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Delivery of fullerene-containing complexes via microgel swelling and shear-induced release

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ABSTRACT

The absorption and release of poly(vinylpyrrolidone)-fullerene C_{60} complexes (PVP/C_{60}) from a model microgel is studied. A dry microgel based on a chemically cross-linked sodium polyacrylate was swollen in the aqueous solutions of complexes which were afterwards released under shear stress. First, gel swelling degree in static conditions in the excess of PVP/C_{60} solutions was studied: the degree of swelling decreases with the increase in PVP/C_{60} concentration. While pure PVP is homogeneously distributed between the gel and the surrounding solution, a slight concentration of complexes outside the gel was recorded. It was attributed to PVP/C_{60} hydrophobicity leading to the decrease in the thermodynamic quality of fullerene-containing solution being gel solvent. The release of PVP/C_{60} solutions induced by shear was studied with counter-rotating rheo-optical technique and compared with PVP solution release under the same conditions. The amount of solution released depends on polymer concentration and shear strain. Contrary to pure PVP solutions in which rate of release decreases with the increase in polymer concentration, PVP/C_{60} complexes are released faster when fullerene concentration inside the gel is higher.

1. Introduction

Polymer gels are hydrophilic polymer networks swollen in aqueous media. They swell/contract and absorb/release solvent in response to changes in the surrounding medium (solvent quality, pH and ionic strength, chemical nature of linear polymers or surfactants) and to external fields (electric field, temperature, mechanical stresses); they have come to be known as "intelligent" systems. Hydrogels are used in tissue engineering and regenerative medicine, diagnostics, cellular immobilisation, separation of biomolecules or cells (Hoare and Kohane, 2008), etc. In the drug delivery area, hydrogels are used as "containers" able to deliver and release solvent as a reaction to temperature (for example, poly-N-isopropylacrylamide gels), pH and/or oppositely charged molecules or polymers present in the surrounding medium (polyelectrolyte gels).

In most of the gel applications (medicinal, paints, cosmetics, food) and also during processing a suspension of microgel particles is subjected to mechanical stresses. Recently we have shown that under shear or compression, a swollen microgel can deform and release its solvent that can be dispersed into the surrounding medium (Zanina et al., 2002; Vervoort and Budtova, 2003; Vervoort and Budtova, 2005; Zeo et al., 2005). The gels used in these studies were based on either synthetic or natural polymers (sodium polyacrylate, sodium alginate) and the solvents released were model synthetic linear polymer solutions.

The goal of this work is to demonstrate that microgels can be used as a matrix to deliver fullerene under mechanical stresses, in a controlled way. C_{60} has been a topic of extensive research due to its specific structure, properties and promising bio-medical applications (see, for example, the following publications (Jensen et al., 1996; Friedman et al., 1998; Da Ros and Prato, 1999; Harhaji et al., 2007; Prylutska et al., 2007). However, because of high hydrophobicity, direct medical and pharmacological applications of fullerene are rather limited. There are several ways to overcome this problem. One is to chemically modify fullerene by grafting-on water-soluble groups, for example, carboxylic groups, followed by synthesis of pendant fullerene polymers (Sun et al., 1999), or to synthesise polymer-fullerene "derivatives" with polyacrylic or methacrylic acids (Yang, J., Li, L., Wanf, 2003; Ravi et al., 2005), poly(ethylene oxide) (Song et al., 2003), synthetic polypeptides (Higashi et al., 2006) or ampholytic block-polymers (Dai et al., 2004). The second way is to prepare polymer-fullerene "complexes", not involving fullerene chemical modification, like inclusion complexes with cyclodextrines or calixarenes (Williams et al., 1994; Takekuma et al., 2000; Murthy and

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Geckeler, 2001; Filippone et al., 2002) or charge-transfer complexes via donor–acceptor interaction, as with poly(vinylpyrrolidone) (PVP) (Zgonnik et al., 1996; Vinogradova et al., 1998; Reznikov et al., 2000; Ungurenasu and Airinei, 2000; Tarassova et al., 2003) or poly(vinylcaprolactam) (Tarabukina et al., 2008). Any of the aqueous solutions cited above can be used as a solvent of a hydrophilic polymer network, if fullerene has to be delivered and released in a controlled way. The hydrogel to choose as a carrier and the external action that should trigger the release obviously depends on the application foreseen.

In this work we present the results on a model system in order to demonstrate the principle of fullerene delivery via microgel swelling and shear-induced release. Aqueous solutions of PVP/(fullerene C_{60}) complexes have been selected as an example of fullerene-containing system. We used cross-linked sodium polyacrylate hydrogels as a system that is easy to handle. The gel particles were swollen in the solutions of different concentrations and fullerene content, immersed in silicon oil and the release-under-shear was studied using rheo-optical set-up. The behaviour of the microgel (swelling, absorption and release) in solutions of the fullerene-containing complex was compared with the one in pure PVP solutions.

2. Experimental

2.1. Materials

For the preparation of the poly(vinylpyrrolidone) complexes with fullerene we used fullerene C_{60}, 99.5% purity, from the Fullerene Technologies Ltd, Russia. Commercial PVP, batch K-15-81390, was from Fluka. As reported in Krasnou et al. (2008), its weight average molecular weight is $M_w = 4 \times 10^3$ (obtained by size exclusion chromatography and confirmed by velocity sedimentation and translational diffusion methods).

Aqua Keep 10 SHNF hydrogel was kindly provided by Kobo Products Inc. It is composed of 75-25 poly(sodium acrylate-acrylic acid) chemically cross-linked with N,N′-methylenebisacrylamide. The initial state of the gel was a powder of dry spherical particles with diameter of 5–60 μm.

A silicone oil, polydimethylsiloxane (PDMS) of type Rhodorsil 47V 200000 (Rhodia, France) with viscosity of 230 Pa s^{-1} was selected as suspending matrix. Silicone oil was chosen because it is transparent, chemically inert with respect to swollen gels and the solutions used and sufficiently viscous, enabling to exert the stresses necessary to deform the gel particles.

Chloroform and toluene were from Vekton, Russia; they were distilled before using. Distilled water was used for the preparation of aqueous solutions.

2.2. Methods

2.2.1. Preparation of PVP/C_{60} complexes

Water-soluble complexes were obtained using a two-step procedure, see details in Yamakoshi et al. (1994); Ratnikova et al. (2003). Chloroform-PVP and toluene-C_{60} solutions were prepared, mixed together and then the solvent was evaporated under vacuum at room temperature. The obtained dry PVP/fullerene was added into water. After equilibrium dissolution was attained, the solution was filtered through a paper filter and the water-soluble fraction lyophilized. Fullerene content in the complex was 0.8 and 1.2 wt%, determined with UV adsorption spectra in chloroform (see next paragraph) and fullerene content was calculated for the total mass of the complex. Higher fullerene content may strongly reduce the solubility of the complex in water. The complexes obtained will be denoted PVP/C60-1.2 and PVP/C60-0.8, respectively. PVP/C_{60} aqueous solutions to be used as gel solvent were prepared by direct mixing of the dry matter with distilled water.

2.2.2. UV spectra and determination of PVP/C_{60} concentration in aqueous solution

Fullerene content in the complex was determined from UV absorption spectra in chloroform-C_{60} solutions at the wavelength 258 nm, the molar extinction coefficient 13,000. The UV spectra were measured with a SF-2000 spectrophotometer (Spectr, Russia).

The concentration of the complex in the aqueous solution after the gel reached equilibrium swelling was determined using PVP/C_{60} UV spectra in water. First, a calibration dependence of the optical density of PVP/C60-1.2 aqueous solution at wavelength 260 nm (usual fullerene band at 258 nm is shifted in aqueous solution of PVP/C_{60} complexes towards 260 nm (Reznikov et al., 2000)) vs known concentration of the complex was obtained (Fig. 1). Then, in the system gel + excess of PVP/C60-1.2 aqueous solution, the supernatant was separated from the gel, its UV absorption at 260 nm was measured and complex concentration was deduced from the calibration dependence.

2.2.3. Gel swelling

Gel degree of swelling Q was determined using gravimetry as $Q = W_{sw}/W_{dry}$, where W_{sw} and W_{dry} are the weights of the swollen and dry gel, respectively. Swollen gels were prepared in two ways. The first was when gel was swollen in the excess of solvent (7 mL of PVP or PVP/fullerene complex aqueous solution was added to 0.01 g of the dry gel). The Q_{eq} are the mean of at least three values. This preparation was used for the determination of gel equilibrium swelling degree Q_{eq}, which corresponds to the maximal absorption capacity of the gel in a given solution, and for the study of repartition of PVP and PVP/fullerene complex between the gel and free solution (supernatant). The second way was used for the rheo-optical experiments: gel was swollen less than its maximal absorption capacity, $Q = 0.7Q_{eq}$, to ensure complete absorption of solution. This lower swelling degree was prepared simply by adding a certain amount of solution to the dry gel powder, knowing previously determined Q_{eq} for each polymer concentration. The experimental errors in Q determination were about 10%.

2.2.4. Rheo-optical set-up

A counter-rotating home-made plate–plate rheo-optical cell was used to generate a simple shear flow. Experimental set-up is

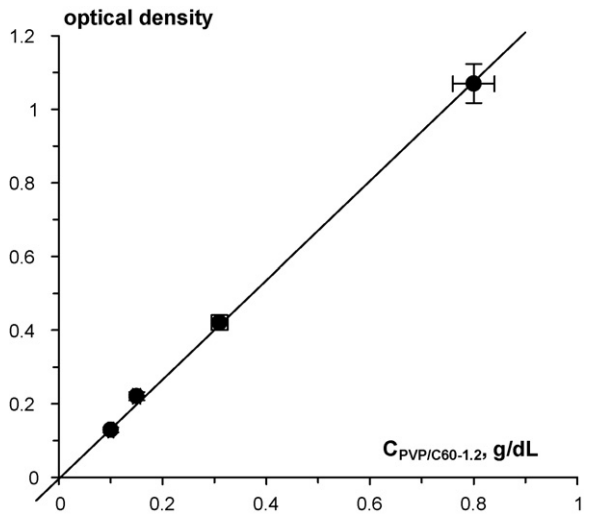

Fig. 1. Calibration dependence of the solution optical density as a function of PVP/C60-1.2 concentration.

described in details elsewhere (Zanina and Budtova, 2002; Zanina et al., 2002; Vervoort and Budtova, 2003, 2005; Zeo et al., 2005). The plates are transparent and rotate in opposite directions. A microscope placed above the upper rotating plate allows observations in the plane formed by the flow direction and the vorticity axis. All experiments were recorded by a CCD camera coupled to the image acquisition unit. The gap between the plates was 700 μm. By adjusting the relative velocities of the plates, a selected gel particle immersed in the PDMS can be immobilised in the laboratory framework and its behaviour can be monitored. The shear rate was varied between 0.5 s^{-1} and 20 s^{-1}. All the experiments were performed at room temperature.

The initial shape of a swollen microgel immersed in the silicon oil is spherical. Under shear the gel deforms, solvent is released and can be detached (Zanina et al., 2002; Vervoort and Budtova, 2003, 2005; Zeo et al., 2005). After stopping the shear, gel recovers its initial spherical shape. In order to measure gel volume loss, its diameter before and after shearing was measured and the relative volume loss $\Delta V/V_0$ (where $\Delta V = V_0 - V$, V_0 being the initial volume and V the volume after shearing in a given relaxed state) was calculated. The experiments were performed in the following way: a selected particle was subjected to a constant shear rate during a certain time (from few minutes to 40–50 min), then shear was stopped and the diameter of the relaxed gel was measured. In subsequent runs, the particle was submitted to other shear rates by modifying the rotation velocities of the plates. The gel diameter was measured by analysing the recorded tapes with the help of image analysis software Visilog from Noesis 2000. The experimental errors of rheo-optical measurements (shear rate, dimensions of objects) were about 10%.

2.2.5. Interfacial tension

Using the same counter-rotating rheo-optical equipment, the interfacial tension (polymer solution)/PDMS was determined using a dynamic method based on Cox theory for small deformations (Cox, 1969). The procedure used is described in Vervoort and Budtova (2003).

2.2.6. Refractometry

The concentration of aqueous PVP in the supernatant (after the gel reaching equilibrium swelling) was measured using an Abbe refractometer. First, the calibration dependence was obtained by measuring the refractive index of aqueous PVP solution as a function of known PVP concentration. In order to deduce if gel is absorbing PVP or not, supernatant refractive index was measured and PVP concentration was determined with the help of the calibration dependence.

3. Results and discussion

3.1. Gel swelling in PVP and PVP/C_{60} solutions in static conditions

The degree of gel swelling at equilibrium in the aqueous solutions of PVP and PVP/C60-1.2 of various polymer concentrations is shown in Fig. 2. The increase in concentration leads to a smooth decrease in swelling, as observed for other similar systems where there are no specific interactions between a gel and a polymer solution (Vasilevskaya and Khokhlov, 1992). The presence of hydrophobic fullerene does not seem to influence gel swelling, at least within experimental errors, probably due to low C_{60} content in the complex and thus in solution. It should be noted that both PVP and PVP/C60-1.2 concentrations studied fall in dilute region: for PVP the overlap concentration C' is 33 g/dL, determined as $C' = 1/[\eta]$, where $[\eta] = 0.03$ dL/g is intrinsic viscosity as reported in Krasnou et al. (2008). The intrinsic viscosity of PVP/C_{60} complexes was shown

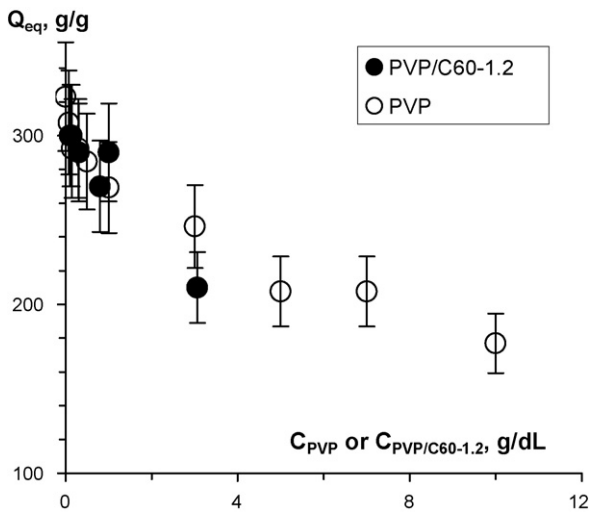

Fig. 2. Gel swelling degree at equilibrium as a function of PVP or PVP/C60-1.2 concentration.

to be very close to the one of the initial PVP (Vinogradova et al., 1998; Sushko et al., 2002; Krasnou et al., 2008).

The next step was to investigate if and how PVP and complexes are absorbed by the gel during swelling. The same set-up as for the determination of Q_{eq} was used. After the equilibrium was reached, a probe from the supernatant solution was taken (Fig. 3) and its concentration, C^*_{PVP} or $C^*_{PVP/C60\text{-}1.2,}$ was determined using calibration dependences (refractive index for PVP and UV spectra for PVP/C60-1.2, see Section 2). The results are presented in Fig. 4 as $\Delta C/C_0$ vs C_{PVP} or $C_{PVP/C60\text{-}1.2}$, where ΔC is the difference between the final C^* and the initial C_0 solution concentrations. If $C^* > C_0$ the solution is concentrated outside the gel, if $C^* < C_0$ the gel is preferentially absorbing the dissolved matter from solution and, finally, if $C^* = C_0$ the matter is homogeneously distributed all over the system gel + solution.

For the case of gel + (PVP solution) the linear polymer is homogeneously distributed in the system. This was predictable: PVP used is of low molecular weight and gel is highly swelling, thus allowing PVP chains free diffusion. There are also no specific interactions between sodium polyacrylate and PVP. The only possible interaction, like hydrogen bonding, leading to a formation of an interpolymer complex, could be expected between polyacrylic acid and PVP. However, polyacrylic acid sequence in the gel and PVP molecular weight are too small for this to be noticeable or even existent (Antipina et al., 1972; Tsuchida et al., 1980; Iliopoulos and Audebert, 1985; Nikolaeva et al., 1999). Another result is

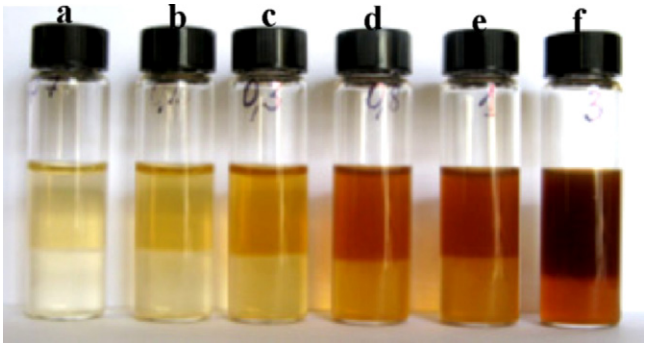

Fig. 3. Photos of swollen microgels (sedimented) at equilibrium in the excess of PVP/C60-1.2 aqueous solutions of 0.07 (a), 0.1 (b) 0.3 (c), 0.8 (d), 1 (e) and 3 (f) g/dL.

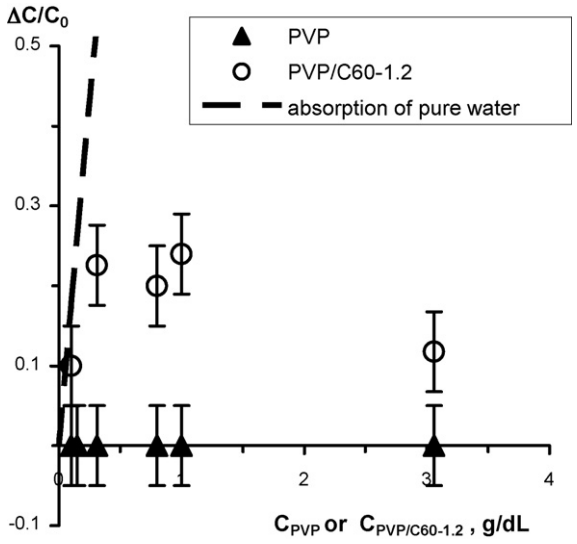

Fig. 4. Illustration of concentration of the complex PVP/C60-1.2 outside the gel and of the homogeneous distribution of PVP over gel + solution. Dashed line corresponds to a hypothetical case of gel absorbing only pure water.

observed for gel + (PVP/C60-1.2 solution): polymer-fullerene complex is concentrated outside the gel. The reason is the decrease in solvent thermodynamic quality due to fullerene hydrophobicity leading to a partial "rejection" of PCP/C_{60} complexes by the microgel.

A calculated hypothetical case when the complex is not at all penetrating into the swollen gel is shown in Fig. 4 by dashed line. All experimental data fall far below the case of gel absorbing only pure water meaning that PVP/C_{60} complex is penetrating inside the gel in a considerable quantity.

3.2. Influence of C_{60} on the interfacial tension PDMS/(PVP/C_{60} aqueous solution)

As shown in Zeo et al. (2005), the interfacial tension between the released solvent and the surrounding fluid (here: PDMS) plays a very important role on the rate and amount of released liquid: lower the interfacial tension, easier is the release. The interfacial tension Γ between PDMS and solution of complex was measured as described in Section 2 for several concentrations and compared with $\Gamma_{\text{PDMS/(PVP solution)}}$ of the same concentrations. The presence of fullerene did not influence the interfacial tension value within the experimental errors. $\Gamma_{\text{PDMS/(PVP/C60 solution)}} = 26 \pm 2$ mN/m, it is lower than the one of PDMS/water, 39 mN/m (Bergeron et al., 1997). This means that the interfacial tension cannot be the reason of the difference in the release-under-shear of PVP/C_{60} or PVP aqueous solutions into the silicon oil.

3.3. Shear-induced release of PVP and PVP/C_{60} from microgel

3.3.1. Visual observations

An illustration of the release of 3 g/dL PVP/C60-0.8 aqueous solution from a swollen gel is given in Fig. 5 which represents gel initial state (Fig. 5a), intermediate state under shear stress (Fig. 5b) and relaxed gel after being sheared (Fig. 5c). At rest and in relaxed state the swollen microgel is spherical (Fig. 5a and c) which easily allows its volume determination. The solution is released in the form of cones oriented in the flow direction (Fig. 5b). Because of a large difference in oil and polymer or complex solution viscosity, of the order of 10^4, solution break-up follows end-pinching mechanism and detached droplets are hardly seen (not seen within the resolution of printed optical micrographs). However, gel volume decrease can be clearly noticed when the shear is stopped and gel is relaxed to the spherical shape (compare images in Fig. 5a–c). The volume decreases with the increase in shearing time t(s) and shear rate γ (1/s). In order to take both parameters into account, cumulated strain $s = t \times \gamma$ and relative volume loss $\Delta V(s)/V_0$ will be used in the following to characterise the release of solution. As shown in Zeo et al. (2005) and also observed here, the relative volume loss does not depend on the initial particle size within the range of samples studied.

The next step was to prove that the solution released from the gel under mechanical stress contains fullerene. The following experimental test was performed. Two suspensions of microgel swollen at degree $Q = 0.7Q_{eq}$ in 1 g/dL PVP/C60-0.8 and in 0.75 g/dL PVP/C60-1.2 aqueous solutions were prepared. The suspension was placed in a syringe with a non-woven filter. Manual pressure was applied to the piston; the liquid released was collected and analysed using UV absorption and calibration dependence (Fig. 1). In both cases PVP/C60 complex solution was released. Moreover, the concentration of the released liquid was higher than the one of the initial solution in which the gel was swollen: for 1 g/dL PVP/C60-0.8 it was 1.84 g/dL and for 0.75 g/dL PVP/C60-1.2–2.06 g/dL. The increase of the complex concentration in the released solution proves that aqueous PVP/C60 is not a very favourable gel solvent: the partitioning occurs under mechanical stress. It can be thus concluded that it is fullerene-containing solution that is released from a microgel under shear stress.

3.3.2. Influence of shear strain, polymer concentration and presence of fullerene on the kinetics of gel volume loss

The microgel volume loss as a function of cumulated shear strain for particles of different sizes swollen in 1 g/dL solutions of PVP and PVP/C_{60} complexes with different fullerene compositions and in 0.07 g/dL PVP/C60-0.8 solution is shown in Fig. 6. Whatever is the sample studied, an almost complete release (98%) can be reached. For example, this is the case if shearing at 10 s^{-1} for about 40 min. Here no influence of fullerene or total polymer concentration can be seen because of very dilute concentrations, within the experimental errors.

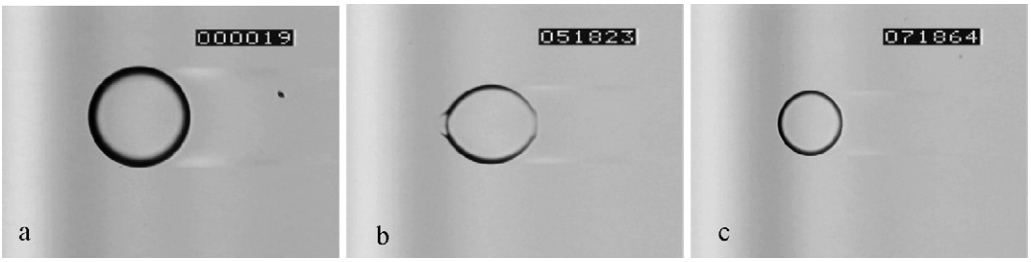

Fig. 5. Rheo-optical micrographs demonstrating the release of 3 g/dL PVP/C60-0.8 aqueous solution from a microgel swollen to $Q = 170$ g/g of the initial diameter 118 μm: (a) initial state: cumulated strain $s = 0$, $t = 0$ s; (b) deformed gel at $\gamma = 14\ s^{-1}$; and (c) $s = 23425$, $t = 1959$ s.

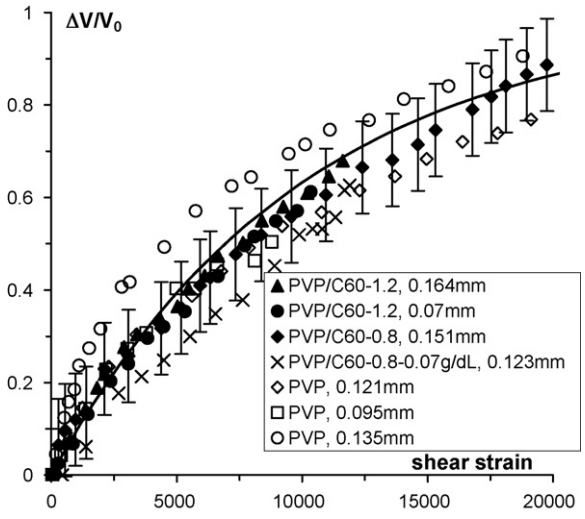

Fig. 6. Microgel volume loss as a function of shear strain for gel swollen in 1 g/dL PVP (open points), PVP/C60-1.2 and PVP/C60-0.8 (dark points) solutions, and in 0.07 g/dL PVP/C60-0.8 solution (crosses). For each type of 1 g/dL solution different microgel sizes are presented. Solid line corresponds to volume loss calculated according to Eq. (1) with $k = 9 \times 10^{-5}$.

As shown in Zeo et al. (2005), a general Weibull approach can be used for the description of shear-induced release of model polymer solutions from a microgel particle. The correlation between gel volume loss and shear strain is as follows:

$$\frac{\Delta V}{V_0} = 1 - \exp(-ks) \quad (1)$$

where k is the rate of volume loss and s is strain. All obtained experimental data were analysed using formula (1) and k values were calculated from the best fit. According to Fig. 6, the release of fullerene complexes with PVP can be reasonably well described by the first-order Weibull approach.

The influence of fullerene starts to be noticeable with the increase in total polymer concentration and thus of fullerene concentration in solution. Fig. 7 shows the release of 3 g/dL PVP and PVP/C_{60} solutions. Even with experimental points being rather scattered, the trend is towards faster volume loss of gels swollen in PVP/C_{60} complexes ($k_{PVP} < k_{PVP/C60\text{-}1.2}$). The reason is the decrease

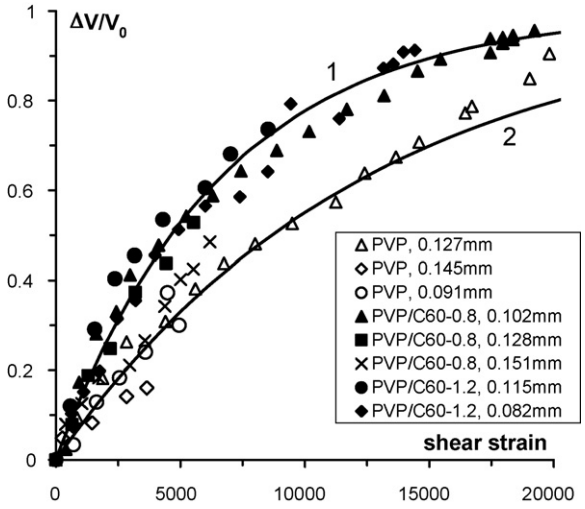

Fig. 7. Release of 3 g/dL PVP, PVP/C60-0.8 and PVP/C60-1.2 solutions from microgels of different sizes. Solid lines correspond to volume loss calculated according to Eq. (1) with $k = 1.15 \times 10^{-4}$ (1) and 8×10^{-5} (2). Experimental errors are the same as in Fig. 6; they are not shown in order not to overload the graph.

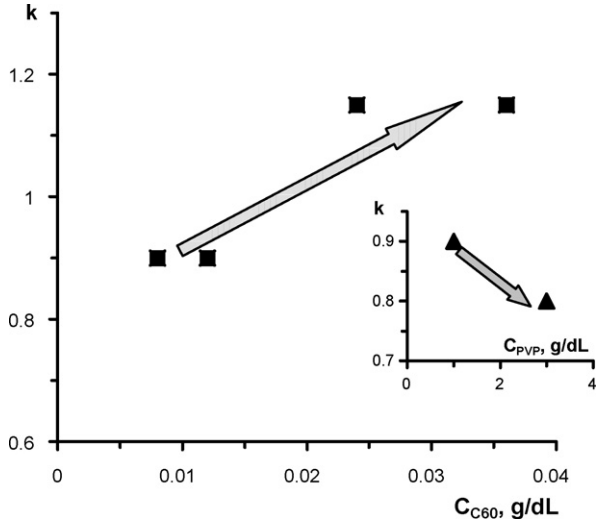

Fig. 8. Release rate as a function of fullerene concentration. Inset: the same as a function of PVP concentration.

in solution thermodynamic quality of PVP/C_{60} complexes as compared with PVP solutions: lower the solution affinity to the gel, easier the solution "extraction" while keeping all the other conditions same.

A specific influence of fullerenes was observed when analysing volume loss of microgels swollen in solutions of various PVP/C_{60} concentrations higher than 1 g/dL. Previously it was shown that the increase in polymer concentration in the solution slows down the speed of release due to the increase in solution viscosity (Zeo et al., 2005). For gels swollen in PVP/C_{60} complexes an opposite behaviour was found: the increase in polymer (and thus of fullerene) concentration facilitated the release. The results are presented in Fig. 8 for the coefficient k from Eq. (1), which reflects the rate of release, as a function of fullerene concentration $C_{C_{60}}$ in the solution absorbed by gel; the inset shows k vs PVP concentration. Fullerene concentration in the complex PVP/C_{60} solution was calculated as $C_{C_{60}} = C_{PVP/C_{60}-1.2} \times 0.012$ or $C_{C_{60}} = C_{PVP/C_{60}-0.8} \times 0.008$.

Higher is the fullerene concentration in the solution in which the gel was swollen, lower is the solution thermodynamic quality as gel solvent and easier is its release despite the fact that the increase of total polymer concentration and solution viscosity slows down the release (see inset Fig. 8 for pure PVP solution).

4. Conclusions

Using a model microgel particle and rheo-optical set-up the possibility of a controlled delivery of fullerenes under shear stress was demonstrated. The amount of fullerene-containing polymer solution released is controlled by strain (higher the strain, more is the solution released: up to 95–98% of gel volume at about 20,000 strain units) and polymer concentration. The presence of fullerene increases the rate of PVP/C_{60} release by about 30% with the increase in solution concentration, contrary to previously observed slow down of the rate of gel volume loss with the increase of polymer concentration. We assume that the phenomenon observed is due to the decrease of gel solvent quality because of the presence of fullerenes.

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