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SHORT COMMUNICATION

Preparation of protected photoinitiator nanodepots by the miniemulsion process

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Abstract The solid photoinitiator Lucirin TPO was encapsulated within a polymer shell by using the miniemulsion process. A solution of Lucirin TPO in methyl methacrylate (MMA) or butyl acrylate (BA)/MMA mixture was miniemulsified in water followed by a polymerization process in which phase separation of the Lucirin TPO and the formed polymer led to amorphously solidified Lucirin TPO nanoparticles encapsulated by polymer. These nanocapsules were freeze-dried and could be redispersed in acidic monomers, which are applied in polymeric dental adhesives. It is shown by ^{1}H nuclear magnetic resonance spectroscopy that the shell separates the Lucirin TPO, which is sensitive to degradation in acidic media, from an ambient acidic monomer phase and protects it from fast decomposition. Investigations of the release kinetics of Lucirin TPO from the nanocapsules reveal that the kinetics are strongly dependent on the composition of the surrounding continuous phase.

Keywords Miniemulsion · Photoinitiator · Nanodepot · Nanocapsule

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Introduction

In the last decades, polymeric nanocapsules or core–shell particles with encapsulated liquid or solid materials have received increasing attention. The potential value of such nanocapsules has been discussed for a variety of applications, such as controlled and persistent drug delivery systems in pharmaceutical products [1, 2] like controlled release of calcitonin [3], for oral delivery of anticancer drugs [4] or as a part of blood substitutes [5]. Filled with solid substances, e.g. inorganic pigment particles, the polymer shell helps to prevent their agglomeration during latex film formation and provides better mechanical properties such as film strength, appearance and durability [6]. Among several techniques for the preparation of core–shell particles like two-stage seeded emulsion polymerization [7–9], interfacial polymerization [10] and solvent evaporation [4, 11], the miniemulsion process has proven to be highly efficient for the encapsulation of solid and liquid materials [12, 13].

By this technique, stable and narrowly distributed droplets in the size range of 50–500 nm are created, which can be used as single nanoreactors for further chemical treatment like encapsulation processes.

The shell of nanocapsules prevents sensitive compounds from decomposition by external triggers. In this paper, we report on the encapsulation process by miniemulsion of the photoinitiator 2,4,6-trimethylbenzoyldiphenyl phosphine oxide (Lucirin TPO, see Fig. 1) as a highly reactive and light-sensitive material, which is unstable under acidic conditions, too. This material is the preferred photoinitiator in polymeric dental fillings, which comprise polymers from acidic monomers like polymerizable phosphonic acids. Hence, an efficient protection against the environment is required, especially as it would be advantageous to apply

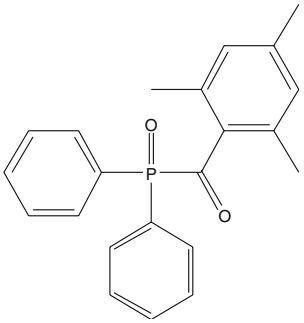

Fig. 1 Chemical structure of the photoinitiator Lucirin TPO (2,4,6,-trimethylbenzoyldiphenylphosphine oxide)

directly a mixture of the monomeric phase and the initiator instead of the commonly used separate components. A further requirement for the polymeric shell of the nanocapsules is permeability to ensure a sufficiently high concentration of the photoinitiator outside the capsules to maintain the initiating properties of the monomer/Lucirin TPO mixture. Thus, the release kinetics has to be adjusted to sustain the functionality of the initiator at least for the demanded storage time of the monomer/initiator mixture.

Experimental part

Materials The monomers methyl methacrylate (MMA) and butylacrylate (BA; both Aldrich) were distilled under reduced pressure before use. *N*,*N*′-Diethyl-1,3-bis(acrylamido)propane (V392), a hydrolytically stable crosslinking agent from Ivoclar Vivadent, sodium dodecyl sulfate (SDS), hexadecane, 1,4-diazine (pyrazine; all Merck), 2,2′-azobis (2-methylbutyronitrile) (V59) from Wako, butylmercaptane (Fluka) and 2,4,6-trimethylbenzoyldiphenylphosphine oxide (Lucirin TPO; BASF) were used as received.

Synthesis of the latexes Six grams of the monomer(s), the respective amount of Lucirin TPO, 100 mg of the initiator V59 and 250 mg of hexadecane as hydrophobe were mixed, and this mixture was added to a solution of 72 mg SDS as surfactant in 24 g of water. After stirring for 1 h at room temperature, miniemulsification was achieved by ultrasonicating the mixture for 120 s with a Branson digital sonifier 450-D at 90% amplitude with a 1/2-in. tip. To avoid thermal initiation, the mixture was cooled in an ice bath during homogenization. The polymerization was started by heating to 72 °C and kept at this temperature overnight. After polymerization, the samples were freeze-dried.

Release kinetics One hundred milligrams of the freeze-dried particles were suspended in 1 ml of a solvent and stirred for a defined time. After that, the capsules were removed by using a syringe filter system with a preliminary filter unit with a pore size of 0.45 μm. For each data point, an own sample was prepared. The release rates were measured at room temperature by ^{1}H nuclear magnetic resonance (NMR) spectroscopy with pyrazine as reference until all encapsulated Lucirin TPO had been released.

Analytical methods The particle size analyses were conducted using a Malvern Zetasizer Nano-ZS ZEN 360 at a fixed angle of 173° using a laser with 633-nm wavelength. The calculation of the results was carried out with a Dispersion Technology Software 4.0.

The molecular weights of the polymers were determined by gel permeation chromatography analysis performed on a Spektra Series P2000 pump with a UV100 detector (λ=234 nm; both from Thermo Separation Products) and a Waters RI 2410 detector with 5 μm 3×800 mm SDV columns with 10^5 and 10^4 Å from Polymer Standard Service and a Waters 5 μm 3×800 mm Styragel column with 10^3 Å in tetrahydrofuran (THF) with a flow rate of 1 ml·min^{-1} at 23 °C. The molecular weights were determined against narrowly distributed polystyrene standards. The samples were dried and redissolved in THF before analysis.

The transmission electron microscopy (TEM) examinations were performed on a Philips EM400 at 80 kV. The diluted latex samples were mounted on 300 mesh carbon copper grids and left to dry. After this, the prepared samples were coated with carbon and RuO_4 to increase the stability in the electron beam and enhance the contrast [14]. No further contrasting was applied.

The glass transition temperatures were measured by differential scanning calorimetry (DSC) with a Perkin Elmer DSC 7 with a heating/cooling rate of 20 °C·min^{-1}.

The ^{1}H NMR data were obtained on a Bruker DRX 500 at 500.1 MHz. Chemical shifts are given in parts per million (ppm) relative to $CDCl_3$ (δ=7.26 ppm) and D_2O (δ=4.79 ppm). For detection of the degree of encapsulation, 50 mg of the dried particles were dissolved in 1 ml $CDCl_3$, with pyrazine as standard to quantify the amount of Lucirin TPO.

For the investigation of the release rates, 100 mg of the freeze-dried capsules were redispersed in 1 ml of solvent (neat ethanol, ethanol/water mixture and 2-propanol, respectively). Pyrazine was used as reference, and D_2O acted as deuterated lock agent.

The solid content was measured with a Kern RH120-3 device.

The density of the particles was measured in a sucrose density gradient with a Beckman L8-55M ultracentrifuge with an SW 4/Ti rotor at 41,000 rpm at 4 °C vacuum for 2 h. The centrifugation tubes were filled with four superposed layers of different density; the bottom one consisted of concentrated sucrose solution (ρ=1.33 g·cm^{-3}), the second one was half concentrated (ρ=1.17 g·cm^{-3}), and the third one was 25% concentrated (ρ=1.08 g·cm^{-3}). The uppermost layer comprised pure water (ρ=1.00 g·cm^{-3}) on which five drops of the latex sample were added.

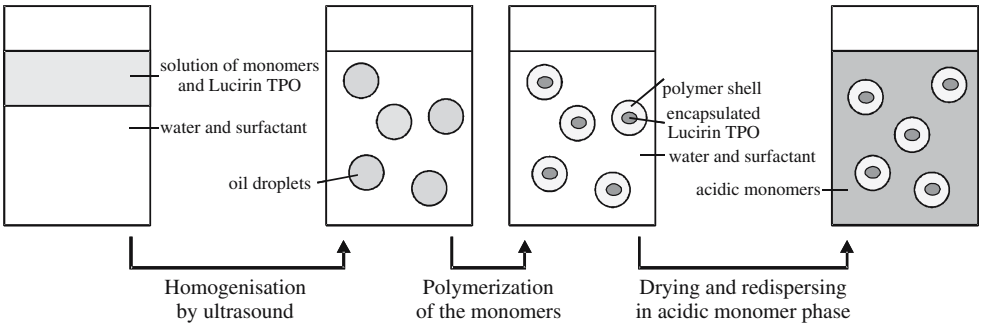

Fig. 2 Scheme of the miniemulsion process and redispersing of the particles

Results and discussion

A two-phase system of the respective monomer/Lucirin TPO/ultrahydrophobe/thermal initiator mixture and a water/surfactant mixture was subjected to ultrasound to create a stable miniemulsion. A small amount of hexadecane (4.2% compared to the dispersed phase) was used as ultrahydrophobe to stabilize the droplets against Ostwald ripening and SDS as effective surfactant to stabilize the emulsion electrostatically against collisions. A hydrophobic azo-compound as thermal initiator (V59) should ensure that the polymerization of the quite hydrophilic monomer MMA only takes place in the droplets to avoid the formation of secondary polymer particles. By thermal initiation, the monomer was polymerized, forming a shell at the interface of the oil droplets and the continuous phase. In the state of miniemulsion, the monomers and Lucirin TPO are miscible, but phase separation occurs during the polymerization process due to the immiscibility of Lucirin TPO and the polymer. Due to the hydrophobic character of the Lucirin TPO and the more hydrophilic character of poly(methyl methacrylate) (PMMA), the formation of nanocapsules with core–shell geometry is expected [15], where the core is formed by Lucirin TPO, which is encapsulated by a PMMA shell.

In the final latex, the photoinitiator Lucirin TPO was amorphously solidified inside the droplets as a solid core, as it could be detected by DSC and wide-angle X-ray scattering (WAXS) measurements. In the DSC diagram, no melting peak was visible at 80 °C, and in the WAXS, only a broad peak could be detected. This is, to our knowledge, the first time that the encapsulating miniemulsion process is used for a solubility–precipitation process in which the efficiency of the initiator character can be preserved. Subsequently, the nanocapsules were freeze-dried and the (little) portion of Lucirin TPO that was not encapsulated was removed by cautious washing with ethanol. After air-drying on filter paper, the sample was freeze-dried again and could be redispersed in an acidic monomer mixture (see Fig. 2).

To investigate the maximum amount of Lucirin TPO that can be encapsulated by polymer, different ratios of Lucirin TPO to MMA were tested (see Table 1). As reference sample, dispersions of neat PMMA particles without any Lucirin TPO fillings were synthesized (MV 127). Stable miniemulsions could be formed at any Lucirin TPO-to-MMA ratio. However, it turned out that after polymerization, only dispersions with a ratio Lucirin TPO/MMA of at most 1:5 are stable at least for several days (MV 131). Therefore, the ratio 1:5 was kept for all further prepared samples. Comparing the particle sizes of the two samples MV 127 and MV 131 by dynamic light scattering (DLS) reveals that they are in the same range (diameter 132 and 146 nm, respectively). Furthermore, a degree of encapsulation of 29% could be detected via ^{1}H NMR.

To increase the content of encapsulated Lucirin TPO and to achieve more homogeneous shells, a crosslinker (*N*, *N*′-diethyl-1,3-bis(acrylamido)propane [V392]) was added to MMA (11 wt% crosslinker relative to MMA, sample MV 188). The addition of the crosslinker led to a particle

Table 1 Characteristics of the samples

Sample name	Composition weight ratio Lucirin/monomer	Degree of encapsulation (%)	Molar mass (g mol^{-1})/polydispersity (PD)	T_g^a (°C)	Particle diameter[b] (nm)	Solid content (%)
MV 127	Neat MMA	–	M_n=268,000, M_w=583,000/PD=2.2	101	146	19.4
MV 131	Lucirin/MMA 1:5	29	M_n=241,000, M_w=513,000/PD=2.1	100	132	17.7
MV 188	Lucirin/MMA/V392 1:4.5:0.5	90	–[c]	86	107	21.0
MV 137 CoPo 30 °C	Lucirin/MMA/BA 1:2.6:2.4	97	M_n=153,400, M_w=475,000/PD=3.1	6	132	19.7
MV 143 CoPo 50 °C	Lucirin/MMA/BA 1:3.4:1.7	71	M_n=321,000, M_w=690,000/PD=2.2	32	106	24.5

[a] Heating rate in the DSC, 20 °C min^{-1}
[b] As determined by dynamic light scattering
[c] Cannot be determined due to the insolubility caused by the crosslinking

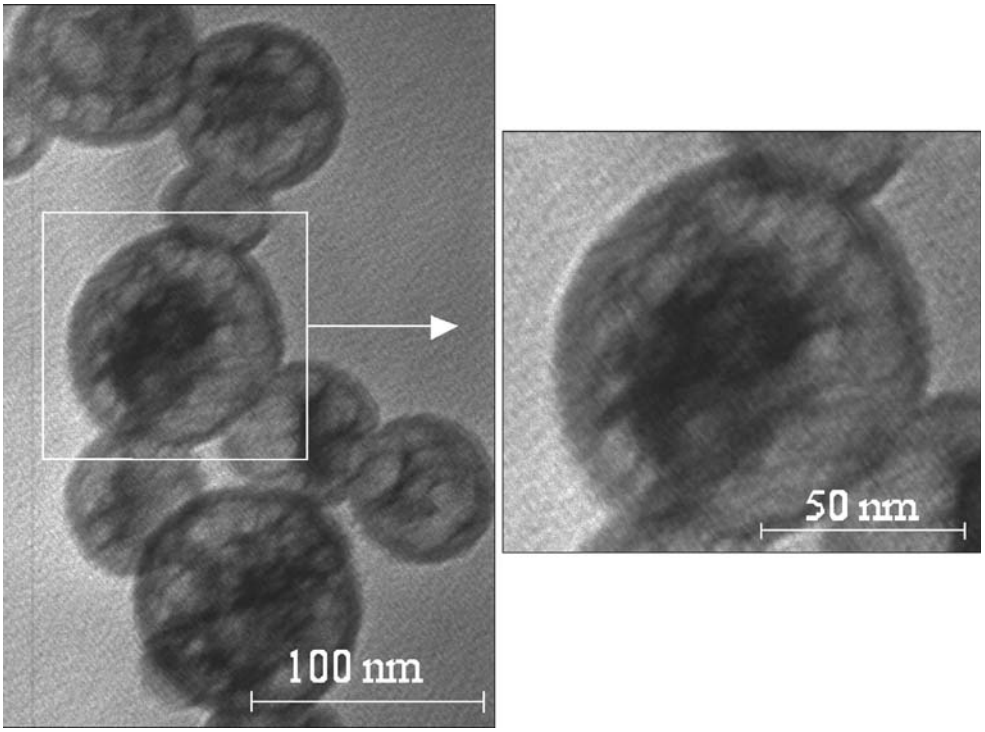

Fig. 3 TEM images of encapsulated Lucirin TPO in polymer shells

diameter of 107 nm, hence significantly smaller than the reference sample (MV 127). This smaller particle size may be a result of the amphiphilic character of the crosslinker, which then also acts as stabilizing agent. The surface activity is shown by measuring a solution of 0.1 g of the water-soluble crosslinker in water. Here, a surface tension of 50 mN/m is detected, compared to 73 mN/m for pure water at 20 °C. Furthermore, the degree of encapsulation could be increased by more than a factor of 3 (90%). Obviously, the crosslinking leads to shells with more stable networks that are able to incorporate Lucirin TPO more efficiently.

However, the increased content of Lucirin TPO by crosslinking is gained at the expense of release rates that are slightly lower than for the neat PMMA capsules (see discussion on kinetic measurements below).

Additionally, the glass transition temperature of the polymer shell was tried to decrease to take advantage of the different properties of the polymer at varying temperatures. Above the glass transition temperature, the consequential higher flexibility of the polymer chains should effect a release rate of Lucirin TPO; below the T_g, it should be prevented. Hence, a change

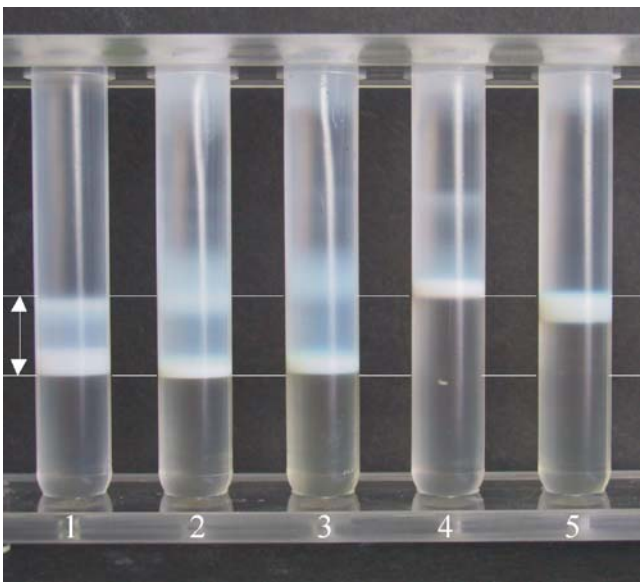

Fig. 4 Photograph of the tubes from ultracentrifugation experiments in a density gradient; *1* unfilled PMMA particles of sample MV 127; *2* with a ratio of 1:5 filled particles of sample MV 131; *3* crosslinked particles of sample MV 188; *4* copolymer particles of sample MV 137; *5* copolymer particles of sample MV 143

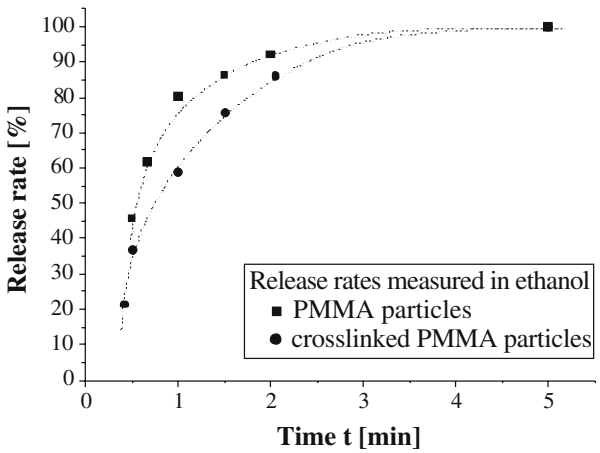

Fig. 5 Release kinetics of Lucirin TPO from PMMA and crosslinked PMMA particles in pure ethanol. The released amount is given in percent of the totally encapsulated material

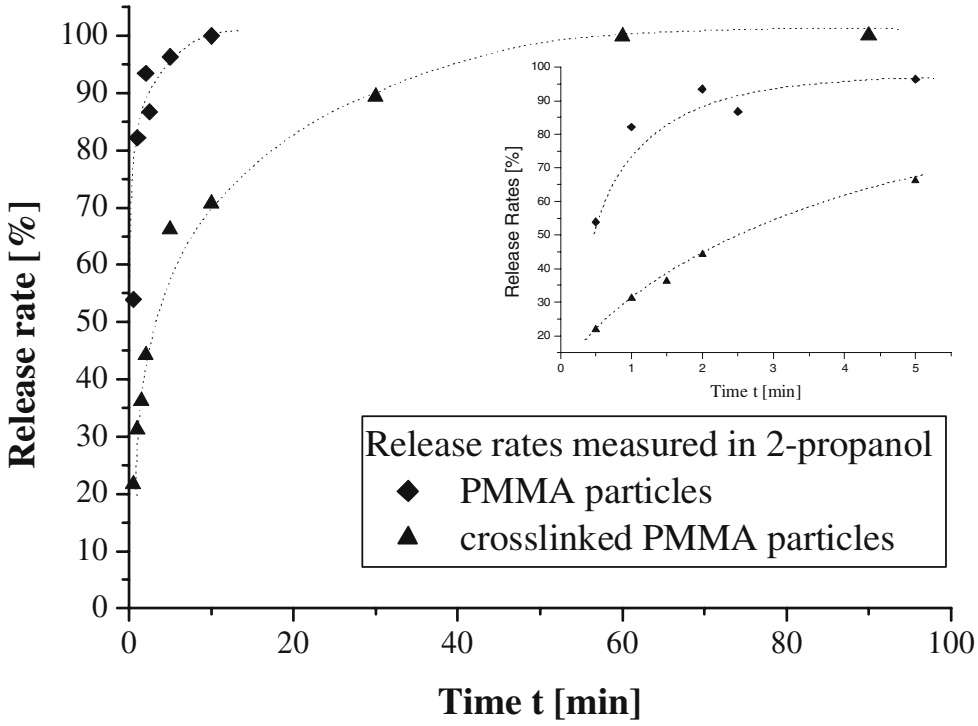

Fig. 6 Release kinetics of Lucirin TPO from PMMA and crosslinked PMMA particles in 2-propanol. The released amount is given in percent of the totally encapsulated material; the *inset* shows the release kinetics of the first 5 min, so that it can be compared to Fig. 5

of temperature might be used as trigger for the release kinetics. Different mixtures of MMA and BA(T_g [PBA]= −54 °C, T_g [PMMA]=105 °C) [16] were employed (MV 137 and MV 143). Via DSC measurements, glass transition temperatures of 6 and 32 °C, respectively, were determined. The Lucirin TPO contents inside the capsules were 97 and 71%, respectively, and thus significantly higher than in sample MV 131 with neat PMMA shell.

The particle sizes (diameter 132 and 106 nm, respectively) of these samples are in the same range as the previous samples. Unfortunately, the low T_g of the copolymer samples hampered an efficient redispersion of the nanoparticles in organic solvents and in the acidic monomer systems as well due to the sticky condition of the material. Therefore, no kinetic measurements were performed with these samples.

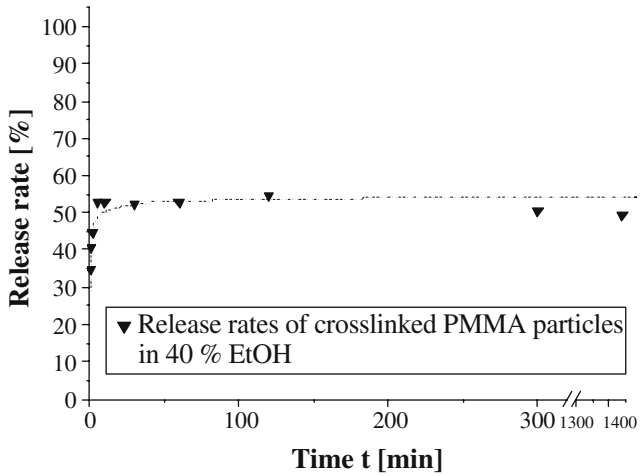

Fig. 7 Release rates of crosslinked PMMA particles in a solution of 40 wt% ethanol in D_2O. The released amount is given in percent of the totally encapsulated material

Verification of the shell–core encapsulation

To show that the prepared capsules were proper core–shell particles in which Lucirin TPO is completely present as core with polymeric shells, electron microscopy examinations were performed. As shown in Fig. 3, Lucirin TPO is located within the particles completely covered by the polymer shell. Thus, a real core–shell structure can be assumed.

Comparing the particle sizes obtained by TEM and by DLS shows a good agreement between both methods. Missing signals for protons of immobilized Lucirin TPO molecules in the ^{1}H NMR spectra of the dispersions due to the low T_2 relaxation time support further the efficient encapsulation of the photoinitiator. After dissolution of the polymer shells, Lucirin TPO could be detected again.

Furthermore, density deviations and differences of the density distribution could be determined by ultracentrifugation in a density gradient (see Fig. 4). Compared to the pure PMMA particles of sample MV 127 (tube 1), the samples MV 131 (tube 2) and the crosslinked sample MV 188 in tube 3 showed broader density distributions. The non-uniform filling of the particles of these samples with Lucirin TPO leads to a larger difference in their density. The most narrow distributions were achieved with the copolymer samples MV 137 (tube 4) and MV 143 (tube 5). Due to their uniform density, the particles must be homogeneously filled with Lucirin TPO.

Kinetics of the release rates of Lucirin TPO

To prove the potential application of the nanocapsules as a delivery system, the release rates of Lucirin TPO out of the polymer capsules into an ambient phase were determined. A mixture of hydrophilic acidic monomers shows good solubility for the Lucirin TPO and a poor solubility for the PMMA shell. A release out of the capsules is that low that the kinetics cannot be determined within the accuracy of NMR measurements. The direct use of the acidic monomers also turned out not to be reasonable for the investigation of the kinetics, as Lucirin TPO degrades in the acidic monomers over time. However, it can be shown that the concentration of intact initiator in the monomer phase, even after several days, is still high enough to start a polymerization, whereas the control system of unprotected Lucirin TPO degrades in the monomer and is not suitable for initiation after a couple of days. This clearly proves that the encapsulation in the PMMA prolongs the lifetime of the initiator substantially.

To measure the release kinetics, a model system should be used in which the Lucirin does not degrade. The model system should be a non-solvent for the polymer but a very good solvent for the Lucirin TPO, which is the case for pure ethanol (non-solvent for PMMA, very good solvent for Lucirin TPO). In a first series of measurements, the release rates of Lucirin TPO out of the PMMA shells of sample MV 131 in pure ethanol were tested. As shown in Fig. 5, the rates were so high that the release had already been completed after 5 min. The same results were obtained from the crosslinked PMMA particles of sample MV 188 (maximum release was scaled to 100%). The curve progression of the crosslinked particles was slightly flatter than that of the pure PMMA shells. The errors of the measurement are in the range of 5 to 10%. This leads to the conclusion that the kind of polymer shell indeed influences the release rates (although it is measured on a very short time scale).

Due to these results, we changed to a slightly less polar and less good solvent and investigated the release rates in 2-propanol [17] (see Fig. 6). It is clearly visible that the release times could be increased to 10 min for PMMA particles and up to 90 min for the crosslinked PMMA particles. These drastic differences support further the finding above that the release rates depend strongly on the kind of polymer shell.

Furthermore, an influence of the redispersing agent on the release rates could be detected. Although the crosslinked PMMA particles showed release times of 5 min in pure ethanol (Fig. 5) and 90 min in 2-propanol (Fig. 6), in a solution of 40 wt% ethanol in D_2O, a balance between the encapsulated Lucirin TPO and the already released one could be detected (see Fig. 7).

In the beginning, the release rates of Lucirin TPO were as fast as in pure ethanol, but after the release of 53%, an equilibrium could be obtained, which stays stable also after several days. Due to the lower solubility of Lucirin TPO in an aqueous solution of 40 wt% ethanol, only 60 mg of the capsules were used for kinetic measurements to guarantee that, in principle, all encapsulated Lucirin TPO is soluble in the given volume of the ethanol solution. As only 50% is released in the first step, a reservoir of the other 50% is still in the capsules, which can be released over a long time period. This is expected also for the mixture of the acidic monomers, and therefore a polymerization of the acidic monomers can still be observed after several days (see above).

Conclusion

The miniemulsion process is a successful technique for the encapsulation of the solid photoinitiator Lucirin TPO in different polymer shells. It could be shown that the capsules are permeable and thus release the initiator in a sufficiently high concentration in the surrounding (monomer) phase to start the polymerization even after a longer time. The release rates clearly vary with the kind of the polymer shell and the employed redispersing agent. The studies of the kinetics show the great potential of these capsules to get applied in polymeric dental filling materials as initiator depots to guarantee the required storage time. In the future, the release rates and the pore sizes of the shells will be tailored to defined values to predict the durability of this core–shell system precisely.

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