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Shear-induced solvent release from gel particles: application to drug–delivery systems

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Abstract

The behaviour of a swollen-in-water hydrogel particle and of a chitosan-alginate micro-capsule immersed in a silicon oil under shear is studied by the rheo-optical method. Both gel and capsule quantitatively behave in a same way. Shear stress leads to a solvent release from a particle and a further increase of shear stress induces the solvent detachment from the released areas. Particle deformation and solvent release are reversible: when stopping the shear, the particle recovers its initial shape and volume. But when some solvent is detached, it flows separately as would do low-viscosity droplets immersed in a high-viscosity matrix. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Gel; Micro-capsule; Shear; Deformation; Controlled release

1. Introduction

The systems that can release active compounds in response to external stimuli in a controlled way have been attracting a lot of interest during the last decade. Such systems can be used in different biomedical application: as drug carriers and bio-vectors in pharmacology, as micro- and nanoparticles with targeted active compounds in cosmetics (skin care and make-up products), etc. To understand the mechanisms governing the controlled release phenomena is an ultimate step in the successful development of drug–delivery products.

In this paper we present the first results on the shear-induced controlled release from two types of particles: model synthetic polymers (hydrogels) and micro-capsules. Hydrogels are chemically cross-linked charged polymer networks that swell in aqueous solutions several hundred times. They swell/contract and absorb/release solvent in response to changes in the surrounding medium (solvent quality, pH, presence of ions or linear polymers) (see for example, Khokhlov et al.,

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1994) or to applied external fields (electric field Shiga, 1997; Budtova and Navard, 2001), temperature (Li and Tanaka, 1992). Being produced by ton to be used as superabsorbents for hygienic applications, hydrogels are very promising materials as thickening and structuring additives and also as drug containers (in the pharmacological, food and cosmetic areas). Micro-capsules are of a core-shell structure. The core is an aqueous solution of the sodium alginate, the shell is a cross-linked interpolymer complex of alginate, chitosan and salts of calcium. Such micro-capsules are considered as drug–delivery systems and they are particularly important for per-oral administration due to protection of the active component from the stomach acid and enzymes. The release is ensured by the pH-dependent properties of the shell.

The question discussed here is as follows: what should happen if a swollen gel or a micro-capsule are compressed or deformed? In most publications dealing with this problem, the hydrogel is deformed less than 10–20% (see, for example, Ilavsky et al., 1995; Mamytbekov et al., 1999a,b; Dubrovskii and Rakova, 1997; Knaebel et al., 1997) and experimental results are interpreted either by classical network-elasticity theory or using a scaling approach (Rubinstein et al., 1996). In rheological and/or compression experiments, it is supposed that there is no solvent release from the deformed gel. In order to reach this, the gel is placed in a bath of a solvent in which it was swollen (Knaebel et al., 1997; Geissler and Hecht, 1982), so that the solvent molecules inside and outside the gel can easily exchange. It is thus supposed that the gel is in the equilibrium state. In this case there is no way to see if there is any solvent release from the gel as a reaction to compression or deformation.

In this paper, we report the experimental results on a rheo-optical study of a hydrogel behaviour under shear. A swollen-in-water hydrogel spherical particle was immersed in silicon oil and sheared. High gel deformations ($>30\%$) and water release from the particles were observed, both effects being far from the classical hypothesis used to describe gel behaviour under compression. It does not seem possible to apply here theories used to interpret either the deformation of a liquid droplet in an immiscible fluid or the behaviour of a rigid particle under shear. Solvent release from a gel under simple shear has never been seriously considered and measured. Rheo-optics gives this opportunity and shows that these effects are not negligible. We also demonstrate that real systems, chitosan-alginate micro-capsules, qualitatively behave in the same way as synthetic hydrogels.

2. Materials and methods

2.1. Materials

Two types of particles were studied. One was a model synthetic hydrogel based on poly (0.75 acrylate–0.25 acrylic acid), cross-linked by *N*,*N*′-methylenebisacrylamide (Aqua Keep 10SH-NF), kindly provided by Kobo Products Inc. The initial state of the hydrogel was dry spherical particles with diameter of 0.01–0.04 mm with a maximal degree of swelling in water of 280 g/g. Gel particles swollen to different extent were prepared by simply mixing dry gel powder with a certain amount of distilled water. The behaviour of the hydrogels of several sizes (from 0.070 to 0.25 mm in a swollen state) and swelling degrees (from 10 to 280 g/g) were investigated. Here we report results for two swelling degrees: $Q = 110$ and 280 g/g.

The second type of particles are classic micro-capsules. The core is a 2 wt.% aqueous sodium alginate solution ($M = 10^5$). The capsules were prepared as follows: a laminar flow of the sodium alginate solution was air-splitted, the droplets were placed in an aqueous solution of chitosan ($M = 2.5\ 10^5$) and $CaCl_2$. Employing this method, the droplets were covered with a shell made of interpolymer chitosan-sodium alginate complex, cross-linked by the calcium chloride. The final shell was a swollen-in-water gel with $Q = 2$ g/g containing 80% of sodium alginate, 20% of chitosan and 3% from the total weight of $CaCl_2$. The capsule size varied from 0.09 to 0.2 mm.

A small amount of particles (either hydrogels or capsules) were immersed into the silicon oil RHODORSIL 47V and gently mixed by hand in order to separate one particle from another. Silicon oil was chosen because it is inert to both types of particles, it is a Newtonian fluid, quite viscous in order to apply a high shear stress, and it has a good optical contrast with both types of particles. In order to get a large interval of shear stresses, we used several silicon oil samples from the same manufacturer with the viscosities from 100 to 300 Pa s. When having the same shear stresses in different silicon oils, the results on the particle deformation were the same within the experimental error.

2.2. Methods

A counter-rotating rheo-optical system was used for in situ study of the particle behaviour under shear. A detail description of the experimental set-up can be found elsewhere (Seyvet and Navard, 2000). This rheometer consists of two transparent plates 3 and 5 (see a schematic drawing on Fig. 1) rotating in the opposite directions. In this geometry, there is an immobile plane between the two rotating plates where the objects are under shear but fixed in the laboratory frame. The shear stress σ was calculated as follows:

$$\sigma = \eta\dot{\gamma} = \eta\frac{(\omega_{\mathrm{u}} + \omega_{\mathrm{l}})r}{h}$$

where $\dot{\gamma}$ is the shear rate, η is the silicon oil viscosity, ω_{u}, ω_{l}–rotation speeds of upper and lower plates, correspondingly, $h = 0.5$ mm is the gap, r is the distance from the centre of the plane. The plate diameter was 40 mm. The observations were performed with an optical microscope 6 positioned below the lower plate 5 and recorded by a CCD camera 7 on a video 8 with a time coded system 9. Videotapes were carefully analysed to measure the evolution of particle dimensions as a function of time and stress.

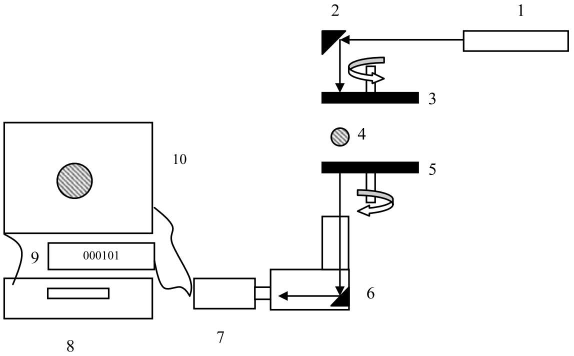

Fig. 1. Schematic drawing of the experimental set-up: light source (1), prism (2), upper rotating plate (3), a particle in the silicon oil (4), lower rotating plate (5), optical microscope (6), CCD camera (7), video recorder (8), timer (9), monitor (10).

The experiments were performed in the following way. First, we fixed the shear rate and measured the development of a particle size as a function of time. Then, when the particle dimensions were not changing in time any more (this case was considered as a steady state), the shear rate was changed and the procedure was repeated. Such a methodology allowed to obtain both the kinetics of a particle deformation at several shear stresses and the dependence of the maximal particle deformation (or deformation in a steady state) on the shear stress. The experimental error in the particle size measurements is ± 5 μm which gives not more than 7–10% relative error in deformation and volume calculation.

3. Results

3.1. Visual observations

3.1.1. Synthetic hydrogels

An example of a swollen-in-water hydrogel behaviour under shear is presented in Fig. 2. It is qualitatively the same for gel particles of any size and of any swelling degree. The initial state of the gel before shearing is a sphere (Fig. 2a) with diameter D_0.

At low stresses the gel deforms and becomes an ellipsoid. In this set-up we measure two particle dimensions–the long axis L and one of the short axis D (see Fig. 2c). Considering the particle volume conservation (before solvent release), the second short axis can be easily calculated. We obtained that it was smaller than D, which means that the gel becomes elongated and flat. We shall use L/D as a measure of the particle deformation.

The increase in the shear stress leads to a solvent release from the swollen hydrogel (see Fig.

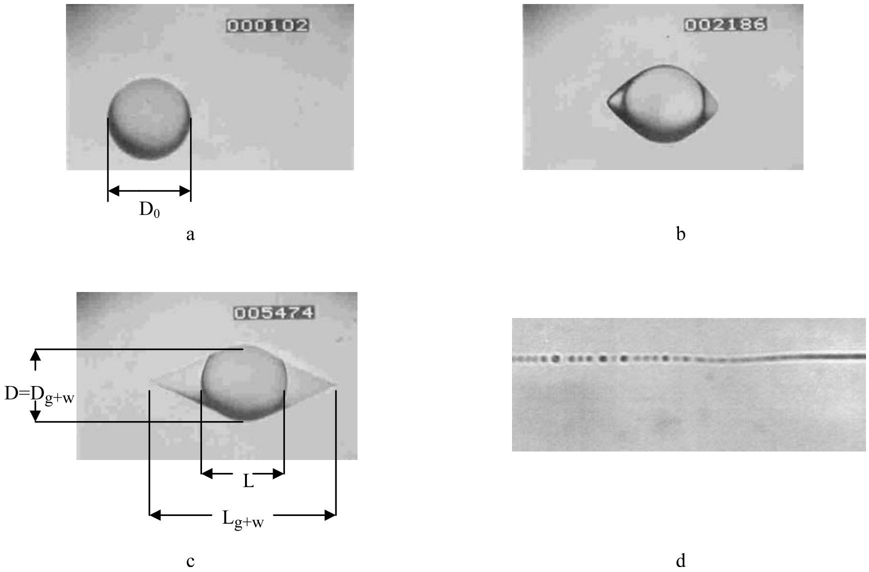

Fig. 2. Optical micrographs of a swollen-in-water gel particle in silicon oil between two transparent plates: initial state (no shear) (a), beginning of water release (about 250 Pa) (b), strong water release (about 800 Pa) (c) and solvent detachment from the gel swollen in water-surfactant solution (d).

2b). This is a very important phenomenon that has never been studied in detail. Two cones of water appear symmetrically at the particle edges in the flow direction. In this case, we shall characterise the gel by two parameters: the deformation of the particle itself L/D (without the cones of water) and the deformation of the particle + water L_{g+w}/D (Fig. 2c). It should be noted that D is the same for the gel particle itself and for the gel + released water. Both gel deformation and water release under shear are reversible phenomena: if stopping to shear, water is absorbed back by the gel and the particle becomes spherical again.

At high shear stresses ($\sigma > 2000$ Pa), water can be detached from the edges of the cones and very tiny water droplets are produced. These droplets flow separately from the gel. This is also a new phenomenon that was never reported before and that can open new perspectives in the hydrogel applications. The detachment looks similar to what happens when a low-viscosity droplet is sheared in a high-viscosity matrix. Due to interfacial tension effects the drop elongates slightly and breaks down according to the end-pinching mechanism (see, for example, Stone, 1994). The loss of water from a hydrogel was too small to be measured and we shall not discuss in detail this phenomenon here. Probably, much higher stresses are needed to record a noticeable decrease in the hydrogel volume, but above a certain shear rate ($\dot{\gamma} > 7–8\ s^{-1}$) it was difficult to ‘keep’ the particle in the immobile plane. Another way to make solvent detachment easier is to decrease the interfacial tension between the solvent and oil. We recorded this when the same gel was swollen in an aqueous solution of a surfactant (synperonic F127, which is a triblock poly(ethylene oxide-propylene oxide) copolymer, see the last photo, Fig. 2d). However, in this article we shall concentrate only on the general comparison of a swollen-in-water hydrogel and core-shell particles under shear.

From visual observations, it was clear that the particle and gel + water long axes are not parallel to the transparent plates. In this set-up it is not possible to measure the particle orientation with respect to the transparent plates. Thus an orientation angle had to be imposed in order to calculate the real value of the long axis. For a water droplet in a silicon oil, Cox equations give an orientation angle of 45°, the ratio of water-to-oil viscosity being very small, 10^{-5}. It is not possible to calculate the same viscosity ratio for a gel particle immersed in silicon oil. However, when water is released from the gel, the gel + water visually behaves as a low-viscosity droplet in a high-viscosity matrix with pointed ends and tiny droplets' detachment from them (Stone, 1994) (see Fig. 2). Thus we used 45° as the orientation angle of a gel particle in shear plane and the deformation values L/D and L_{g+w}/D were calculated taking this angle into account. Such an approximation being very rough does not influence the phenomena discussed in this paper.

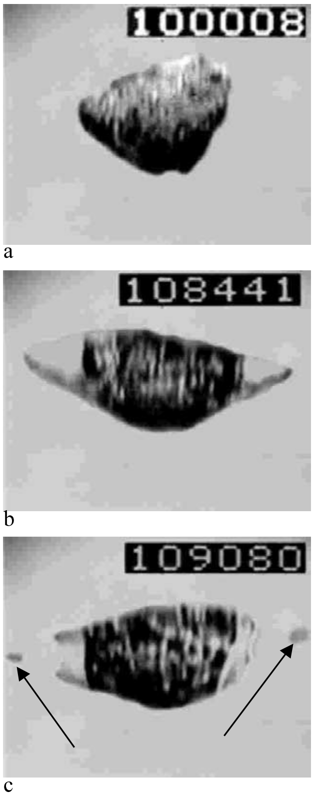

Fig. 3. The same as Fig. 2 but for chitosan-alginate capsules: initial state (a), solvent release at 600 Pa, time of shearing 5.6 min (b) and solvent detachment, droplets shown by arrows (600 Pa, time of shearing 6 min) (c).

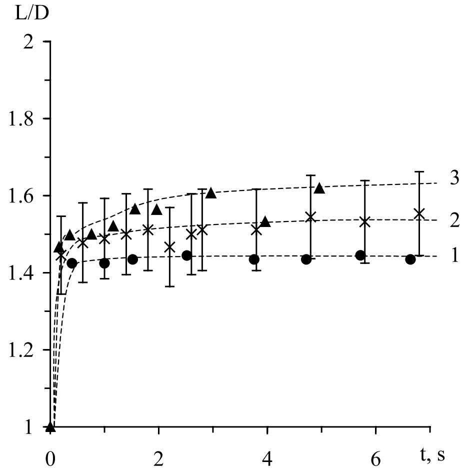

Fig. 4. Kinetics of a gel particle ($Q = 280$ g/g, $D_0 = 0.14$ mm) deformation at 78 Pa (1), 280 Pa (2) and 1070 Pa (3). Lines are given to guide the eye.

3.1.2. Chitosan-alginate capsules

The microphotographs of chitosan-alginate capsules under shear are shown in Fig. 3. The shape of a capsule at rest is difficult to determine (Fig. 3a), but as a rough approximation we took it as a sphere. Under shear a capsule behaves as a synthetic hydrogel particle: first it deforms, then solvent is released (Fig. 3b) and at a certain moment solvent is detached (Fig. 3c). Thus chitosan-alginate capsules behaviour under shear will be analysed in the same way as for hydrogel particles.

3.2. Particles under shear: deformation kinetics, steady-state deformation and solvent release

3.2.1. Synthetic hydrogels

An example of the kinetics of a gel particle deformation under different shear stresses is presented in Fig. 4. Here the gel was swollen up to its maximal degree, $Q = 280$ g/g. After the beginning of the shear, the gel particle starts to deform and in a few seconds the deformation reaches its maximal value of about 1.5–1.6. A steep increase of the deformation values at the beginning is an artefact which is caused by the immediate imposing of the 45° orientation angle. It is clear that the orientation angle must smoothly change in time but we cannot measure its kinetics. The steady state is reached rather quickly, within 5–10 s. When water is released, the ratio L/D for the particle remains constant in time, but the absolute values of the gel dimensions decrease. Higher is the shear stress, higher is the particle deformation (curves 1–3 in Fig. 4 for stresses from 80 to 1070 Pa). However, this difference is practically within the experimental error.

The kinetics of (gel + water) deformation is shown in Fig. 5 for two gel swelling degrees at two different shear stresses. Gel + released water is reaching the steady state also within 5–10 s. L_{g+w}/D is obviously greater than L/D (compare, for example, curve 3 in Fig. 4 and curve 4 in Fig. 5 that correspond to the same gel swollen to 280 g/g). Higher is swelling degree, more water is released from the gel being at the same stress and thus larger is the deformation L_{g+w}/D (compare curves 1 and 3 or 2 and 4 in Fig. 5).

The dependence of the maximal (steady-state) deformation of a gel particle $(L/D)_{max}$ and of (gel + released water) $(L_{g+w}/D)_{max}$ for gels swollen at 110 and 280 g/g on the shear stress is shown in Fig. 6. A remarkable feature is that the gel deformation in the steady state practically does not depend on either its degree of swelling (curve 1 corresponds to both swelling degrees) or on the applied shear stress. More gel is swollen, more (gel + released water) deformation is affine-like, as for a droplet of water.

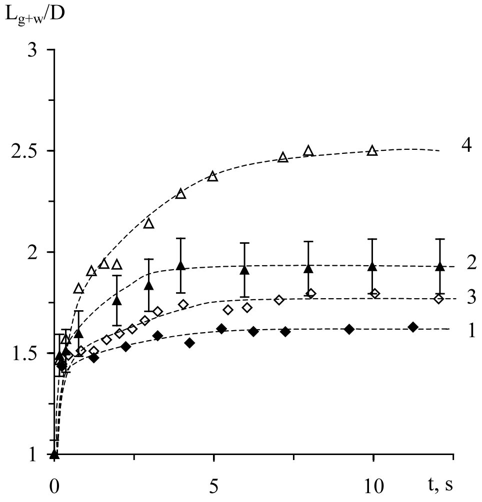

Fig. 5. Kinetics of gel + released water deformation for a gel particle of $Q = 110$ g/g at 540 Pa (1) and 1030 Pa (2); of $Q = 280$ g/g at 540 Pa (3) and 1070 Pa (4). $D_0 = 0.14$ mm for both swelling degrees. Lines are given to guide the eye.

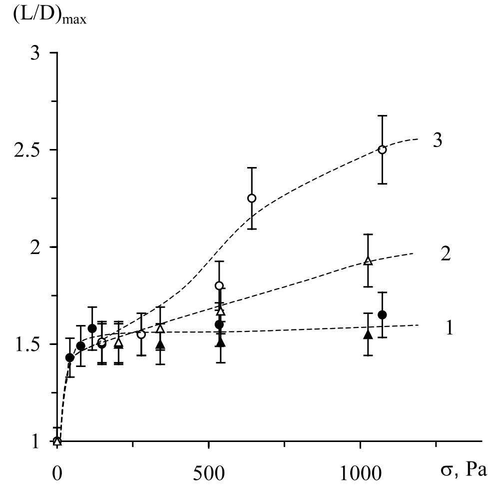

Fig. 6. Steady state: deformation as a function of shear stress for a gel particle of 110 and 280 g/g (1), gel + released water, gel swollen at 110 g/g (2) and gel + released water, gel swollen at 280 g/g (3). $D_0 = 0.14$ mm for both swelling degrees. Lines are given to guide the eye.

Time t_{max} needed to reach a steady state for several gel and gel + water particles sheared at different stresses was analysed. We obtained that t_{max} does not depend on the shear stress and it is practically the same for a gel and gel + water particle–(7.5 ± 1.5) s for a gel at its maximal swelling 280 g/g and (10 ± 2) s for a gel at $Q =$ 110 g/g. These values are 1.5–2 times higher than that for a droplet of water of the same size that was measured separately (5.5 ± 1) s. Since the time to reach equilibrium is independent on shear stress, it must be controlled mainly by the internal relaxation time of the gel deformation. Thus a criterion characterising the moment of reaching the steady state is time.

It would be interesting to find a criterion reflecting the moment of solvent release that should be independent on shear stress. Fig. 7 shows the dependence of the moment of solvent release t_{rel} (time counted from the beginning of the shear up to the moment of the first appearance of the solvent cones) as a function of the shear stress for different particle sizes. Time strongly decreases with the stress increase, but there is no dependence on the gel size within the experimental errors. It is a certain deformation value $L/D \approx 1.5$ that is needed to be reached when the reaction of the gel to shear increase (above 200–250 Pa) is not to increase its deformation, but to release water. This value does not depend either on gel size or on the swelling degree within the studied region.

The volume V of released water was roughly estimated as a sum of the volumes of the two equal cones at both sides of the gel particle. The dependence of the relative value of released volume in a steady state $(V/V_0)_{\max}$ (V_0 being the volume of the spherical gel particle at rest) as a function of the shear stress for both swelling degrees is given in Fig. 8. The amount of water released can be very high, up to 50% of the initial gel size. Higher are shear stress and degree of swelling, more solvent is released.

3.2.2. Chitosan-alginate capsules

As far as it is difficult to determine the dimensions of alginate-chitosan capsules because of their uncertain shape, we cannot quantitatively discuss the kinetics and shear stress dependence of capsule' deformation. As shown in Fig. 3, the general behaviour of capsule — deformation and appearance of solvent cones around — is similar to synthetic gels.

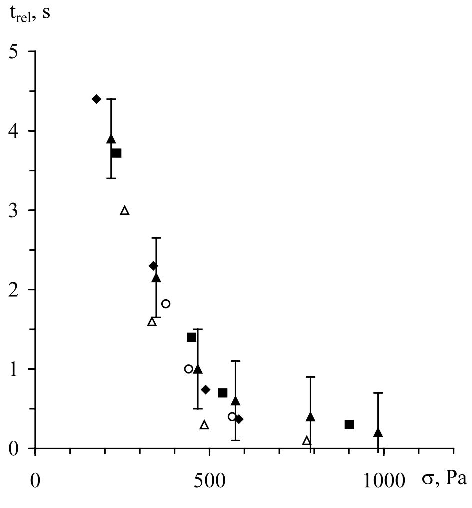

Fig. 7. Beginning of solvent release t_{rel} vs. shear stress for gel particles of $D_0 = 0.13$, 0.14, 0.15, 0.16 and 0.19 mm.

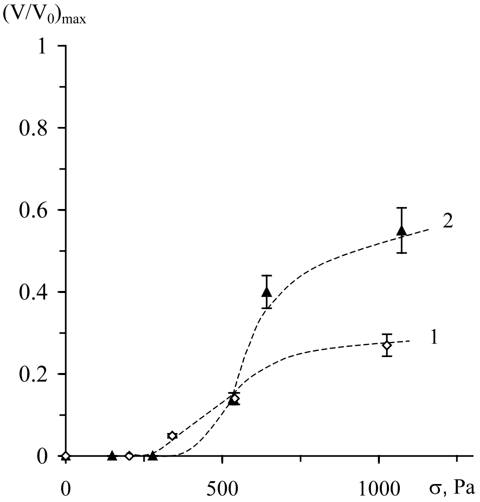

Fig. 8. Steady state: relative volume as a function of shear stress for a gel swollen at 110 g/g (1) and 280 g/g (2). $D_0 = 0.14$ mm. Lines are given to guide the eye.

Despite that chitosan-alginate capsules behave like a soft gel and release solvent, at the same time they behave like solid particles and rotate under shear. The period of rotation T was measured as a function of the shear rate $\dot{\gamma}$ and compared with the theoretically predicted rotation period for rigid spheres in a Newtonian fluid (Jeffery, 1922):

$$T = \frac{4\pi}{\dot{\gamma}} \tag{1}$$

The results for particles of several sizes are presented in Fig. 9. Keeping in mind that approximation of a capsule by a sphere is very rough (see Fig. 3), one could conclude that the calculated dependence (straight line) correlates well with experimental points. It should be noted that capsule continue to rotate even when solvent is released. Thus under shear the capsules behave both like a rigid particle and like a soft gel.

The critical stress for the solvent cones appearance is about 350–450 Pa, a bit higher than for gel particles. This difference can be explained by a higher density of the capsule shell (and thus a lower deformability) as compared the gel particle: total polymer concentration in the capsule shell is 50% and in the swollen gel at $Q = 280$ g/g–0.36%.

The moment of the solvent release t_{rel} as a function of the shear stress for the capsules of different sizes is plotted in Fig. 10. Contrary to gel particles, at a fixed stress, larger particle is, quicker solvent is released. A master plot describing the correlation between the moment of solvent release t_{rel}, capsule volume V and shear stress σ is shown in the inset of Fig. 10 (dark points). All data for capsules of different sizes are presented as $t_{\text{rel}}.V = f(\sigma)$ and they fall on an exponentially descending curve. The influence of the size (or volume) is reflecting, in general, a liquid-like behaviour of the capsule. Indeed, for a liquid droplet in an immiscible matrix it is known (see, for example, Stone, 1994), that a droplet deformation is determined by a capillary number $\text{Ca} = \eta\dot{\gamma}\text{R}\Gamma$, which is directly proportional to the droplet diameter R and represents the ratio between the viscous stress $\eta\dot{\gamma}$ (η being the matrix viscosity) that tend to deform the droplet and the interfacial tension stresses Γ that tend to keep it spherical.

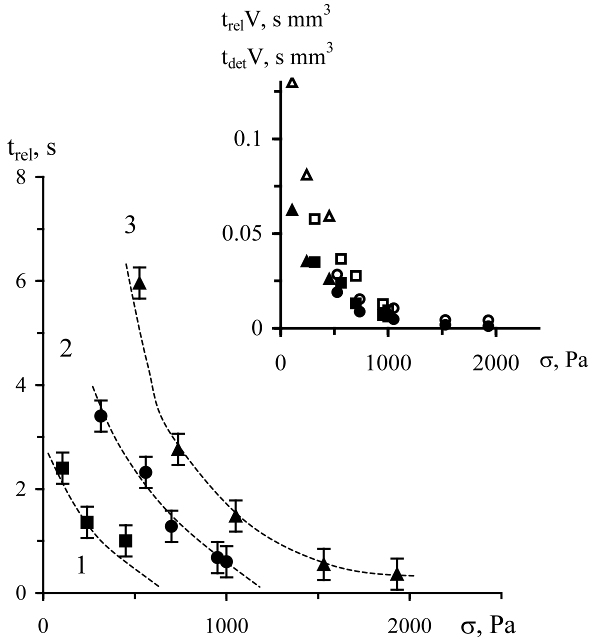

Fig. 10. Beginning of solvent release t_{rel} vs. shear stress for capsules of $V = 0.026$ mm^3 (1), 0.01 mm^3 (2) and 0.0032 mm^3 (3). Lines are given to guide the eye. Inset: master plot for beginning of solvent release $t_{\text{rel}}V$ and beginning of solvent detachment $t_{\text{det}}V$ for the same capsules.

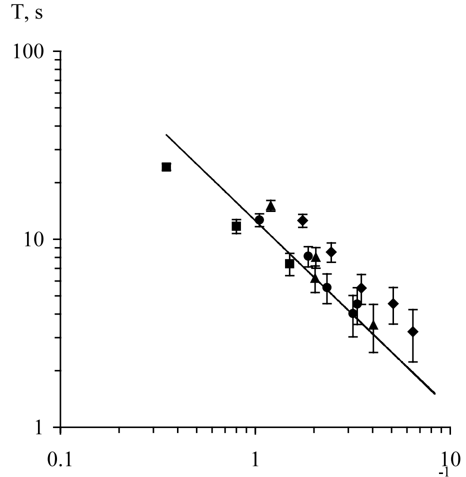

Fig. 9. Period of capsules' rotation as a function of the shear rate for several volumes (from 0.003 to 0.03 mm^3). Straight line corresponds to the theoretical prediction (see Eq. (1)) for spherical particles.

Another difference with hydrogel particles is that for capsules the solvent is detached at the same shear stress at which it is released. As soon as solvent is released, it is then detached in a few seconds. The process is continued in a periodical way: when solvent is detached, cones grow and then solvent is detached again. The period of solvent detachment is approximately a half-period of the capsule rotation. When shear is stopped, the solvent cones are absorbed by the capsule. The moment of solvent detachment t_{det} (time counted from the beginning of the shear up to the first appearance of detached droplets) depends on the shear stress and capsule volume V in the same way as the moment of solvent release: $wt_{\text{det}}V = f(\sigma)$. A master plot is shown in the inset of Fig. 10 (open points). The data for the moment of solvent detachment are taken for the same capsules for which the solvent release is shown. As far as at a fixed shear stress t_{rel} and t_{det} differ in a few seconds, both master plots $t_{\text{rel}} \cdot V = f(\sigma)$ and $t_{\text{det}}V = f(\sigma)$ are very close to each other.

4. Discussion

The behaviour either of a gel or of a capsule can be qualitatively understood by considering both particles as a certain intermediate case between two extreme ones–a droplet of a liquid in an immiscible matrix and a liquid inside a rigid (or non-deformable) frame. If a particle should behave just as a liquid droplet in an immiscible liquid, it should deform under shear in an affine way, the deformation depending on the balance between the relation of the droplet and the matrix viscosity, the shear stress, the interfacial tension between the droplet and the matrix and the droplet size. A deformed droplet may break into small ones according to different mechanisms. If a partilce should be just a liquid inside a non-deformable 'frame', the liquid should be released immediately after the beginning of the shear. In our case, both the gel and the capsule' shell can be deformed, but only to a certain extent. Above a critical deformation value that is determined by the shear stress solvent is released.

In the case of a gel, due to the internal chain elasticity, polymer network chains can be extended under shear stress until reaching a new balance with intrinsic chain elasticity and swelling forces. As soon as all forces are counterbalanced, further increase in the shear stress leads to the solvent release. This explains why solvent is not released immediately after the beginning of the shear and also why the beginning of solvent release is determined by a certain deformation value.

In the case a of capsule, the deformation of the bulk solvent is restricted by the shell which is an elastic polymer gel. Under shear, the shell can be deformed to a certain extent until reaching a new steady-state where all forces are counter-balanced. Thus the beginning of solvent release from a capsule can be seen in the same light as for the gel particle.

Another similarity between the gel and the capsule behaviour under shear is that both rotate like a rigid particle. It was not possible to accumulate data on rotation of swollen gels because of their smooth surface (only for some particles the rotation was seen). However, the analysis of unperfect capsules showed that the period of their rotation obeys the classical law for spherical rigid particles in a newtonian fluid.

The difference between the gel and the capsule is in a 'liquid-like' capsule behaviour under shear: the moment of solvent release from a capsule is a function of its volume, while for a gel particle t_{rel} is volume-independent. The explanation of this feature is obviously in the different structure of the particles: gel is a continuous network and capsule is a core-shell particle, the core being a sodium alginate solution.

Another difference between gel and capsule is that within the studied shear stress interval we did not observe any solvent (water) detachment from a gel, while from capsules solvent was easily detached in a few seconds after it was released. The reason is the lower interfacial tension of silicon oil-sodium alginate solution as compared with the one of silicon oil–water. A similar effect was observed for a gel swollen in a surfactant solution: as soon as solution was released, small droplets were detached almost immediately. The interfacial tension decrease is caused by higher hydrophobicity of sodium alginate solution as compared with pure water, thus sodium alginate is acting in this case as a sort of surfactant. The result obtained demonstrates the important role of the interfacial tension between the solvent and the matrix. The variation of the interfacial tension by adding a small amount of a surfactant will allow to control and predict solvent detachment from gels or capsules.

5. Conclusions

Rheo-optics is shown to be a powerful tool for investigation of a particle (either gel or a microcapsule) behaviour under shear. Three regimes were found. First, at low stresses and low deformation, the particle deforms and becomes a flat ellipsoid. At a certain deformation, solvent starts to release from the particle but stays around it. Finally, at high strains, solvent can be permanently detached from the particle. The first two phenomena are reversible–after stopping the shear, the particle recovers its initial shape and volume and solvent is re-absorbed. But the last stage is irreversible–detached solvent becomes a thin filament that breaks into tiny droplets.

The parameter determining the beginning of solvent release does not depend on the shear stress and gel degree of swelling. It is the particle deformation. Above a critical deformation which is reached at a certain stress, solvent is released. The reaction of a particle to an increase of shear stress is not a further deformation, but a solvent release. This phenomenon occurs for both soft gels and capsules and is important in the understanding and predicting the drug–delivery properties.

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