Title Polyurea microcapsules with a photocleavable shell: UV-triggered release

Authors Dispinar Tugba, Colard Catheline A.L., Du Prez Filip E.

In: Journal, Volume (Issue), pages, year. Polymer Chemistry, 4(3), 763-772, 2013.

Optional:

Polyurea microcapsules with photocleavable shell: UV-triggered release

*Tugba Dispinar[a], Catheline A. L. Colard[a,b†] and Filip E. Du Prez[a,b]**

a. Department of Organic Chemistry, Polymer Chemistry Research Group, Ghent University, Krijgslaan, 281, S4-bis, B-9000 Ghent, Belgium

b. SIM, Technologiepark Zwijnaarde 904, B-9052 Ghent, Belgium

KEYWORDS

Microcapsules, photocleavable, light-triggered, nitroveratroxycarbonyl, UV.

ABSTRACT

We report the preparation and characterization of photocleavable polyurea microcapsules. First, an isocyanate end functionalized oligomer, bearing the photolabile 6-nitroveratroyloxycarbonyl group was synthesized. This oligomer, in combination with diethylenetriamine, was then utilized in the preparation of polyurea microcapsules. Polyurea microcapsules (50-300 μm), loaded with a hydrophobic dye solution and consisting of a dense capsule shell were prepared via an interfacial polymerization in a stable oil-in-water emulsion system. Thanks to the intra-molecular photocleavage mechanism, the UV-triggered rupture of the photocleavable capsule shell occurred both in solution and in solid state, leading to the successful release of the encapsulated liquid core.

INTRODUCTION

Polymeric capsules have received increased interest in the last few years due to the many attractive application possibilities regarding the delivery of encapsulated material.[1, 2] For example, liquid filled capsules are used in new printing technologies, in agriculture, in cosmetics and in food industries. Moreover, recently they lead to important developments in the areas of drug delivery, self-healing and biosensing. Polymeric capsules with liquid core can be prepared in several ways including colloidosome formation, polymer precipitation by phase separation, interfacial polymerization, layer-by-layer polyelectrolyte deposition, polymer growth by surface polymerization and copolymer vesicle formation.[3, 4] Each of these methods have different characteristics, thus the choice of an appropriate synthetic method depends on the properties of the shell material, encapsulated material and the final applications of the capsules. Similarly, the release of the content from polymeric capsules also depends on the application area and can be achieved through a number of mechanisms.[1, 2] Capsules might on one hand release their content by mechanical rupture, such as in the case of autonomous self-healing applications, but they can on the other hand response to a change in the local environment such as a chemical/biological trigger or to an external stimulus. Recently, the last two mechanisms have been much investigated since they offer the advantage of controlled delivery of the encapsulated material.

The chemical nature of the capsule shell is an important criterion when the controlled release of the encapsulated material is targeted. Especially, the utilization of stimuli-responsive, degradable groups in the shell structure is interesting since it gives the advantage of burst release kinetics as a chemical response to an applied stimulus. Recently, Broaders and *et al.* reported the synthesis of acid-degradable solid-walled microcapsules via an interfacial polycondensation method. Thanks to the presence of acid-sensitive ketal groups in the shell structure, the rapid

solubilization of the capsule shell and the burst release of the encapsulated material was observed under acidic condition.[5] As another option for degradation, disulfide bridges were utilized in a layer-by-layer deposition technique for capsule synthesis to achieve redox-responsive burst release from microcapsules, which might be suitable for therapeutic applications.[6, 7] As interesting as the stimuli-responsive degradable groups, self-immolative polymers have recently attracted attention for the construction of stimuli-responsive degradable capsules. Esser-Kahn and co-workers used a self-immolative polymer to design the stimuli-responsive capsule shell via the interfacial polycondensation method.[8] In this case, the presence of certain chemicals in the medium, such as HCl or piperidine, initiated the head-to-tail depolymerization of the capsule shell, and simultaneously the release of the encapsulated material.

It should be noted that the above mentioned examples need a local change in the environment to trigger the release from capsules. On the other hand, certain applications might require an external trigger to control the release in a remote way.[9] In this respect, light offers an outstanding advantage as an external stimulus since it can be applied remotely in a precise manner and enables the solid state release from microcapsules without requiring any solvent-based environment. To achieve the light-triggered release from capsules, most reported studies take the advantage of light absorbing materials such as gold[10, 11], silver[12] nanoparticles or carbon nanotubes[13]. Indeed, these materials are capable to absorb near-infrared (NIR) light effectively. When they are localized inside the capsules, absorption of NIR-light by these materials causes localized heating (> 600°C for gold and silver nanoparticles, ~ 170°C for carbon nanotubes) of the particles inside the capsule shell, which consecutively results in an explosion of the shell and burst release of the content. The use of NIR-light is mainly beneficial for biological systems since it is less detrimental to living cells.[14] In a similar approach, titanium oxide (TiO_2)

nanoparticles have been utilized in microcapsules to achieve an UV-light triggered release, which is most likely to be applied in cosmetics and agricultural applications.[15]

Another approach to obtain light-triggered release from capsules is the incorporation of either photoresponsive or photocleavable groups in the shell structure. As a well-known photoresponsive group, azobenzenes have already been introduced in the capsule shell structure via layer-by-layer deposition technique.[16] As azobenzene groups are known to change geometry under the influence of light, this property can be used to change the permeability of the capsule shell and to achieve a controlled release. On the other hand, when the burst release from microcapsules is targeted, photocleavable groups are more advantageous since the capsule wall is completely destroyed under the influence of light. However, studies on solid-walled capsules with photocleavable shell structures are rare. Recently, Rosenbauer and *et al.* prepared polyurethane nanocapsules consisting of an aqueous core and azo bonds containing polymeric shell via interfacial polymerization in an inverse miniemulsion medium.[17] In this case, it was not only light but also two other stimuli, namely temperature and pH, that were responsible for the cleavage of azo bonds and simultaneous collapse of the capsule shell.

As another photodegradable functionality, *o*-nitrobenzyl moieties, known to be the most widely used photolabile protecting group in organic synthesis, have recently become a popular type of photo-cleavable junction for polymeric materials.[18] *o*-Nitrobenzyl based functional groups have been used to design different photodegradable polymeric systems such as bulk hydrogels[19, 20], microgels[21], photo-cleavable block copolymers[22-25] and micelles[26]. Recently, they gained further interest as protecting group in the UV-responsive release of certain functional groups such as thiols.[27,28] Especially, 6-nitroveratroyloxycarbonyl (NVOC) derivatives containing two methoxy groups on the benzene ring gained more interest since they display an

absorption maximum around 350 nm and therefore require less dangerous, long-wave UV light for the degradation process.[29] Moreover, recent studies reported that NVOC-based moieties are also sensitive to NIR light with slower degradation kinetics in comparison to UV-light irradiation.[30, 31]

In this study, a straightforward method will be reported to design photocleavable microcapsules by the introduction of NVOC units in the shell structure. For this purpose, an NVOC-based diisocyanate oligomer has been synthesized from a photolabile diol and toluene 2,4-diisocyanate (TDI) in a condensation polymerization and used for the synthesis of photocleavable polyurea microcapsules. It will be described how such microcapsules, loaded with a hydrophobic dye solution as a model system for other hydrophobic compounds, have been prepared via interfacial polymerization in a stable oil-in-water emulsion system. The cleavage of the NVOC junction and therefore the time-dependent release of the encapsulated dye under the influence of UV light with a specific wavelength of 365 nm will be discussed in detail.

EXPERIMENTAL SECTION

Materials. Acetovanillone (> 98 %), potassium carbonate (> 99 %), acetic anhydride (> 99 %), fuming HNO_3 (> 99.5 %), sodium borohydride (> 99 %), toluene 2,4-diisocyanate (> 95 %), di-*n*-butylamine (> 99.5%), dibutyltin dilaurate (95 %), gum arabic, diethylenetriamine (99 %), solvent blue 35 (98 %), anhydrous chlorobenzene (99.8 %), anhydrous ethyl acetate (99.8 %), 1,1,1-tris(hydroxymethyl)ethane (99 %) were purchased from Sigma-Aldrich. Methyl-4-bromoacetate (99 %) was purchased from Across Organics. The other solvents were all HPLC grade and obtained from Aldrich. All reagents have been used without any further purification.

Synthesis of photolabile diol (3). *Methyl 2-(4-acetyl-2-methoxyphenoxy)acetate (1)*: Acetovanillone (40 g, 249 mmol) was dissolved in DMF (200 mL) in a 500 mL round bottom flask and potassium carbonate (50 g, 360 mmol) was added to the solution. Afterwards, methyl-4-bromoacetate (25.3 mL, 267.2 mmol) was slowly transferred to the reaction flask and the reaction mixture was stirred overnight at room temperature. The precipitated salt was filtered from the solution and the solution was mixed with 400 mL of ethyl acetate. After addition of 100 mL of water, the organic phase was collected while the aqueous phase was washed with 100 mL of ethyl acetate. The organic phases were combined, subsequently dried over magnesium sulfate and evaporated. The residual liquid was precipitated in cold water (700 mL). The precipitate was filtered and dried in a vacuum oven at room temperature. The product was obtained as a white powder with 80 % yield. ^{1}H NMR (300 MHz, $CDCl_3$) 2.54 ppm (s, 3H, Aromatic-COC*H*$_3$), 3.78 ppm (s, 3H, COOC*H*$_3$), 3.92 ppm (s, 3H, Aromatic-OC*H*$_3$), 4.75 ppm (s, 2H, Aromatic-OC*H*$_2$-$COOCH_3$), 6.77 ppm (d, 1H, Aromatic-*H*), 7.49-7.53 (m, 2H, Aromatic-*H*). ES-MS (*m/z*) 239 (100 %) [$M + H^+$].

Methyl 2-(4-acetyl-2-methoxy-5-nitrophenoxy)acetate (2): Compound 1 (10 g, 0.042 mol) was dissolved in acetic anhyride (150 mL) using an ultrasonic bath and the reaction flask was placed in an ice bath at 0°C. Fuming HNO_3 (3 mL, 0.063 mol) was slowly added to the solution. Once the color of the solution turned to a yellow-orange color, precipitation started to occur. This suspension was stirred for 45 min and then poured into cold water (600 mL). Afterwards, the precipitate was filtered and successively washed with saturated sodium bicarbonate solution ($NaHCO_3$ – 200 mL) and then extensively with water. The compound was recrystallized in ethanol to a white powder with 85 % yield. ^{1}H NMR (300 MHz, $CDCl_3$) 2.48 ppm (s, 3H, Aromatic-COC*H*$_3$), 3.82 ppm (s, 3H, COOC*H*$_3$), 3.97 ppm (s, 3H, Aromatic-OC*H*$_3$), 4.77 ppm

(s, 2H, Aromatic-OC*H*$_2$-COOCH$_3$), 6.76 ppm (s, 1H, Aromatic-*H*), 7.54 (s, 1H, Aromatic-*H*). ES-MS (*m/z*) 284 (100 %) [M + H$^+$], 306 (24 %) [M + Na$^+$].

Photolabile diol- [(hydroxy 2-(4-(1-hydroxyethyl)-2-methoxy-5-nitrophenoxy)ethane] (3): Compound 2 (2 g, 0.007 mmol) was suspended in a 150 mL THF:MeOH mixture (100 mL THF, 50 mL MeOH). Sodium borohydride (0.8 g, 0.021 mmol) was added and the reaction flask was immersed into an oil bath, thermostated at 41^{o}C. After 1 hour, the reaction flask was taken to room temperature and 100 mL of water was added. Afterwards, the organic phase was evaporated and the aqueous phase was extracted with dichloromethane (3×80 mL). The dichloromethane solution was dried with anhydrous $MgSO_4$ before the solvent was removed on a rotary evaporator. The resulting yellow sticky compound was crystallized in water and dried in a vacuum oven at 40°C overnight. A pale yellow, solid product was obtained with 77 % yield. ^{1}H NMR (300 MHz, $CDCl_3$) 1.52 ppm (d, 3H, Aromatic-CHC*H*$_3$-OH), 3.95 ppm (s, 3H, Aromatic-OC*H*$_3$), 3.98 ppm (m, 2H, Aromatic-OCH$_2$-C*H*$_2$-OH), 4.15 ppm (m, 2H, Aromatic-OC*H*$_2$-CH$_2$OH), 5.56 (q, 1H, Aromatic-C*H*CH$_3$-OH), 7.29 ppm (s, 1H, Aromatic-*H*), 7.58 (s, 1H, Aromatic-*H*). ES-MS (*m/z*) 258 (100 %) [M + H$^+$], 280 (19 %) [M + Na$^+$].

Synthesis of NVOC-based diisocyanate oligomer. Prior to polymerization, glassware was dried in an oven at 80°C overnight and cooled to room temperature under argon atmosphere. Toluene 2,4-diisocyanate (2,9 mL, 0.02 mol) was transferred to a 500 mL two-necked round bottom flask. After the addition of anhydrous ethyl acetate (400 mL) and dibutyltin dilaurate (25 ml, 0.042 mmol), the reaction flask was immersed into an oil bath thermostated at 70°C. In a separate flask, compound 3 (1 g, 0.004 mol) was dissolved in 40 mL anhydrous ethyl acetate and then added dropwise to the reaction mixture in 40 min. After the addition was completed, the reaction continued for another 40 min. Afterwards, ethyl acetate was partially removed on a

rotary evaporator. Around 50 mL of ethyl acetate was left in the reaction flask and this solution was subsequently precipitated dropwise in hexane (400 mL). The precipitate was filtered and dried under vacuum at room temperature for two days, yielding the diisocyanate oligomer (2.3 g) with a molecular weight of 1050 g mol^{-1} and PDI of 1.2. The ^{1}H-NMR spectrum (in $CDCl_3$) is shown in Scheme 2.

Preparation of polyurea microcapsules. A previously described procedure for the synthesis of polyurea microcapsules has been adapted.[32] An aqueous solution of gum arabic (12 mL, 14 % w/w in dd-H_2O) was prepared in a 40 mL vial to be used as the continuous phase of the emulsion in the microcapsule synthesis. To prepare the organic phase, 300 mg of photodegradable oligomer was dissolved in 0.6 mL of anhydrous chlorobenzene. Application of a heat gun and vigorous stirring were needed to obtain complete dissolution. In another vial, 20 mg of the hydrophobic dye (solvent blue 35) was dissolved in 0.2 mL of anhydrous chlorobenzene and added to the solution of the photodegradable oligomer. This solution was stirred for two minutes and slowly transferred into the gum arabic solution. This mixture was vortexed for two minutes at 2200 rpm to produce the emulsion. Afterwards, vortexing was slowed down to 1000 rpm and an aqueous solution of diethylenetriamine (0.1 mL, 21 % w/w in dd-H_2O) was added dropwise during one minute. The resulting mixture was vortexed another two minutes and immersed into an oil bath at 80°C for one hour without stirring. Afterwards, the vial was cooled to room temperature and 10 mL of deionized water was added to the vial. After the microcapsules settled down inside the vial, most of the water was removed with a pasteur pipette and fresh water was added to the vial. This washing procedure was repeated three times to get rid of the gum arabic stabilizer. Small amounts of formed polymeric fibers were also removed physically during this washing step. Afterwards, the suspension was added to 100 mL of deionized water and filtered

through a filter paper. The microcapsules were then washed with an additional amount of 100 mL deionized water and air-dried for 48 hours before further analysis. The resulting dried microcapsules appeared in a blue color as non-agglomerated solids. The average yield of microcapsules was about 55 wt %. The microcapsules were found (by TGA analysis) to be composed of 60 % core solvent.

Titration of isocyanate (NCO) content in photodegradable isocyanate oligomer. The synthesized photodegradable diisocyanate oligomer (150 mg) and anhydrous chlorobenzene (25 mL) were mixed in a 250 mL erlenmeyer flask with a stopper. The photodegradable oligomer was dissolved with the help of mechanical stirring and a heat gun. Di-*n*-butylamine (2 mL) was added via a pipette. After 45 min of stirring at room temperature, methanol (100 mL) and bromophenol blue indicator solution (3-4 drops) were added to the erlenmeyer flask. Three titrations were performed with hydrochloric acid (0.1 N). Blank titrations run without photodegradable oligomer. The NCO content was calculated according to the following equation:

$$\%\,\mathrm{NCO} = \frac{\mathrm{V_{blank}} - \mathrm{V_{sample}} \times \mathrm{N} \times 4.2}{\mathrm{W_{sample}}}$$

in which V_{blank} and V_{sample} represent the volumes of HCl (in mL) used for the blank and the photodegradable oligomer titrations, respectively. N stands for the normality of HCl. W_{sample} is the weight of photodegradable oligomer (in grams) used during the titration.

Yield of the capsules. Yield of the capsules was roughly calculated according to a previously described equation:[33]

$$\text{Yield}\ \% = \frac{\mathrm{W_{capsule}}}{\mathrm{W_{oligomer}} + \mathrm{W_{DETA}} + \mathrm{W_{dye}} + \mathrm{W_{Clbenzene}}} \times 100$$

in which $W_{capsule}$ is the mass of the collected microcapsules after drying, and $W_{oligomer}$, W_{DETA}, W_{dye}, $W_{clbenzene}$ are the masses of NVOC-based diisocyanate oligomer, diethylenetriamine, dye (solvent blue 35) and chlorobenzene, respectively.

Photolysis of diisocyanate oligomer under UV light. 1 mg mL^{-1} solution of diisocyanate oligomer in DMSO in a quartz cuvette was placed inside a 900 W VL 400-L UV lamp and irradiated at 365 nm with an intensity of 12 mW cm^{-2} for specified periods of time. Absorption spectra were collected after each irradiation using an Analytic Jena-Specord 200 UV Spectrophotometer in the wavelength range from 225 to 600 nm.

Photolysis of diisocyanate oligomer for NMR analysis. 10 mg mL^{-1} solution of diisocyanate oligomer in d-DMSO in a quartz cuvette was placed inside a 900 W VL 400-L UV lamp and irradiated at 365 nm with an intensity of 12 mW cm^{-2}. At certain time intervals, samples were taken and ^{1}H NMR spectra were recorded at 300 MHz on a Bruker Avance 300 spectrometer at room temperature.

UV triggered dye release from microcapsules. *75 min UV irradiation in hexane:* Microcapsules (15 mg) were dispersed in hexane (2.3 mL) inside a quartz cuvette and an absorption spectrum of this solution was recorded prior to UV exposure. Afterwards, microcapsules were exposed to UV-light of 365 nm (12 mW cm^{-2}) for 75 min. During this irradiation, absorption spectra of the hexane solution were collected every 5 min via an UV-spectrometer. Afterwards, microcapsules were manually ruptured and the absorption spectrum of this last solution was also recorded to be used as the 100 % value for the dye release conversion.

20 min UV irradiation in hexane: Microcapsules (15 mg) were dispersed in hexane (2.3 mL) inside a quartz cuvette. After the collection of absorption spectrum of the solution, the quartz

cuvette was placed under UV-light of 365 nm (12 mW cm^{-2}) for 20 min. Then, the quartz cuvette containing microcapsules was placed in the UV-spectrometer and the absorption of the solution was recorded every 20 min for 48 hours. After 48 hours, microcapsules were manually ruptured and the absorption spectrum of this last solution was also recorded to be used as the 100 % value for the dye release conversion.

20 min UV irradiation of solid capsules: Microcapsules (15 mg) were dispersed in a quartz cuvette and exposed to UV-light of 365 nm (12 mW cm^{-2}) for 20 min. After UV-exposure, 2.3 mL of hexane was added to the quartz cuvette and the absorption of the solution was recorded every 20 min for 48 hours. Then, a similar procedure as described before was followed.

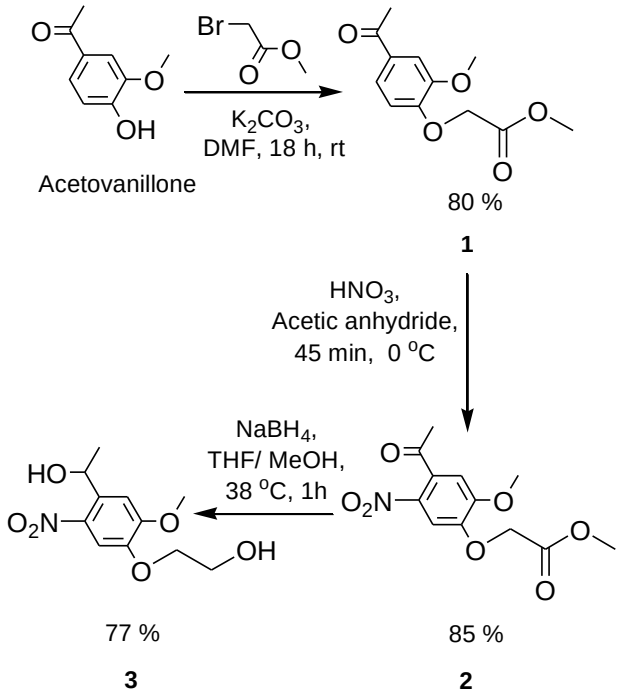
Control experiments: In all control experiments, microcapsules in quartz cuvettes were kept in an oil bath of 50°C without UV irradiation.

Instrumentation. *Ultraviolet (UV) irradiation* was performed with a 900 W Vilber Lourmat VL 400-L filtered UV-lamp that emits at 365 nm with an intensity of 12 mW cm^{-2} at this specific wavelength. *Nuclear magnetic resonance (^1H NMR) spectra:* were recorded at 300 MHz on a Bruker Avance 300 spectrometer at room temperature. *Size-exclusion chromatography:* was performed on a Waters 2414 instrument, using DMA as eluent containing LiBr (0.42 g L^{-1}) with a flow rate fixed at 1 mL min^{-1} (with poly(methylmethacrylate) standards). *Scanning Electron Microscopy* (SEM) images: were recorded with a Phenom FEI scanning electron microscope operated at an acceleration voltage of 5 kV. Samples were directly analyzed without any metal coating. Optical microscopy images were taken with an Omnilabo Olympus optical microscopy. *Electrospray Ionization Mass Spectra (ESI-MS):* were recorded with an Agilent technologies 1100 instrument equipped with a single quad MS detector with electrospray and APCI (Atmospheric Pressure Chemical Ionization) source. *Thermogravimetric analysis:* was

performed with a Mettler Toledo TGA/SDTA851e instrument under air atmosphere at a heating rate of 20°C min^{-1} from 25°C to 800°C to analyze the thermal stability of the prepared capsules and the content amount.

RESULTS AND DISCUSSION

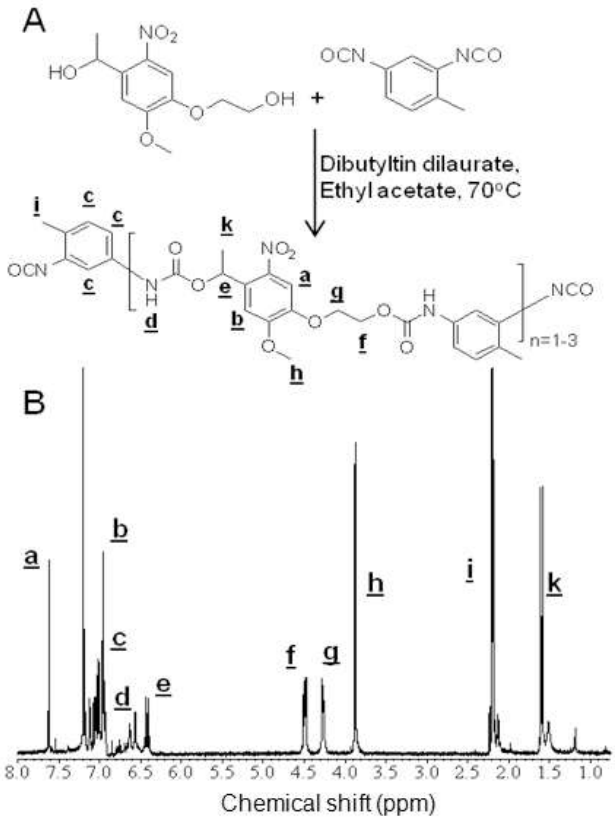
Synthesis of NVOC-based diisocyanate oligomer. For the preparation of the NVOC-based diisocyanate oligomer, a photolabile diol was first synthesized from commercially available acetovanillone in a three-step procedure (Scheme 1). During the synthesis, acetovanillone was alkylated with methyl-4-bromoacetate and subsequently nitrated with fuming nitric acid according to previously reported synthetic protocols with slight modifications.[34] In the last step, the ketone and methyl ester groups were reduced with sodium borohydride in a MeOH/THF system to yield the photolabile diol (3).



Scheme 1. Synthetic route for the preparation of the photolabile diol (3).

In order to obtain the NVOC-based diisocyanate oligomer, the photolabile diol was polymerized with toluene 2,4-diisocyanate in anhydrous ethyl acetate at 70°C in the presence of dibutyltin dilaurate catalyst (Scheme 2A). An excess amount of toluene 2,4-diisocyanate was used in the polymerization for two reasons. First, it ensured the isocyanate end functionality and secondly, a low molecular weight oligomer could be obtained. The latter was also supported by low monomer concentrations and slow addition of the diol monomer to the polymerization solution. Synthesis of low molecular weight diisocyanate oligomers was targeted to avoid potential solubility problems as a result of the rigid-urethane structure during the microcapsule synthesis. Moreover, a low molecular weight diisocyanate oligomer provides a high isocyanate content during the microcapsule synthesis, consequently leading to the formation of a robust shell.[32]

The number-average molecular weight (M_n) of the diisocyanate oligomer, as determined via SEC, is 1050 g mol^{-1} while its polydispersity index (PDI) reached 1.2. The isocyanate content of the oligomer was determined as 11 wt % via titration. Combination of these results with ^{1}H-NMR data analysis reveals that the diisocyanate oligomer consists of short polyurethane chains with one to three repeating monomer units, among which the diisocyanate compound with only one repeating monomer unit comprises around 70 % of the diisocyanate oligomer. Hydroxyl terminated chains could not be detected anymore in the ^{1}H-NMR spectrum of the diisocyanate oligomer (Scheme 2B), proving that both the primary and secondary alcohol groups of the photolabile diol reacted quantitatively with isocyanate moieties.



Scheme 2. A) Synthesis of the NVOC-based diisocyanate oligomer. B) ^{1}H NMR spectrum of the NVOC-based diisocyanate oligomer.

Preparation of polyurea microcapsules. Polyurea microcapsules loaded with a hydrophobic dye solution, as a model system, have been prepared via interfacial polymerization in a stable oil-in-water emulsion system. In a first step, the NVOC-based diisocyanate oligomer and a hydrophobic dye (solvent blue 35) were dissolved in chlorobenzene to yield the oil phase. This oil phase was then poured into an aqueous solution of gum arabic surfactant for the generation of an oil-in-water emulsion at room temperature by using a vortex mixer. Afterwards, an aqueous solution of diethylenetriamine (DETA) was added dropwise to the emulsion in order to start the encapsulation process. The reaction between the amino groups of the DETA in the aqueous phase and the isocyanate end groups of the NVOC-based oligomer in the oil phase takes place at

the interface and rapidly produces a polyurea membrane around the oil droplets. However, this rapid membrane formation restricts the diffusion of the unreacted DETA. Thus, for increased stabilization of the shell, the emulsion was cured in an 80°C oil bath for one hour.[35]

After successive washing and drying steps, microcapsules were obtained as non-agglomerated solids. In Figure 1, the optical microscopy and SEM images show the spherical morphology and solid shell structure of the capsules. The shell thickness was measured to be 1 μm on the SEM image (Figure 2B). To check the stability of the capsule shell, capsules were immersed in DMSO, a good solvent for the polyurea chains. Although sudden release of the dye has been observed, capsules were stable and hold their spherical morphology. This observation clearly proves the crosslinked nature of the capsule shell. By optical microscopy, microcapsules in the range of 50 to 300 μm in diameter are observed (Figure 1A-1B), which is also confirmed by particle size analysis with a mean value of 180 μm (see Figure S1). This large size dispersity of the capsules is related to the emulsification method for which a high shear force tool is used. The size of the capsules, basically their surface-volume ratio, and the wall thickness are important factors to dictate the release kinetics. Although the size distribution of the microcapsules could be in principle improved, for example by using a homogenizer, good control on the dye release was already observed. It should also be noted that polydisperse dispersions also present advantages in industrial applications as they keep the viscosity relatively low for high solids (capsules) content dispersions.

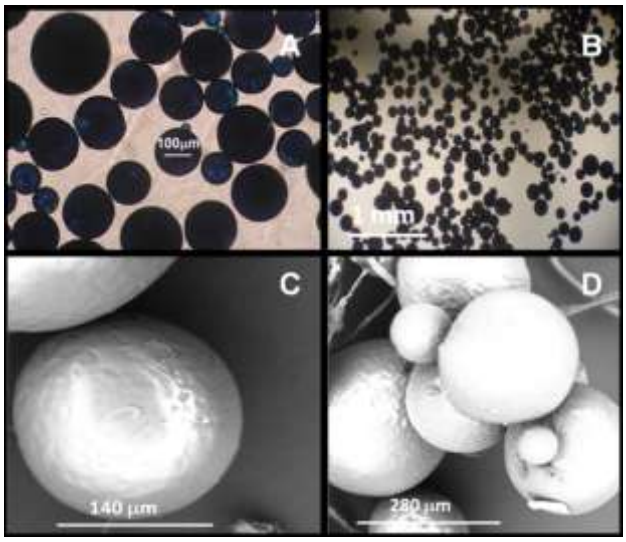


Figure 1. A-B) Optical microscopy images of microcapsules. C-D) SEM images of microcapsules.

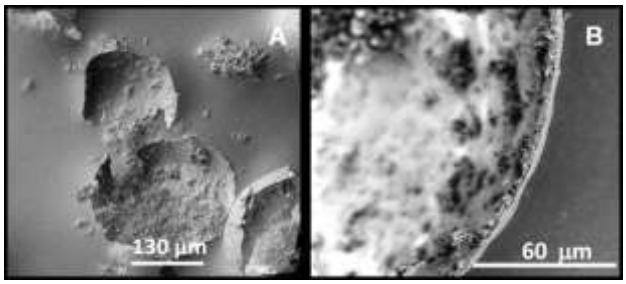


Figure 2. SEM image of A) a broken microcapsule, B) a cross-section of the microcapsule wall.

The reaction rates between isocyanate and amino groups are known to be much higher than those between isocyanate and hydroxyl groups.[36] Due to this high reactivity of both primary and secondary amine groups in DETA compared to the hydroxyl groups in water or in the structure of the surfactant, we assumed that side reactions with hydroxyl groups were not significant in the process of the shell formation. Moreover, once the DETA was replaced with a triol, namely 1,1,1-tris(hydroxymethyl)ethane, a stable microcapsule formation was not observed under the same reaction conditions. Thus, we concluded the diisocyanate oligomers react more rapidly with DETA to construct the capsule shell in the shape of a crosslinked structure. As shown in

literature studies, unreacted amine groups are always present to some extent in the shell structure and they can be used to functionalize the capsule surface.[37]

Photolysis of NVOC-based diisocyanate oligomer. As mentioned earlier, the 6-nitroveratroyloxycarbonyl (NVOC) group with the two additional methoxy groups on the benzene ring displays an absorption maximum around λ=350 nm and therefore enables a safer degradation process with long-wave UV light.[29] Moreover, the presence of an α-methyl group on the benzylic carbon is also beneficial since it accelerates the photo cleavage process and leads to the formation of less reactive nitroso ketone as photolysis product. The molecular attachment, integrating the NVOC group to the photodegradable structure, is also important since it determines the chemical structure of the other liberated product. For example, in our case, the polycondensation reaction between the photolabile diol and TDI incorporates the α-methyl-NVOC group into the diisocyanate oligomer via carbamate bonds. Therefore, photolysis of the NVOC group produces, on one side, a nitroso ketone and, on the other side a carbamic acid that spontaneously decarboxylates to generate a free amine (Figure 3A).

The photolysis of the NVOC-based diisocyanate oligomer was studied by UV spectroscopy. The oligomer solution in DMSO (1 mg mL^{-1}) was exposed to UV light (365 nm) for various periods of time. Upon UV-irradiation, a decrease in the absorption was observed at 291 nm, along with a red shift in the absorption band from 340 nm to 375 nm, which is assigned to the newly formed nitroso ketone.[38, 39] A steady state in the absorption spectrum was reached upon 5 min of UV irradiation, indicating that complete photocleavage occurred (Figure 3B). It is to note that further changes in the spectra were observed for significantly longer irradiation times (see Figure S2). These changes are consistent with previously reported results and can be explained by additional photoreactions such as the formation of azobenzene compounds.[21, 40]

Furthermore, the photolysis of the NVOC-based diisocyanate oligomer was also investigated by ^{1}H NMR. In a relatively concentrated solution of the oligomer in d-DMSO (10 mg ml^{-1}), photolysis process was traced by following the reduction of the peak assigned to the protons of the α-methyl group in the benzylic position. During the photolysis, this peak disappeared and simultaneously, a new peak assigned for the same α-methyl group in the structure of the nitroso ketone appeared. A complete shift of this peak occurred in 4 hours, confirming the successful photocleavage (see Figure S3). Moreover, the red shift to 375 nm in the UV spectrum of the oligomer after 4 hours clearly proves the presence of a new nitroso ketone based compound (see Figure S4).

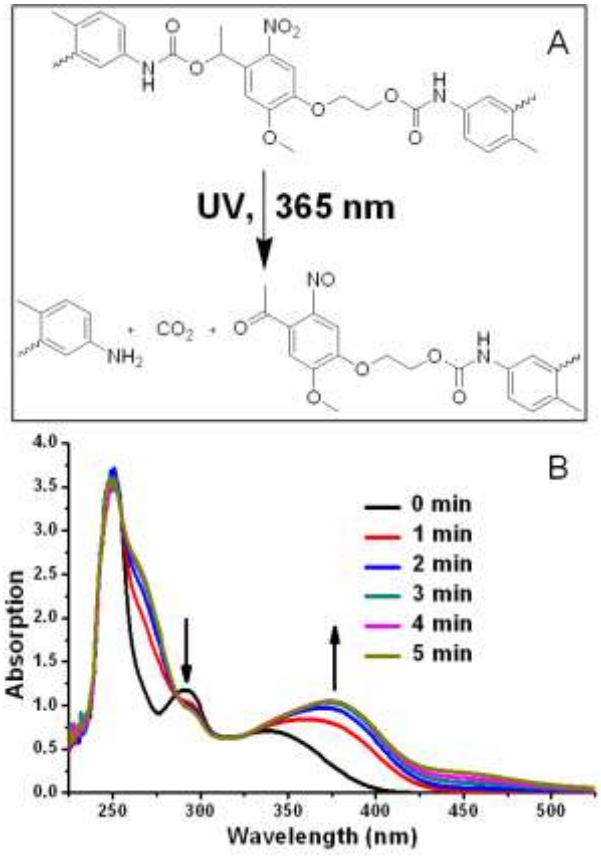


Figure 3. A) Photolysis of the NVOC-based diisocyanate oligomer. B) UV spectra of the NVOC-based diisocyanate oligomer in DMSO (1 mg mL^{-1}) after different UV irradiation times (0-5 min).

UV-triggered dye release studies from microcapsule. Having confirmed the photocleavage of the NVOC groups in the diisocyanate oligomer structure, we next tested if the dye release from the microcapsules could be triggered by means of UV-light. To evaluate this UV-triggered release of the oil soluble dye inside the microcapsules, the presence of an organic continuous phase was necessary to assess the diffusion of the dye in that phase. Therefore, hexane was added to the microcapsules and UV-irradiation was performed following three different experimental protocols. In the first experiment, *Release (1)*, the dye release was examined in hexane every single minute of UV-irradiation for 75 minutes in total. In the second experiment, *Release (2)*, microcapsules added to hexane were first exposed to UV-light for 20 min and then the dye release was monitored for 48 hours without applying further irradiation. In the last experiment, *Release (3)*, we investigated release from microcapsules, which were first exposed in their dried state to UV-light for 20 min and then dispersed in hexane in order to monitor the dye release for 48 hours, again without irradiating further the sample. In order to take into account the effect of other parameters such as potential dye leakage from solvation effects, control experiments were also performed for each experiment.

UV-irradiation of the samples was performed in a controlled way in the UV-box. The quartz cuvettes were placed horizontally under the UV-source at a certain distance. At this specific position, UV-intensity was measured to be 12 mW cm^{-2} and the temperature was recorded as 50°C. To take into account this temperature effect, control experiments were done by keeping

the samples in an oil bath at 50°C. Thus, the effect of temperature on the dye release during UV-irradiation was reflected to the control experiments.

***Release (1):* 75 min UV irradiation in hexane.** Microcapsules were dispersed in hexane inside a quartz cuvette and exposed to UV-light at 365 nm (12 mW cm^{-2}). Every 5 min, the absorption of the hexane solution was monitored via UV-VIS spectroscopy. Figure 4 shows that the absorption of the hexane solution increases as a result of dye release from microcapsules. Upon 75 min of UV irradiation, the absorption reached a steady state, so that the experiment was stopped and the microcapsules were manually ruptured in order to obtain the final absorption spectrum, further referred to as the 100 % release state.

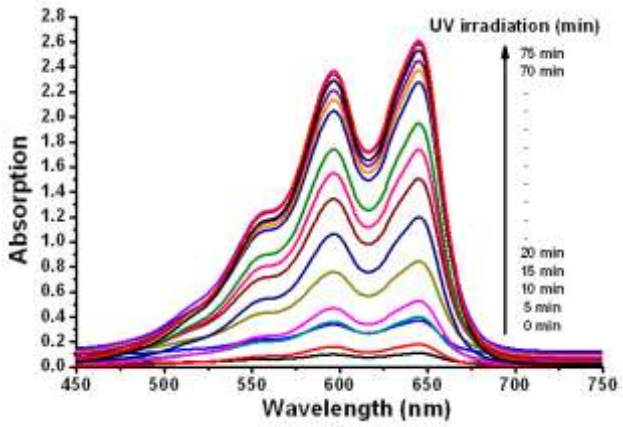


Figure 4. Release of the dye (solvent blue 35) from microcapsules in hexane solution during 75 min UV irradiation, monitored by changes in dye absorbance at 597 and 645 nm.

The absorption results are therefore presented as the percentage of the dye release relative to that final release upon manual rupture of the microcapsules. Figure 5 shows that the dye release increases exponentially for the first 50 min of UV irradiation. At this point, microcapsules have already released 70 % of the dye content. After 75 min of UV-irradiation, 80 % of dye release was observed. In contrast, a control experiment has shown less than 7 % of dye release. This exponential increase in the dye release profile could be related to the diffusion rate of the dye

solution. As more damage occurs on the microcapsule shell in time, the diffusion rate of the dye solution should increase. Moreover, the formation of the damage on the shell could be correlated with the microcapsule size distribution and the variations in the shell thickness.

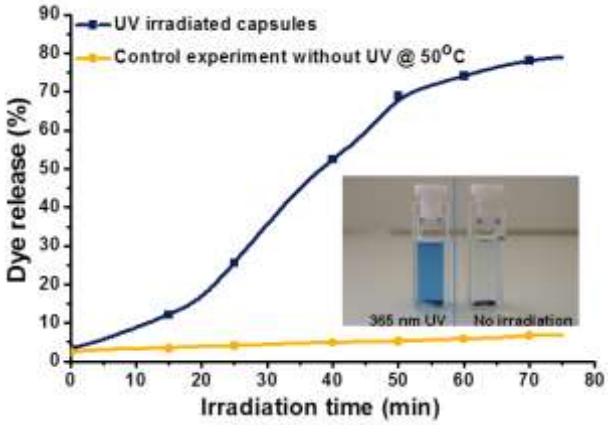


Figure 5. Release kinetics of dye (solvent blue 35) from microcapsules during 75 min UV irradiation.

***Release (2):* 20 min UV irradiation in hexane.** Once a crack occurs on the microcapsule, the release should start automatically and continue to some extent – limited by the diffusion rate – without requiring the complete collapse of the microcapsule. To assess this fact, microcapsules dispersed in hexane were subjected to 20 min to UV-irradiation, after which the dye release from microcapsules was monitored every 20 min for 48 hours via UV-spectroscopy. During this experiment, microcapsules were first placed in hexane inside a quartz cuvette and the absorption value of this dispersion was used as the reference value before UV-irradiation (time = 0) (see Figure S5). Subsequently, after 48 hours of online measurements, the microcapsules were ruptured manually and an absorption spectrum was recorded in order to calculate the percentage of dye release. Figure 6 shows the release kinetics during this experiment. In this graph, the zero value at time axis corresponds to the release percentages before UV irradiation and the first measurement after 20 min UV irradiation. Thus, 20 min UV-irradiation caused a burst release

from microcapsules and 17 % dye release was reached right after irradiation. As assumed, the dye release continued after UV-irradiation and reached up to 47 % in 15 hours. After this point, the dye release slowed down and 57 % of total dye release was finally observed after 48 hours. This result clearly shows that light causes rupture of the microcapsule surface, thereby simultaneously initiating the dye release. In the control experiment, the dye release was around 10 % after 48 hours (Figure 6).

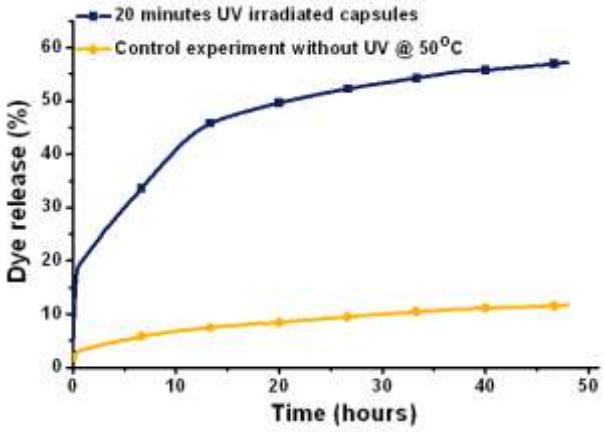


Figure 6. Release kinetics of dye (solvent blue 35) from microcapsules after 20 min UV-irradiation in hexane.

***Release (3):* 20 min UV irradiation in the solid state.** The photocleavage mechanism of *o*-nitrobenzyl groups involves a Norrish II type intra-molecular rearrangement. Since the reaction proceeds intramolecular, the photocleavage can occur both in solution and in the solid state.[41] In the microcapsule system, light-triggered cleavage in the solid state and consecutive release of the encapsulated material might be more advantageous for certain applications. Therefore, as the last release experiment, we explored the release kinetics from microcapsules after exposure to UV-irradiation in their solid state. During the experiment, microcapsules were spread inside the quartz cuvette and exposed to the UV-light (12 mW cm^{-2}) for 20 min. After UV-irradiation, hexane was added to the quartz cuvette and the absorption of the solution was monitored for 48

hours (see Figure S6). As in the previous cases, these absorption values were converted to the percentages to present the dye release kinetics. As shown in Figure 7, right after UV irradiation, around 12 % dye release was observed, which demonstrates that UV-light can also break the microcapsules in their solid state, thus without requiring any solvent based medium. However, due to the decreased mobility in the solid state, this cleavage was not as efficient as it was in solvent based environment. At the end of the 48 hours online measurements, only 35 % of dye release was observed from the microcapsules. On the other hand, the dye release in the control experiment was around 10 % after 48 hours (Figure 7).

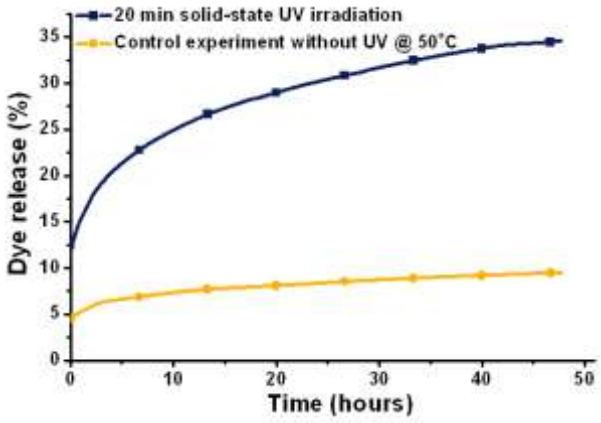


Figure 7. Release kinetics of dye (solvent blue 35) from microcapsules after 20 min UV-irradiation in the solid state.

TGA analysis and stability of the microcapsules. The volatile core content (chlorobenzene) percentage in the microcapsules is estimated as 60 % via TGA analysis. However, after storing the capsules for one month in a dark environment, the core solvent content dropped around 10 %, showing that chlorobenzene diffuses slowly through the capsule shell (Figure 8). The effect of this weight loss in the core solvent was also observed in the dye release experiments. After one month of synthesis, a dye release experiment was repeated. The microcapsules were subjected to UV-light for 20 min in hexane and their dye release was monitored for 48 hours. It was observed

that the initial dye release percentage, prior to UV irradiation, increased around 5 %, clarifying that the dye solution diffused through to the capsule shell and easily released when immersed to a solvent. In parallel with this increase in the initial dye release percentage, a 5 % increase was measured in the control experiment after 48 hours. On the other hand, these dye release experiments proved that microcapsules were still UV-sensitive and released their content upon UV-irradiation (Figure 9).

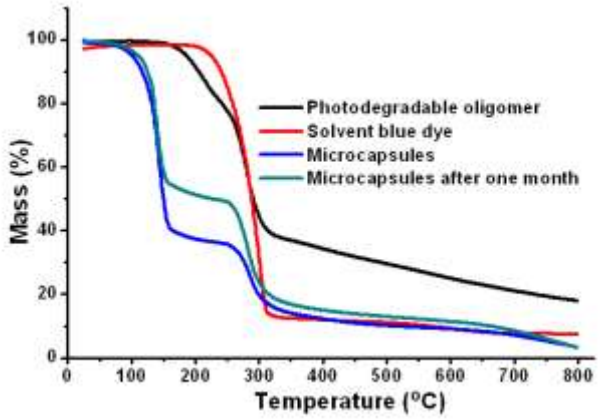


Figure 8. TGA of microcapsules, photodegradable oligomer and dye (solvent blue 35).

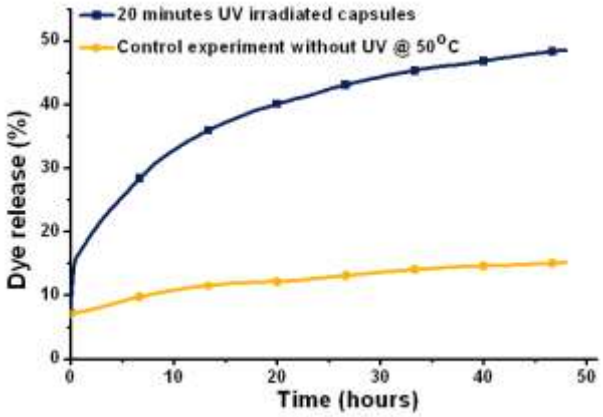


Figure 9. Release kinetics of solvent blue dye from microcapsules after one month of synthesis upon 20 min UV-irradiation in hexane.

CONCLUSIONS

We have reported a straightforward route for the preparation of microcapsules with photocleavable solid shells. A polyurethane oligomer bearing photo-labile NVOC moieties and isocyanate end groups was prepared as a photocleavable precursor and subsequently utilized in the interfacial polymerization technique for the synthesis of polyurea microcapsules. In this way, polyurea microcapsules consisting of a photocleavable shell with a hydrophobic liquid core were successfully produced as free-flowing solids. UV-triggered rupture of the capsule shells and simultaneous controlled release of the encapsulated liquid core were presented. It was also shown that UV-triggered release from microcapsules could not only be performed in solution but also in their solid state due to an intra-molecular photocleavage mechanism. In long term, microcapsules were permeable to some extent to the encapsulated volatile core solvent. Optimization of the interfacial polymerization process (increase of shell thickness) would further improve the long-term stability. Although less dangerous, long-wave UV light (365 nm) has been used as photo-trigger, it could also be interesting to study the light-triggered release with NIR light since the NVOC groups are both UV and NIR light sensitive.

ASSOCIATED CONTENT

Supporting Information Dynamic size distributions of microcapsules, UV spectra of the NVOC-based diisocyanate oligomer after different UV irradiation times (0-60 min), ^{1}H NMR spectrum of NVOC-based diisocyanate oligomer before and after 4 hours of UV-irradiation, UV spectrum of the NVOC-based diisocyanate oligomer after 4 hours of UV irradiation, absorption spectra showing the release of the dye (solvent blue 35) from microcapsules in hexane solution. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* E-mail: filip.duprez@ugent.be

Present Addresses

†Université de Lyon, Univ. Lyon 1, CPE Lyon, CNRS UMR 5265, Laboratoire de Chimie, Catalyse, Polymères et Procédés (C2P2), LCPP team, 43 Bd du 11 Novembre 1918, F-69616, Villeurbanne, France

ACKNOWLEDGMENT

T.D. and F.D.P. acknowledge the Belgian Program on Interuniversity Attraction Poles initiated by the Belgian State, Prime Minister's office (Program P7/05) for financial support. T.D thanks UGent for a PhD scholarship. C.A.L.C thanks the Strategic Initiative Materials (SIM) project by the Agency for Innovation through Science and Technology (IWT) for a postdoctoral fellowship. The authors thank Prof. Annemie Adriaens and Michel De Keersmaecker for their kind assistance with SEM characterization of the microcapsules.

REFERENCES

1. A. P. R. Johnston, G. K. Such and F. Caruso, *Angew. Chem. Int. Ed.*, 2010, **49**, 2664-2666.
2. A. P. Esser-Kahn, S. A. Odom, N. R. Sottos, S. R. White and J. S. Moore, *Macromolecules*, 2011, **44**, 5539-5553.
3. H. N. Yow and A. F. Routh, *Soft Matter*, 2006, **2**, 940-949.
4. D. Lensen, D. M. Vriezema and J. C. M. van Hest, *Macromol. Biosci.*, 2008, **8**, 991-1005.
5. K. E. Broaders, S. J. Pastine, S. Grandhe and J. M. J. Frechet, *Chem. Commun.*, 2011, **47**, 665-667.
6. A. L. Becker, A. N. Zelikin, A. P. R. Johnston and F. Caruso, *Langmuir*, 2009, **25**, 14079-14085.
7. S. De Koker, R. Hoogenboom and B. G. De Geest, *Chem. Soc. Rev.*, 2012, **41**, 2867-2884.
8. A. P. Esser-Kahn, N. R. Sottos, S. R. White and J. S. Moore, *J. Am. Chem. Soc.*, 2010, **132**, 10266-10268.

9. M. F. Bedard, B. G. De Geest, A. G. Skirtach, H. Moehwald and G. B. Sukhorukov, *Adv. Colloid Interface Sci.*, **158**, 2-14.
10. A. S. Angelatos, B. Radt and F. Caruso, *J. Phys. Chem. B*, 2005, **109**, 3071-3076.
11. B. Radt, T. A. Smith and F. Caruso, *Adv. Mater.*, 2004, **16**, 2184-2189.
12. A. G. Skirtach, A. A. Antipov, D. G. Shchukin and G. B. Sukhorukov, *Langmuir*, 2004, **20**, 6988-6992.
13. S. J. Pastine, D. Okawa, A. Zettl and J. M. J. Frechet, *J. Am. Chem. Soc.*, 2009, **131**, 13586-13587.
14. W. G. Fisher, W. P. Partridge, C. Dees and E. A. Wachter, *Photochem. Photobiol.*, 1997, **66**, 141-155.
15. K. Katagiri, K. Koumoto, S. Iseya, M. Sakai, A. Matsuda and F. Caruso, *Chem. Mat.*, 2009, **21**, 195-197.
16. X. Tao, J. B. Li and H. Mohwald, *Chem. Eur. J.*, 2004, **10**, 3397-3403.
17. E.-M. Rosenbauer, M. Wagner, A. Musyanovych and K. Landfester, *Macromolecules*, 2010, **43**, 5083-5093.
18. C. G. Bochet, *J. Chem. Soc., Perkin Trans. 1*, 2002, 125-142.
19. A. M. Kloxin, A. M. Kasko, C. N. Salinas and K. S. Anseth, *Science*, 2009, **324**, 59-63.
20. K. Peng, I. Tomatsu, B. van den Broek, C. Cui, A. V. Korobko, J. van Noort, A. H. Meijer, H. P. Spaink and A. Kros, *Soft Matter*, 2011, **7**, 4881-4887.
21. D. Klinger and K. Landfester, *Soft Matter*, 2011, **7**, 1426-1440.
22. M. Kang and B. Moon, *Macromolecules*, 2009, **42**, 455-458.
23. E. Cabane, V. Malinova and W. Meier, *Macromol. Chem. Phys.*, 2010, **211**, 1847-1856.
24. J.-M. Schumers, J.-F. Gohy and C.-A. Fustin, *Polym. Chem.*, 2010, **1**, 161-163.
25. H. Zhao, W. Gu, E. Sterner, T. P. Russell, E. B. Coughlin and P. Theato, *Macromolecules*, 2011, **44**, 6433-6440.
26. D. Han, X. Tong and Y. Zhao, *Macromolecules*, 2011, **44**, 437-439.
27. G. Delaittre, T. Pauloehrl, M. Bastmeyer and C. Barner-Kowollik, *Macromolecules*, 2012, **45**, 1792-1802.
28. T. Pauloehrl, G. Delaittre, M. Bastmeyer and C. Barner-Kowollik, *Polym. Chem.*, 2012, **3**, 1740-1749.
29. A. Patchornik, B. Amit and R. B. Woodward, *J. Am. Chem. Soc.*, 1970, **92**, 6333-6335.
30. I. Aujard, C. Benbrahim, M. Gouget, O. Ruel, J.-B. Baudin, P. Neveu and L. Jullien, *Chem. Eur. J.*, 2006, **12**, 6865-6879.
31. N. Fomina, C. McFearin, M. Sermsakdi, O. Edigin and A. Almutairi, *J. Am. Chem. Soc.*, 2010, **132**, 9540-9542.
32. J. Yang, M. W. Keller, J. S. Moore, S. R. White and N. R. Sottos, *Macromolecules*, 2008, **41**, 9650-9655.
33. M. Huang and J. Yang, *J. Mater. Chem.*, 2011, **21**, 11123-11130.
34. C. P. Holmes, *J. Org. Chem.*, 1997, **62**, 2370-2380.
35. J. Li, A. P. Hitchcock, H. D. H. Stoever and I. Shirley, *Macromolecules*, 2009, **42**, 2428-2432.
36. M. E. Bailey, *J. Chem. Educ.*, 1971, **48**, 809-813.
37. J. Li, M. A. J. Mazumder, H. D. H. Stoever, A. P. Hitchcock and I. M. Shirley, *J. Polym. Sci., Part A: Polym. Chem.*, 2011, **49**, 3038-3047.
38. M. Alvarez, A. Best, S. Pradhan-Kadam, K. Koynov, U. Jonas and M. Kreiter, *Adv. Mater.*, 2008, **20**, 4563-4567.

39. J. Ottl, D. Gabriel and G. Marriott, *Bioconjugate Chem.*, 1998, **9**, 143-151.
40. M. A. Kostiainen, D. K. Smith and O. Ikkala, *Angew. Chem. Int. Ed.*, 2007, **46**, 7600-7604.
41. E. Reichmanis, B. C. Smith and R. Gooden, *J. Polym. Sci., Part A: Polym. Chem.*, 1985, **23**, 1-8.

For Table of Contents use only:

Polyurea microcapsules with photocleavable shell: UV-triggered release

Tugba Dispinar, Catheline A. L. Colard and Filip E. Du Prez

Polyurea microcapsules loaded with a hydrophobic dye liquid core and consisting of a photocleavable shell have been prepared via interfacial polymerization.