International Journal of Pharmaceutics 244 (2002) 163–168

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

A comparison between the use of dynamic mechanical analysis and oscillatory shear rheometry for the characterisation of hydrogels

Tom K.L. Meyvis [a], Barbara G. Stubbe [a], Mies J. Van Steenbergen [b], Wim E. Hennink [b], Stefaan C. De Smedt [a,*], Joseph Demeester [a]

[a] *Laboratory of General Biochemistry and Physical Pharmacy, Department of Pharmaceutics, Ghent University, Harelbekestraat 72, 9000 Ghent, Belgium*

[b] *Department of Pharmaceutics, Utrecht Institute for Pharmaceutical Sciences, University of Utrecht, 3508 TB Utrecht, The Netherlands*

Received 4 January 2002; received in revised form 17 June 2002; accepted 21 June 2002

Abstract

In this study the use of dynamic mechanical analysis (DMA) for the mechanical characterisation of pharmaceutical hydrogels was evaluated. DMA was used in two different modes, the “controlled force” and the “multi-strain” (MS). The results obtained on dextran methacrylate hydrogels of various compositions were compared to those obtained using an oscillatory shear rheometer. The best agreement was found between the MS-DMA and the rheometer results. The moduli measured in MS-DMA were extrapolated towards zero compression to obtain the modulus of the hydrogels. This procedure resulted in good agreement with the data obtained with the rheometer. Hydrogels were analysed after swelling to equilibrium with both methods, DMA and rheology. A scaling between the elastic modulus (G') and the equilibrium swollen polymer volume fraction ($v_{2,s}$) could be found, although the best correlation between G' and $v_{2,s}$ was obtained with the rheometer. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Hydrogels; Oscillatory shear rheometry; Dynamic mechanical analysis

1. Introduction

A variety of methods have been used for the mechanical analysis of hydrogels. The most used involve elongation/compression analysis, dynamic mechanical analysis (DMA) and oscillatory rheometry. These analyses provide information on the gel strength expressed as viscosity or elasticity and the relation of this strength with the gel composition and its stability. The basic theory as well as the most used techniques were recently reviewed by Anseth et al. (1996) and Jones (1999). The latter focussed on the pharmaceutical application of DMA. Due to practical problems related to the measurements on hydrogels, DMA is currently mostly used in combination with thermal analysis for the determination of changes in the glass temperature as a function of the composition of

---

* Corresponding author. Tel.: +32-92648076; fax: +32-92648189

E-mail address: stefaan.desmedt@rug.ac.be (S.C. De Smedt).

PII: S0378-5173(02)00328-9

various materials. As hydrogels become increasingly important from a pharmaceutical point of view, understanding their mechanical properties can also greatly help to improve their formulation and applicability.

What complicates the mechanical analyses of hydrogels most is their high water content (up to 99%). In previous work (Meyvis et al., 1999) we have shown that using a specific methodology all kinds of hydrogels could be characterised rheologically with an oscillatory shear rheometer. Compressional DMA is widespread as a tool for the mechanical characterisation of strong materials; however, in this study we evaluated the use of DMA for the characterisation of hydrogels. A parallel-plate geometry was used to clamp the hydrogels. Two different measuring modes were tested and the results were compared to those obtained using an oscillatory shear rheometer.

2. Materials and methods

2.1. Dextran methacrylate preparation and characterisation

The dextran methacrylate (dex-MA) batches were prepared and characterised as described in detail elsewhere (Van Dijk-Wolthuis et al., 1995, 1997). The degree of MA substitution (DS, i.e. the number of MA molecules per 100 glucopyranose residues) was determined by proton nuclear magnetic resonance spectroscopy (^{1}H-NMR) in D_2O with a Gemini 300 spectrometer (Varian). DS of the batches used in this study varied from 2.5 to 11.3.

2.2. Preparation of the dex-MA hydrogels

Dex-MA hydrogels were prepared by radical polymerisation of aqueous dex-MA solutions (made with phosphate buffer (PBS): 10 mM Na_2HPO_4; 0.02% sodium-azide, adjusted with 1 N HCl to pH 7.0) as a function of the dex-MA concentration and the degree of MA substitution. The polymerisation reagents were N,N,N',N'-tetramethylene-ethylenediamine (TEMED; 20% v/v in deoxygenated PBS, pH adjusted to 8.5 with hydrochloric acid) and potassium persulphate (KPS; 50 mg/ml in deoxygenated PBS) (De Smedt et al., 1997). Adding 50 μl/g hydrogel TEMED solution, followed after stirring by 80 μl/g hydrogel KPS solution started gelation. All the recipients in which gelation occurred had been coated with a polyethyleneglycol solution (PEG 20 000 g/mol; 10% solution in PBS) to simplify the removal of the hydrogel after gelation. On average, a complete gelation took 1 h at room temperature.

2.3. Mechanical characterisation of the hydrogels

The rheological measurements were performed on an AR1000-N controlled stress rheometer (TA Instruments, Inc., Ghent). The rheometer was adapted for the measurement of hydrogel slabs by sticking sandpaper (grid No 280) to the geometry. The bottom plate was replaced with a Plexiglas® plate with a roughened surface that was fixed on the rheometer with clamps. All measurements were performed with an acrylic top plate (diameter 2 cm) equipped with a solvent trap to avoid evaporation. Unless described otherwise, all experiments were done in oscillation mode at 1 Hz by applying a constant strain of 0.5%. Further details on the method used were described in detail elsewhere (Meyvis et al., 1999).

The DMA measurements were performed on a DMA 2980 Dynamic Mechanical Analyser (TA Instruments, Inc.) in two different modes, the DMA “multi-strain” (MS-mode) and “controlled force” (CF-mode) mode. The hydrogels were clamped between a parallel-plate compression clamp with a diameter of 0.6 cm. To increase the grip on the hydrogels, sandpaper (grid No 280) was stuck to the geometry. In the MS-mode, an oscillatory deformation with an amplitude of 10 μm and a frequency of 1 Hz was applied at various static forces ranging from 0.01 to 0.4 N (depending on the gel strength). The auto strain mode was disabled during all experiments. In the CF-mode a force ramp from 0.001 to 0.1 or 0.3 N (depending on the gel strength) at a rate of 0.05 or 0.1 N/min was applied. Fig. 1 schematically illustrates the main differences in the set-ups of

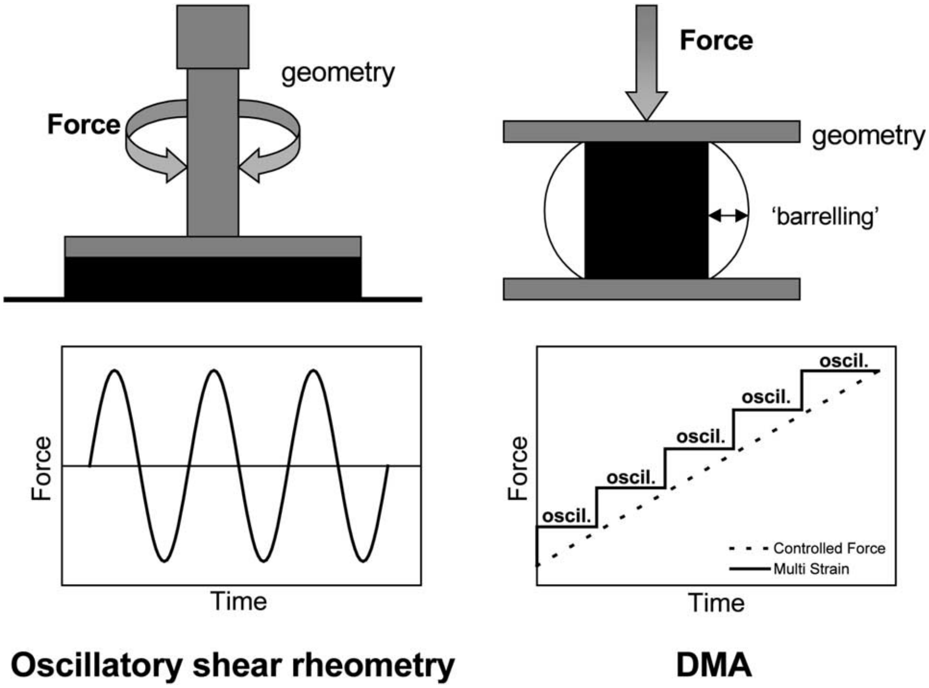

Fig. 1. Schematic illustration of the set-ups for oscillatory shear rheometry (left) and DMA (right). In the right drawing an important artefact called "barrelling" is also illustrated. The graphs under each drawing show the forces applied during the different experiments as a function of time. The vertical oscillations (oscil.) performed with a fixed amplitude at each static force level in the MS-mode are also indicated on the graph.

DMA and oscillatory shear rheometry as well as the types of forces used in the different measuring modes.

3. Experimental results and discussion

Comparing an oscillatory shear rheometer (referred to as rheometer in the following sections) and DMA, an overlap exists in the range of forces at which they operate. The main difference between both techniques is that the rheometer applies shear forces while DMA applies compression forces. The most used geometry on a rheometer for measuring "solid" materials is known to be the parallel plate. For DMA, various geometries and related measuring procedures exist; however, the parallel-plate clamp was to be chosen. Due to the characteristics of hydrogels, the parallel-plate clamp was by far the most suited. The used geometries are therefore essentially the same on both instruments. However, as different types of forces are applied samples with a different shape should be used. For the rheometer the samples should have slab geometry, while for DMA, using parallel-plate clamps, cylindrically shaped samples should be used. Clamping high hydrogel cylinders between parallel plates was nevertheless not straightforward. Due to the high water content of the hydrogels, a thin water layer between the hydrogel surface and the geometry acted as lubricant. If the hydrogel surfaces were not perfectly parallel with the plates of the geometry, the hydrogel would slide from in-between the plates upon application of force. Moreover the high hydrogel cylinders easily bent and subsequently broke when the compression force was increased. To overcome these problems waterproof sandpaper was applied to the parallel plates. Also, hydrogel cylinders with a small difference between height (0.7 cm) and diameter (0.5 cm) were made.

Two different measuring modes of DMA were evaluated. In the MS-mode a series of pre-set static forces (Fig. 1) was applied to the hydrogel. At each static force an oscillatory deformation with an amplitude of 10 μm was applied. From this oscillatory deformation the compressional storage modulus (E') was calculated. In CF-mode a continuously increasing compression force (Fig. 1) was applied to the sample and the resulting compression was monitored. Young's modulus (E') of the hydrogel could be extracted plotting the compressional force versus the observed deformation, expressed as a deformation factor λ (the ratio of the deformed to the undeformed height of the sample). The absolute value of the slope equals E'. The compressional storage modulus E' is not equal to the shear storage modulus G' since they are obtained using different kinds of deformations. Both moduli are related to each other by:

$$E' = 2G'(1+\mu), \tag{1}$$

with μ, the Poisson number, equalling to 0.5 for ideal rubbers which shows the best resemblance with the used hydrogels (Macosko, 1994). This relation allowed comparing the results obtained with the rheometer with those obtained by DMA.

Using DMA, the applicable range of compressional forces was limited as the samples broke or showed significant broadening of their diameter towards the middle of the cylinder ("barrelling", Fig. 1). Normally, "barrelling" can be reduced by allowing a lubricated compression, without sandpaper on the geometry. However, the studied dex-MA hydrogels could not be measured in that way since they slipped from between the plates of the geometry. As "barrelling" causes a deformation in the horizontal direction, it results in an extra shear force. As illustrated in Fig. 2, this could be observed as an upward deviation from the linear relation between the applied stress and the measured deformation in the CF-mode. The least concentrated hydrogels were the weakest and showed a pronounced deviation which already occurred at low stresses. As the dex-MA concentration increased, the deviation became somewhat less pronounced and occurred at higher stress levels. The deviation was limited for the most concentrated hydrogels as they were more rigid and rather broke than deformed upon further compression. To limit these effects the normal force range was limited. Some typical compression profiles are shown in Fig. 3. In order to extract the storage moduli from these profiles a linear fit was applied to that part of the curve yielding the highest correlation. As a result the initial parts of the compression profiles were always omitted. The deviation from linearity in these initial parts was explained by the lack of contact between the geometry (with sandpaper) and the hydrogel surface at very low compression forces.

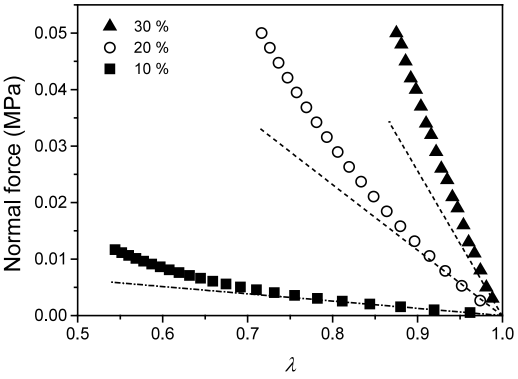

Fig. 2. Compression profiles (stress vs. deformation factor) as measured for dex-MA hydrogels (DS 4.7) of different concentrations in the CF-mode. Straight lines illustrate the deviation from linearity caused by "barrelling" of the sample.

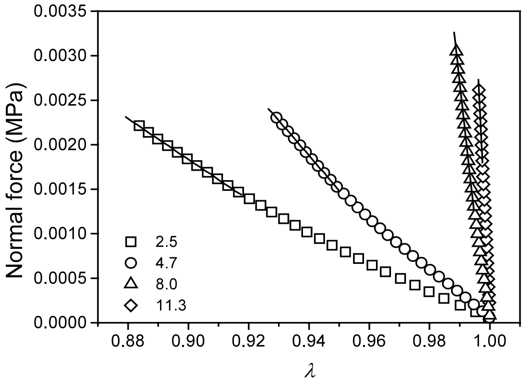

Fig. 3. Compression profiles (stress vs. deformation factor) as measured for dex-MA hydrogels (30%) with different DS in the CF-mode.

Measuring in the MS-mode a continuous increase of the storage modulus with increasing

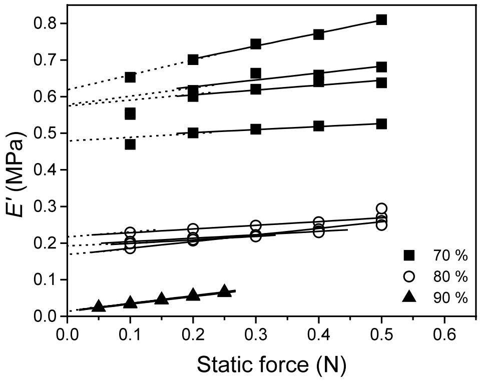

Fig. 4. The storage modulus (E') as a function of the static force applied in MS-mode for dex-MA hydrogels (DS 8.0) of different concentrations. The fitted straight lines (solid lines) and the extrapolation towards zero static force (dotted lines) are also shown.

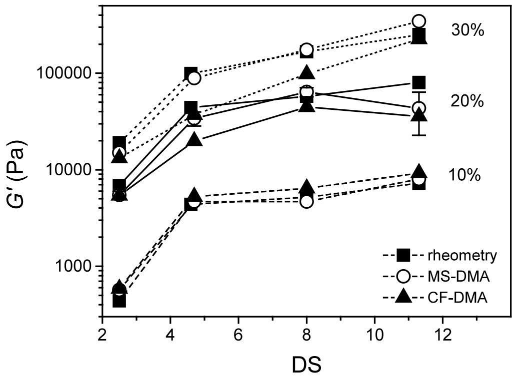

Fig. 5. G' as measured by three different techniques of dex-MA hydrogels with different concentrations (10–30%) and DS. All data are averages of at least three repeats; error bars are not shown when smaller than the symbol.

static force was observed (Fig. 4). In contrast to the rheological methodology (Meyvis et al., 1999) no plateau was found when the static force was further increased. The reason for this increasing modulus has been found in the "barrelling" of the sample. As the static force increased, the additional shear component caused by the "barrelling" increased accordingly. A similar observation was made by Cascone (1997) when measuring poly(vinyl alcohol)/hyaluronic acid hydrogels. To compare the different E' of hydrogels, Cascone (1997) used the modulus measured at a specific value of the static force. Due to the different force ranges applied in our experiments it was decided to extrapolate our data towards zero compression (static force = 0 N). A linear fit was performed on the individual compression profiles. For the most concentrated dex-MA hydrogels the first point was neglected since it systematically deviated from the linear relation. This deviation was caused by a lack of contact between the geometry and the most concentrated hydrogels at low static force.

Using the rheometer, MS-DMA and CF-DMA a series of dex-MA hydrogels were analysed. E' values were converted to G' using Eq. (1). Fig. 5 summarises the results for the non-swollen (directly after gelation) hydrogels. Generally, G' increased as the dex-MA concentration and DS of the hydrogels increased. A full explanation of the observed trends in G' as a function of concentration and DS was described in details elsewhere (Meyvis et al., 1999). G' as measured with the rheometer and MS-DMA were in good agreement. The CF-DMA results only correlated well with the rheometry results obtained on the weakest hydrogels (lowest dex-MA concentration). As explained above, the compression force was strongly reduced in the CF-mode to reduce the "barrelling" of the hydrogel cylinders. For the strongest dex-MA hydrogels this resulted in very small strains (0.005–0.01%). It is likely that these were too small to obtain a full contact between hydrogel and geometry (with sandpaper). Although linearity was observed between the stress and the deformation factor this was probably obtained with only a part of the geometry in contact with the hydrogel. This may have resulted in smaller moduli than measured by both other techniques.

All hydrogels were analysed with the different techniques after swelling to equilibrium. In Fig. 6, G' measured at equilibrium swelling was plotted as a function of the equilibrium swollen polymer volume fraction ($v_{2,s}$). A straight line could be drawn through all the data, which was in agreement with the theory of de Gennes (1979). As discussed in detail elsewhere the slope from G' to $v_{2,s}$ profiles of dex-MA hydrogels deviates from the 2.25 predicted by de Gennes (1979) for ideal networks. This deviation was confirmed by the DMA data. The best correlation between G' and

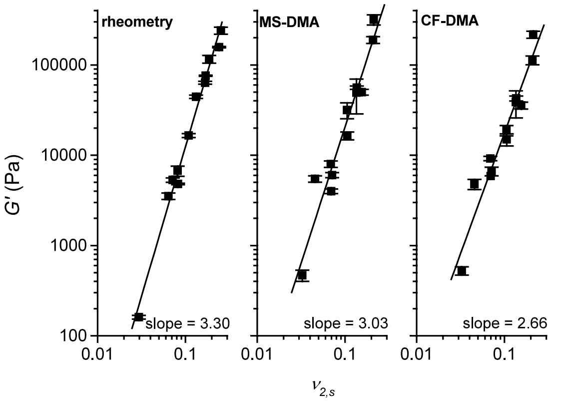

Fig. 6. G' of dex-MA hydrogels (different DS and concentration) after swelling to equilibrium as a function of the equilibrium $v_{2,s}$. Apparent linear fits of the data are also shown.

$v_{2,s}$ was obtained with the rheometer (0.994 compared to 0.970 for DMA in both modes). The slope of the curve obtained with MS-DMA agreed best with that obtained with the rheometer. These results show that also for swollen hydrogels the best results could be obtained by using DMA in MS-mode.

4. Conclusions

In this study DMA both in MS and CF-mode was evaluated for characterising the mechanical properties of pharmaceutical hydrogels. Extrapolation towards zero static force of the moduli measured with MS-DMA at different static forces allowed a comparison with the moduli measured in oscillatory shear rheometry. This extrapolation eliminated the errors induced by the “barrelling” of the hydrogels upon compression. Both data on swollen and non-swollen hydrogels showed that next to the rheometer DMA in MS-mode was best suited for the rheological characterisation of hydrogels. The choice of method for mechanical characterisation of hydrogels which become increasingly important in pharmaceutics, depends on the desired accuracy, speed of measurement (DMA is much faster than the procedure used on the rheometer), the amount of sample available (much smaller amounts are necessary when DMA is used) and the range of G' to be measured.

References

Anseth, K.S., Bowman, C.N., Brannon-Peppas, L., 1996. Mechanical properties of hydrogels and their experimental determination. Biomaterials 17, 1647–1657.

Cascone, M.G., 1997. Dynamic–mechanical properties of bioartificial polymeric materials. Polym. Int. 43, 55–69.

de Gennes, P.G., 1979. Scaling Concepts in Polymer Physics. Cornell University Press Ltd., London.

De Smedt, S.C., Meyvis, T.K.L., Demeester, J., Van Oostveldt, P., Blonk, J.C.G., Hennink, W.E., 1997. Diffusion of macromolecules in dextran methacrylate solutions and gels as studied by confocal scanning laser microscopy. Macromolecules 30, 4863–4870.

Jones, D.S., 1999. Dynamic mechanical analysis of polymeric systems of pharmaceutical and biomedical significance. Int. J. Pharm. 179, 167–178.

Macosko, C.W., 1994. Rheology: Principles, Measurements and Applications. VCH Publishers, New York.

Meyvis, T.K.L., De Smedt, S.C., Hennink, W.E., Demeester, J., 1999. Rheological monitoring of long-term degrading hydrogels. J. Rheol. 43, 933–950.

Van Dijk-Wolthuis, W.N.E., Franssen, O., Talsma, H., Van Steenbergen, M.J., Kettenes-Van Den Bosch, J.J., Hennink, W.E., 1995. Synthesis, characterization and polymerization of glycidyl methacrylate derivatized dextran. Macromolecules 28, 6317–6322.

Van Dijk-Wolthuis, W.N.E., Kettenes-Van Den Bosch, J.J., Van der Kerk-Van Hoof, A., Hennink, W.E., 1997. Reaction of dextran with glycidyl methacrylate: an unexpected transesterification. Macromolecules 30, 3411–3413.