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Description and validation of an apparatus for gel strength measurements [+]

Franca Ferrari, Moreno Bertoni, Carla Caramella *, Aldo La Manna

Department of Pharmaceutical Chemistry, University of Pavia, viale Taramelli 12, 27100 Pavia, Italy

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Abstract

The increasing interest in gel-like dosage forms and in systems that undergo gelification upon contact with biological fluids (like hydrogels and hydrophilic swellable matrices) suggests the importance of gel strength measurements. For example, it has been suggested that the strength rather than the viscosity of the gel layer plays a major role in drug release from hydrophilic matrices. Nevertheless, probably due to the lack of a user-friendly and suitable apparatus, the gel strength parameter is not routinely investigated in preformulation and formulation studies of such dosage forms. In the present work, an apparatus, which had been previously designed for the characterisation of industrial polymers, was modified to make it suitable for measuring the gel strength of pharmaceutical systems and its performance was validated under differing experimental conditions. The results of gel strength measurements effected on hydroxypropylmethylcellulose solutions and on κ-carrageenan and carboxyvinyl polymer gels are reported herein.

Key words: Hydroxypropylmethylcellulose solution; κ-Carrageenan gel; Carboxyvinyl polymer gel; Gel strength apparatus; Rheological testing

1. Introduction

Gels are commonly used as vehicles in pharmaceutical and cosmetic preparations for many types of applications (dermatological, ophthalmic and intramuscular injectable). Gels have recently attracted attention as controlled delivery systems (bioadhesive gels, in situ gel-forming systems, etc.) (Gurny and Peppas, 1990; Middleton et al., 1990; Davies et al., 1991; Kim et al., 1992)

Gel formation is also involved in drug release mechanisms from hydrophilic swellable matrices, which are widely used in prolonged medication (Colombo et al., 1987; Conte et al., 1988). In such systems, polymer hydration results in the formation of an outer gel layer that controls drug diffusion and that eventually undergoes erosion. Therefore, drug release also depends on the physical and mechanical properties of the gel layer and it has been suggested that the strength rather than the viscosity of the gel layer plays a

* Corresponding author.

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major role in the drug release process (Van Aerde and Remon, 1988; Herman and Remon, 1989; Herman et al., 1989).

Nevertheless, probably due to the lack of a user-friendly and suitable apparatus, the gel strength parameter is not routinely investigated in preformulation and formulation studies of such dosage forms.

In the present work, an apparatus, which had been previously designed for the characterisation of industrial polymers (Boevink, AKZO, Arnhem, personal communication), was modified to make it suitable for measuring the gel strength of pharmaceutical systems and its performance was validated under differing experimental conditions.

The apparatus basically consists of a sample holder placed on an electronic microbalance which is connected to a recorder. A probe is lowered into the sample by means of a motor. As the probe is lowered, a force is measured by the balance and is recorded. The force increase with time, besides the buoyancy effect, is mainly a function of the mechanical resistance of the sample to the penetration of the probe.

The gel strength parameter or mechanical resistance of the gel is defined as the ratio between the force (penetrating force) displayed on the balance at a given time and the displacement covered by the probe inside the sample.

Some modifications have been made to adapt the apparatus to our purposes: the motor driving the probe is equipped with a speed transformer to allow measurements at different velocities and the microbalance is connected to a computer instead of a recorder to allow automatic collection and further treatment of experimental data.

The influence of the the following variables on the measurements has been examined: lowering speed of the probe, sample holder shape and test duration.

The results of gel strength measurements effected on hydroxypropylmethylcellulose solutions and on κ-carrageenan and carboxyvinyl polymer gels are reported herein.

To determine whether a relationship exists between the gel strength and the rheological properties, polymer solutions and gels were also tested using dynamic (oscillatory) rheometry.

2. Materials and methods

2.1. Materials

2.1.1. Polymers

The following polymers were employed: hydroxypropylmethylcellulose (Methocel® K4M, Colorcon, Orpington, U.K.), κ-carrageenan (Satiagel® HMR XZ, Sanofi Bio-Industries, Paris, France) and carboxyvinyl polymer (Carbopol® 940, B.F. Goodrich Co., Breksville, U.S.A.).

2.1.2. Sample preparation

4 and 6% (w/w) aqueous hydroxypropylmethylcellulose solutions were obtained after complete cold hydration.

A 1.5% (w/w) gel of κ-carrageenan was prepared by dispersion in cold distilled water using magnetic stirring.

Carboxyvinyl polymer gels (1 and 2% w/w) were obtained by dissolving the polymer in distilled water and then adjusting to pH 6.0 by means of a 1 : 1 water/triethanolamine mixture.

Samples were centrifuged at $1500 \times g$ for 20 min (centrifuge model AHT, Tecnofarma, Pavia, Italy), to exclude any possible effects from air entrapment, then put into sample holders to allow the systems to repose overnight in refrigerant. Prior to testing, samples were allowed to stand at ambient temperature for 1 h.

2.2. Methods

2.2.1. Gel strength test

The apparatus for gel strength measurements is represented schematically in Fig. 1.

The apparatus consists of a sample holder which is placed on an electronic microbalance (Sartorius L420P, Gottingen, Germany; range, 1 mg–420 g; accuracy, 1 mg; precision, 0.1 mg).

The microbalance is interfaced to an IBM AT personal computer (IBM Italia, Milan, Italy) for automatic collection and further treatment of experimental data. A cylindrical probe (diameter = 15 mm), made of plexiglass, is linked by means of a lateral arm to a motor equipped with a speed transformer.

The probe is lowered at a constant rate inside

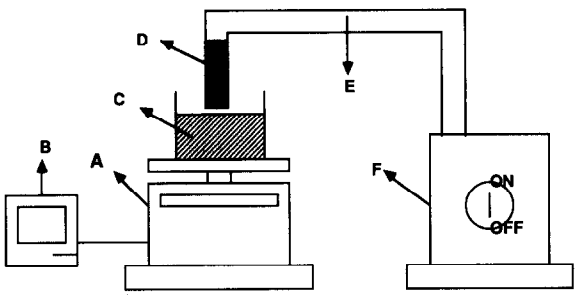

Fig. 1. Design of the apparatus for gel strength measurements. (A) Balance; (B) computer; (C) sample; (D) probe; (E) lateral arm; (F) motor.

the sample: after contact between the probe and the sample has been established, the force increase is measured on the balance and recorded as a function of time on the computer by means of a suitable data collection programme.

Since the lowering speed is known, the displacement covered by the probe as a function of time can be calculated and the gel strength parameter or mechanical resistance of the gel system is then expressed as the ratio between the penetrating force displayed on the balance at a certain time and the relative depth at which the probe has moved inside the sample at that time. Measurements were performed at three lowering speeds: 4, 7, 10 mm/min.

The sample-holder was either a Petri dish (h = 18 mm, diameter = 90 mm) or a beaker (h = 80 mm, diameter = 50 mm). The depth of the sample was fixed at 15 mm for the Petri dish and at either 15 or 65 mm for the beaker. Unless specified otherwise, measurements in the beaker were performed at 65 mm.

At a constant lowering speed of 7 mm/min, the duration of the test was varied; measurements lasted 30, 50 or 100 s for the Petri dish and 50,150, or 300 s for the beaker.

For each test variable measurements were performed in three replicates. Each replicate was effected on a fresh sample of a given solution or gel.

2.2.2. *Rheological measurements*

Rheological analysis was performed with a Bohlin CS Rheometer (Bohlin Reologi, Lund, Sweden) connected to a personal computer (Bull Micral 200; Bull, Milan, Italy) which analysed parameters and processed data.

A cone-plate geometry (CP 4/20) was employed as the measuring system. All measurements were carried out at 25 ± 0.2°C. The rest time in the cup, before viscosity determinations were run, was 3 min.

Oscillatory 'stress sweep' tests were performed by applying increasing oscillatory stresses at a constant frequency of 1.0 Hz and by recording both the storage or elastic modulus (G') and the loss or viscous modulus (G'').

Three replicates were made for each sample examined.

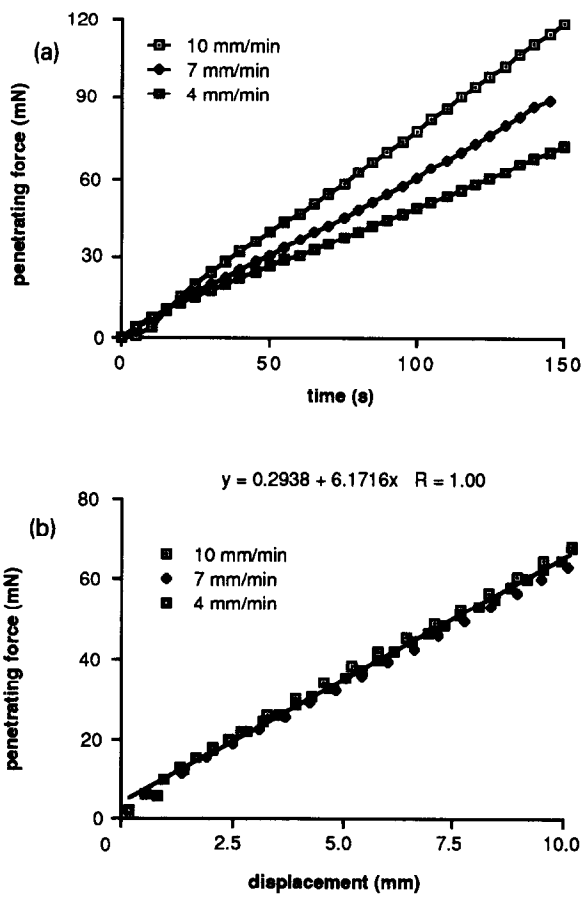

Fig. 2. Force vs time (a) and force vs displacement (b) profiles obtained at three different lowering speeds on a 6% (w/w) hydroxypropylmethylcellulose solution.

3. Results and discussion

In Fig. 2–8 mean penetrating force vs displacement profiles for the various materials are given. Each profile is the mean of three measurements (C.V. less than 5%).

3.1. Influence of the lowering speed of the probe

Fig. 2a shows the force vs time profiles obtained at three different lowering speeds for a 6% (w/w) hydroxypropylmethylcellulose solution.

The force increase is linear with time and the slope increases on increasing the lowering speed.

By transforming the force vs time curves into force vs displacement curves, three superimposable lines at the three different lowering speeds were obtained (Fig. 2b). Therefore, the relationship between force and displacement is expressed by a unique linear slope, thus indicating that the gel strength (mechanical resistance) of the sample is not affected by the lowering speed of the probe.

Influence of the sample holder shape

Fig. 3 depicts the profiles obtained for a 6% (w/w) hydroxypropylmethylcellulose solution with the two different sample holders, the Petri dish or the beaker. Fig. 3a refers to measurements effected with different sample depths, while Fig. 3b corresponds to measurements effected at the same depth.

Different line slopes are obtained with the two

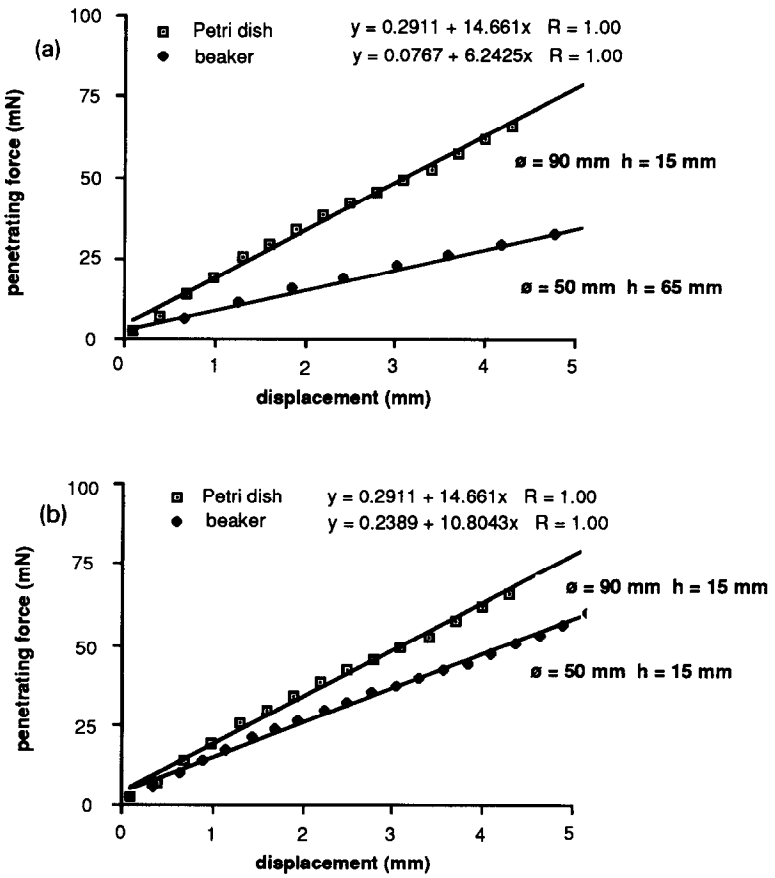

Fig. 3. Force vs displacement profiles obtained on a 6% (w/w) hydroxypropylmethylcellulose solution in the two different sample holders: (a) different depth of the sample; (b) same depth of the sample.

different sample holders. The slopes are always greater for the Petri dish than for the beaker, even though the difference is less pronounced when samples of the same depth are considered (Fig. 3b).

The differences observed are probably due to the different diameter/depth ratios of the sample in the two different sample holders and are to be expected due to the different shear and surface tension forces involved.

Analogous differences between the Petri dish and beaker were also been observed for the 4%

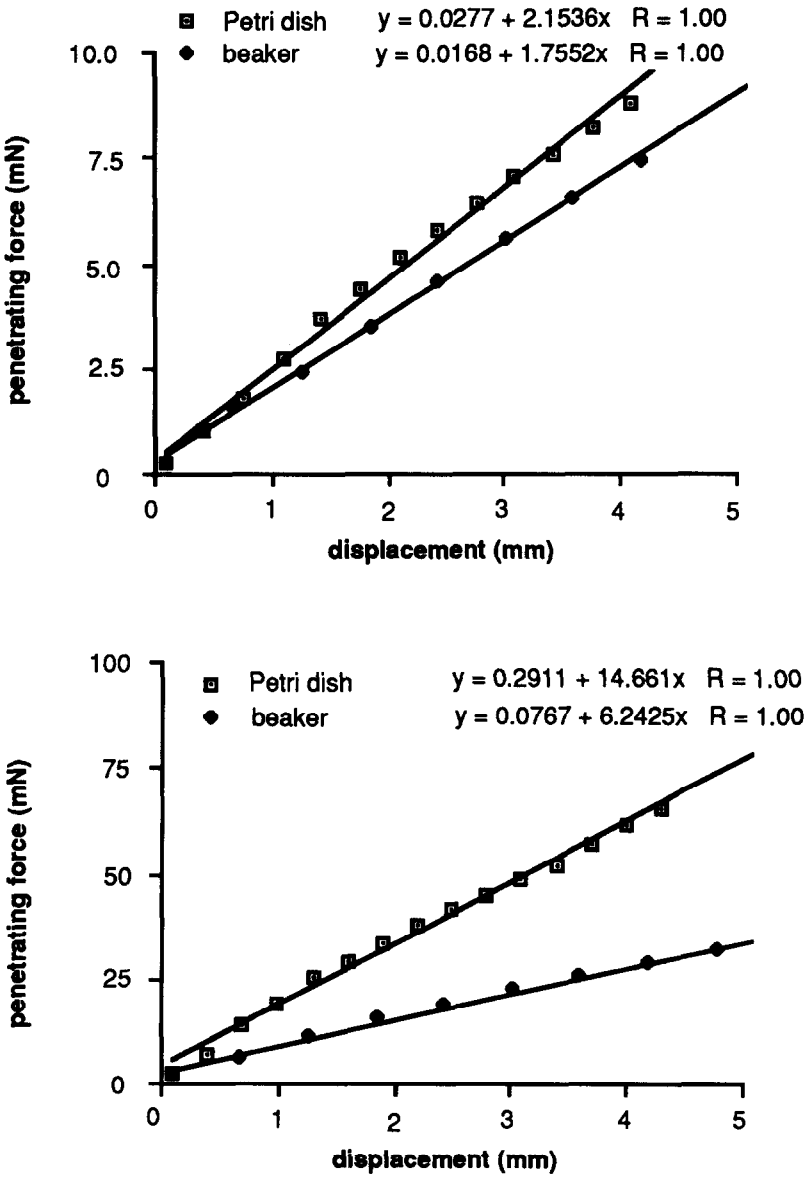

Fig. 4. Force vs displacement profiles obtained in the two different samples holders on hydroxypropylmethylcellulose solutions: (top) (a) 4% (w/w); (bottom) (b) 6% (w/w).

(w/w) hydroxypropylmethylcellulose solution and for the other systems examined, as shown in the subsequent figures.

3.2. Hydroxypropylmethylcellulose solutions

Fig. 4 (a and b) shows the profiles obtained for 4 and 6% (w/w), hydroxypropylmethylcellulose solutions, respectively.

Since the force vs displacement profile is linear, the gel strength parameter, described by the force/displacement ratio, is constant and equal to the slope of the straight line which interpolates the experimental points.

The gel strength value is greater for the 6% (w/w) solution than for the 4% (w/w) solution, as expected on the basis of the higher rheological potential of the more concentrated solution.

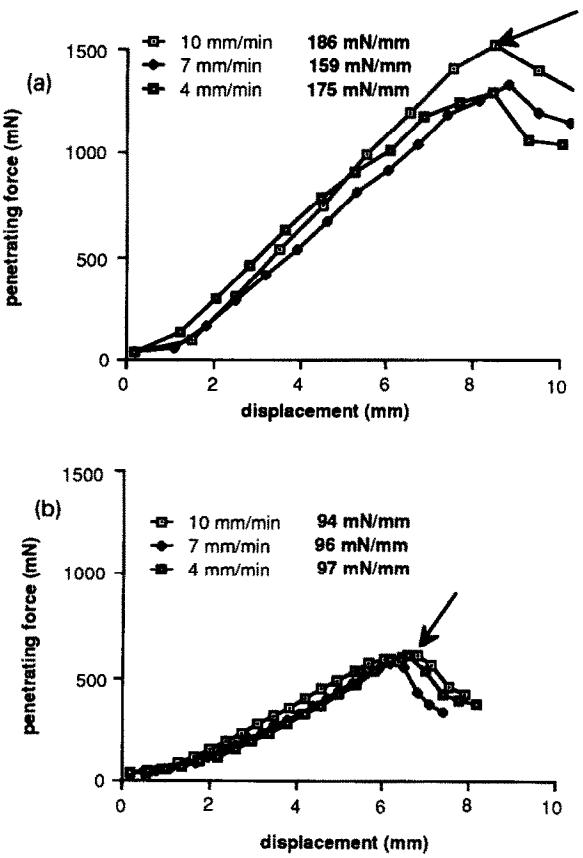

Fig. 5. Force vs displacement profiles obtained at three different lowering speeds on κ-carrageenan gel: (a) Petri dish; (b) beaker.

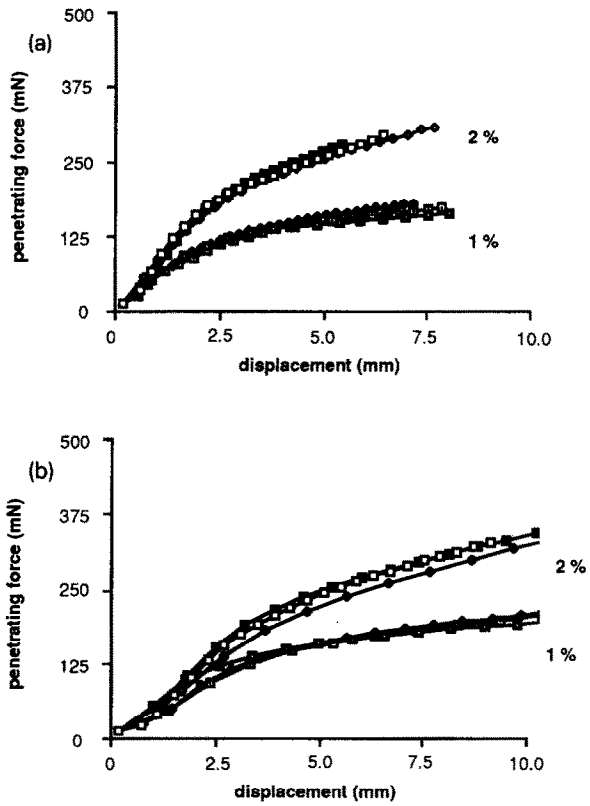

Fig. 6. Force vs displacement profiles obtained at the three different lowering speeds on carboxyvinyl polymer gels of different concentrations: (a) Petri dish; (b) beaker.

3.3. κ-Carrageenan gels

Fig. 5 (a and b) illustrates the profiles obtained (at three different lowering speeds) for κ-carrageenan gels with the Petri dish and beaker, respectively.

Like hydroxypropylmethylcellulose solutions, the κ-carrageenan gel shows almost identical profiles at the three different lowering speeds.

Unlike hydroxypropylmethylcellulose solutions, the force vs displacement profiles are not linear over the entire range examined, but show a force peak value (which presumably corresponds to the gel structure break point).

It is proposed that the gel strength of the sample is expressed as the force/displacement ratio calculated at the force peak value, as shown by the arrows in Fig. 5.

Finally, it is observed that the gel strength parameter depends on the shape of the sample holder and its values (given in the figure) are always greater with the Petri dish.

3.4. Carboxyvinyl polymer gels

Fig. 6 (a and b) shows the force vs displacement profiles obtained (at three different lowering speeds) for 2 and 1% (w/w) carboxyvinyl polymer gels with the Petri dish and beaker, respectively.

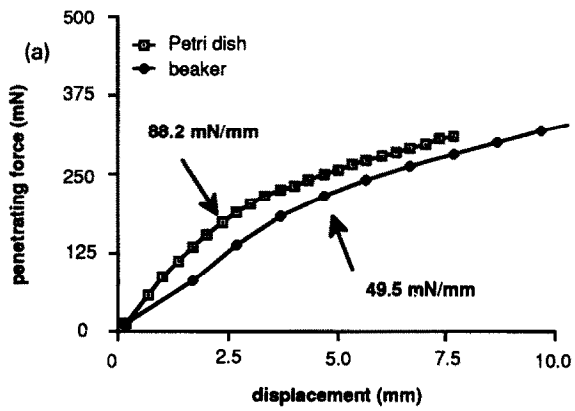

Fig. 7. Comparison of gel strength parameters (arrows) obtained on carboxyvinyl polymer gels tested in the two different sample holders: (a) 2%(w/w); (b) 1% (w/w).

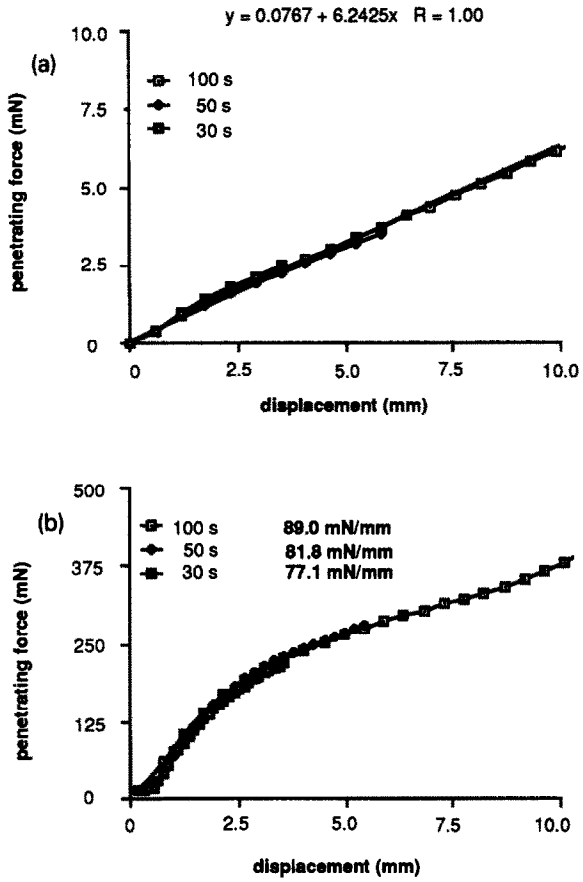

Fig. 8. Influence of test duration on gel strength parameter measurement: (a) hydroxypropylmethylcellulose, 6% (w/w); (b) carboxyvinyl polymer, 2% (w/w).

Once again, almost identical profiles are obtained at the three different lowering speeds. The force vs displacement patterns are not linear but, after an initial steeper portion, tend to bend and to level off at a maximum value.

Fig. 7 (a and b) displays the profiles obtained (at a fixed lowering speed of 7 mm/min) with the Petri dish and beaker for 2 and 1% (w/w) carboxyvinyl polymer gels, respectively.

Since the force/displacement ratio varies continuously, it is not possible to identify a unique gel strength parameter. It is proposed to calculate the force/displacement ratio at each experimental point and to take the highest value of this ratio as the gel strength parameter. This value corresponds to the gel structure break point.

The arrows in Fig. 7 indicate the experimental points at which the maximum force/displacement ratio values occurr. The gel strength parameter depends on the shape of the sample holder, especially for the 2% (w/w) gel; gel strength values (given in Fig. 7) are always higher with the Petri dish.

3.5. Influence of test duration

In Fig. 8 the influence of test duration (at a fixed lowering rate of 7 mm/min) on gel strength measurements is shown. The measurements were carried out in the Petri dish and lasted 30, 50 or 100 s.

Fig. 8a shows the curves for 6% (w/w) hydroxypropylmethylcellulose solution: the slope remains constant in all these experiments, which demonstrates that the duration of the test does not affect the gel strength value.

Fig. 8b refers to measurements carried out on a 2% (w/w) carboxyvinyl polymer gel.

Since the force vs displacement profiles are not linear, the experiment must be performed over a time period long enough to reach the maximum value of the force/displacement ratio, i.e., the system break point, otherwise, as shown in Fig. 8, the calculated gel strength values decrease as the duration of the test is decreased.

3.6. Comparison between rheological properties and gel strength

In Fig. 9 and 10 the results of the 'stress sweep' test performed on the three different materials are presented. Each profile is the mean of three measurements (C.V. < 3%). In the insets, the corresponding gel strength profiles are given.

The stress sweep curves show the patterns of the elastic (G') and viscous (G'') modulus vs the applied stress. It has been suggested that, in structured systems like gels, the simultaneous occurrence of a maximum in the G'' pattern and of an inflection point in the continuously decreasing G' pattern identifies the occurrence of a yield point (Dumortier et al., 1990).

For hydroxypropylmethylcellulose solution (Fig. 9), both G' and G'' patterns continuously decrease with increasing shear stress, which indicates the absence of a yield point.

This demonstrates that the sample behaves as an unstructured polymeric solution and is in agreement with the linear profile obtained in the gel strength experiment where no detectable break point is observed.

On the other hand, when κ-carrageenan and carboxyvinyl polymer gels are considered (Fig. 10a and b, respectively), an inflection point in G' patterns and a maximum in G'' patterns are ob-

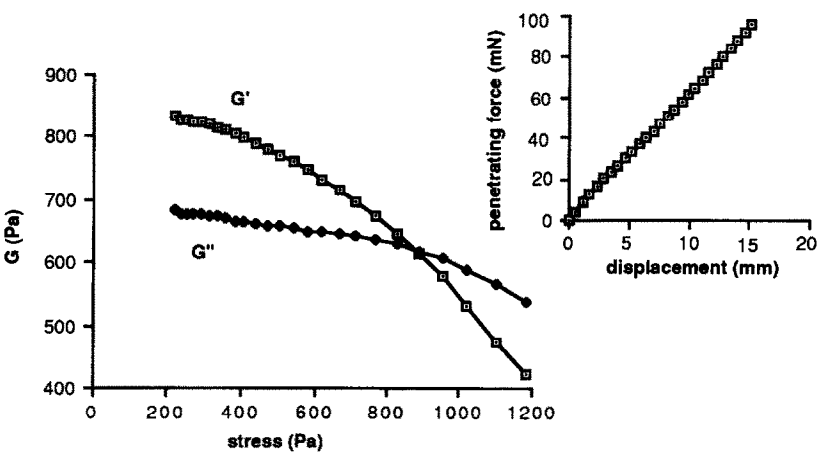

Fig. 9. Comparison between rheological and gel strength patterns (inset) of a hydroxypropylmethylcellulose solution 6% (w/w).

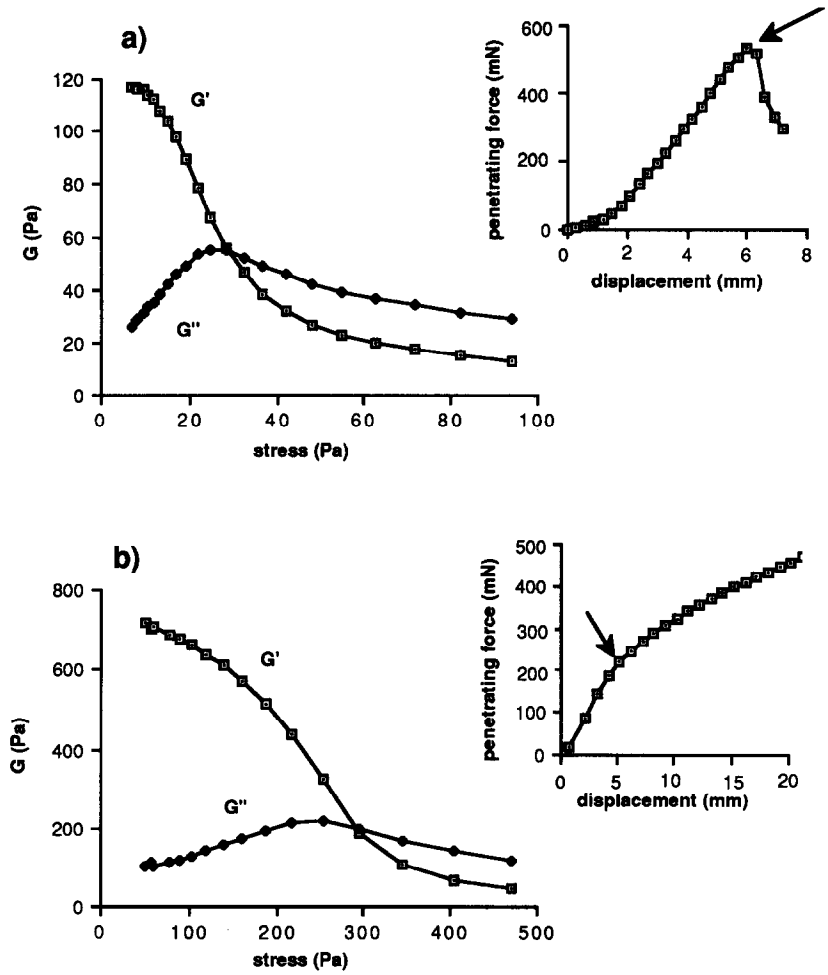

Fig. 10. Comparison between rheological and gel strength patterns (insets): (a) κ-carrageenan gel, 1.5 % (w/w); (b) carboxyvinyl polymer gel, 2% (w/w).

served, which indicates the presence of a yield point.

This confirms that both samples behave as true gels, i.e., structured systems. This is in line with the results of the gel stength patterns, shown in the respective insets, where break points can be identified.

Moreover, the analysis of the stress sweep test showed that the ratio between the viscous and elastic moduli (G''/G') is lower for carboxyvinyl polymer than for κ-carrageenan over the entire range of stress. This indicates that carboxyvinyl polymer gels present more pronounced elastic properties than κ-carrageenan gels (Ferry, 1970).

4. Conclusions

Different patterns of penetrating force vs displacement profiles are obtained depending on the polymeric system examined. These differences allow differentiation between true gels (like κ-carrageenan and carboxyvinyl polymer), which are characterised by a break point and viscoelastic solutions (like hydroxypropylmethylcellulose), in which no break point is observed.

The different gel strength patterns observed for κ-carrageenan and carboxyvinyl polymer are conceivably linked to their different viscoelastic properties.

Meaningful gel strength parameters that are capable of describing the mechanical characteristics of the samples can be derived from the force vs displacement curve.

A relationship exists between gel strength and rheological properties: when a break point is observed in the gel strength profiles, a yield point is also observed.

The gel strength measurements are influenced by the sample holder shape, and, depending on the polymeric system, also by the duration of the experiment.

It is envisaged that the differences observed with the different sample holders are due to the different stresses (compressive and shear forces) involved in gel strength measurements; however, given the shape of the probe employed in the present work, it has not been possible to distinguish between the contribution of the two stresses.

Measurements are in progress with alternative probes and geometries in order to investigate further and possibly to quantify these contributions.

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