer chains simply diffuse into the buffer medium.

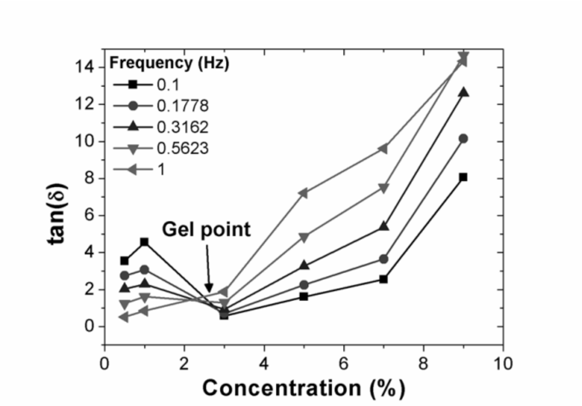

Figure 8: The viscoelastic loss tangent as a function of the concentration of HPMC at the frequencies indicated.

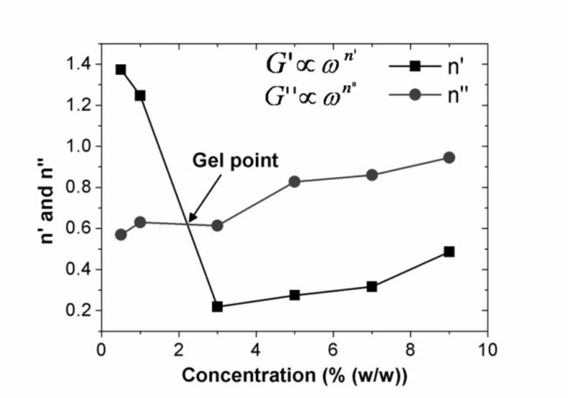

Figure 9: The changes in the apparent viscoelastic power law exponents, n' and n'', versus the concentration of the HPMC.

CONCLLUSIONS

The results showed that UV imaging combined with rheology measurements can provide detailed information on the behaviour of HPMC in buffer solution. It was found that the gel formation during rapid swelling was limited by the yield strength. Thereafter un-dissolved and partially dissolved particles contribute to the gel formation in addition to erosion front. Finally, the system reached a condition where erosion front was most dominating feature determined by a concentration consistent with the gel point.

These findings have great importance when investigating prolonged release matrix tablets composed of a swelling polymer. In general, the API has to dissolve and diffuse into the surroundings in order to finally absorb and produce the desired pharmacological effect. In systems where the main ingredient is a swelling polymer, the API release rate is directly dependent on the physico-chemical properties of the polymer. The hydration of the polymer restricts the dissolution of API, and gelling together with erosion are the main barriers for the API diffusion. Therefore, based on an in-depth understanding of the polymer behaviour, matrix tablets can be designed giving the desired release rate of the API.

REFERENCES

1. Amigo, J.A. (2010), "Practical issues of hyperspectral imaging analysis of solid dosage forms", Anal. Bioanal. Chem., 398, 93-109.

2. Østergaard, J., Ye, F., Rantanen, J., Yaghmur, A., Weng Larsen, S., Larsen, C., Jensen, H. (2011), "Monitoring lidocaine single-crystal dissolution by ultraviolet imaging", J. Pharm. Sci., *in press*

3. Østergaard, J., Meng-Lund, E., Weng Larsen, S., Larsen, C., Petersson, K., Lenke, J., Jensen, H. (2010), "Real-time UV imaging of nicotine release from transdermal patch", Pharm. Res. 27, 2614-2623