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Native and Functionalized Micrometre-sized Cellulose Capsules Prepared by Microfluidic Flow Focusing

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Christopher Carrick,[a] Per A. Larsson,[a] Hjalmar Brismar,[b] Cyrus Aidun[c] and Lars Wågberg[a,d]

[a] KTH Royal Institute of Technology, School of Chemical Science and Engineering, Department of Fibre and Polymer Technology, , SE-100 44 Stockholm, Sweden.
[b] KTH Royal Institute of Technology, School of Engineering Sciences, Department of Applied Physics, Sci Life Lab, S-10691 Stockholm, Sweden.
[c] Georgia Inst Technol, GW Woodruff Sch Mech Engn, Atlanta, GA 30332 USA.
[d] KTH Royal Institute of Technology, School of Chemical Science and Engineering, Wallenberg Wood Science Centre, WWSC, , SE-100 44 Stockholm, Sweden.

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Cellulose capsules with average outer and inner radii of approximately 44 µm and 29 µm respectively were prepared from cellulose dissolved in a mixture of lithium chloride and dimethylacetamide using a microfluidic flow focusing device (MFFD). The MFFD had three inlets where octane oil in a cellulose solution in silicone oil was used to produce a double emulsion containing a cellulose capsule. This technique enables the formation of capsules with a narrow size distribution which can be beneficial for drug delivery or controlled release capsules. In this respect, cellulose is a highly interesting material since it is known to cause no autoimmune reactions when used in contact with human tissue. Furthermore, by controlling the chemical properties of the cellulose, it is possible to trigger a swelling of the capsules and consequentially the release of an encapsulated substance, e.g. a model drug, when the capsule becomes exposed to an external stimulus. To demonstrate this, capsules were functionalized by carboxymethylation to be pH-responsive and to expand approximately 10% when subjected to a change in pH from 3 to 10. The diffusion constant of a model drug, a 4 kDa fluorescently labelled dextran, through the native capsule wall was estimated to be $6.5 \cdot 10^{-14}$ m^2/s by fitting fluorescence intensity data to Fick's second law.

Key words: Cellulose, Cellulose capsules, Extended release, Microfluidics, MFFD, pH responsive.

Introduction

A general microcapsule emulsification technique involves the mixing of oil and water by mechanically shearing the system so that a polydisperse mixture of droplets is formed. This, droplet formation has been intensively studied during the last decade since it enables the controlled delivery of drugs, and contrast agents for ultra sound imaging and diagnostic purposes.[1] These microcapsules have been made from a variety of different materials depending on the required functionalities such as biocompatibility, pH and salt concentration responses. There are several benefits in using native cellulose capsules in, for example, medical applications, since cellulose possesses features such as excellent biocompatibility with human tissue,[2] and high durability in vivo.[3] This has led to a large interest in cellulose-based biomedical in vivo applications.[4] Furthermore, the absence of immunostimulatory reactions and the lack of enzymatic in vivo degradation of cellulose means that cellulose has an excellent potential for use in pharmaceuticals, e.g. as a drug delivery matrix.[5] Nowadays, medical delivery systems are usually based on microcrystalline cellulose (MCC) or carboxymethylated cellulose (CMC), as a dispersion agents in drug and food applications.[6] Furthermore, bacterial cellulose has shown promising features in wound-care treatments[7] and as artificial blood vessels.[8]

Cellulose consists of D-glucose building blocks, forming a linear and stiff homopolymer chain, and has characteristics such as hydrophilicity, chirality and biodegradability and is readily available for chemical modification.[2] Therefore, an interesting route is to encapsulate an active substance in a

cellulose capsule and to chemically modify the cellulose to render it stimuli responsive and so that the formed capsule could ultimately target or adhere specifically to an infected/affected area and there release an encapsulated drug or to be used for diagnostic purposes.

Recently, a new technique has been described for the preparation of millimetre-sized capsules from pure cellulose for controlled release i.e. capsules for use in medical applications, but these capsules are too large for example for controlled release applications and new techniques for their preparation are therefore needed. In this respect, microfluidics[9, 10] is an interesting route for capsule preparation. Microfluidic technology has been intensely investigated during recent years mainly because it is a highly controllable system, and a variety of applications have been developed.[11, 12] There are two main branches within microfluidics: T-junction systems[11, 13, 14] and microfluidic flow focus devices (MFFDs).[15-18] The most frequently used is the T-junction system, which is based on micro-channels of polydimethylsiloxane (PDMS). They usually have two fluid inlets where a droplet is pinched off at the intersection of the two inlet channels. These PDMS channels can be custom-built to fit numerous kinds of liquid flow geometry. The other microfluidic system, MFFD, is constructed from capillary glass tubes placed inside square glass tubes that are aligned to create a symmetric junction where up to three different fluids are injected into a collection tube. To create double emulsions and to be able to form capsules, three separate fluid inlets are needed. Since the main objective with our work was to prepare cellulose capsules with a narrow size distribution, the MFFD was the only technique that was considered.

When one liquid is injected into another immiscible liquid, there is a break-up into drops.[19-21] In a MFFD, this liquid break-up can be either close to the orifice or further down in the collection tube. If the break-up is close to the orifice, which is usually the case at low velocities, a high degree of emulsion monodispersity is achieved.[16] At faster flow rates, a jet is formed that breaks up further downstream from the orifice due to Rayleigh-Plateau instability.[22, 23] Consequently, depending on where the droplet pinches off, the system is said to be in either the dripping or the jetting regime. The mechanism of drop formation is also affected by parameters such as device geometry, viscosity, surface tension, density and flow rate of the immiscible fluids.[15] Several interesting materials have recently been developed using microfluidics, for example thermo-responsive poly(N-isopropylacrylamide) (PNIPAAm) spheres,[24] and capsules for the controlled release of encapsulated drugs,[25] cosmetics[26] and pesticides.[27] However, to the best of our knowledge, microfluidics have never earlier been used to create capsules based on native cellulose, the most abundant and renewable polymer on Earth.[28, 29] This might be explained by the insolubility of native cellulose in most common solvents and its high molecular weight, which, when dissolved, results in highly viscous solutions already at about 1.5 wt% of cellulose.[30]

In this paper, we present a method for producing capsules from unmodified high-molecular-weight cellulose, dissolved in a mixture of lithium chloride and dimethylacetamide (LiCl-DMAc). We have also investigated the release behaviour of an encapsulated model drug, a 4 kDa dextran, and have estimated its diffusion constant through the cellulose shell by fitting the experimental data to Fick's second law. Furthermore, we have prepared capsules from functionalized cellulose fibres with a higher charge density, introduced by carboxymethylation, to introduce responsiveness mediated as a change in capsule size due to a change in osmotic pressure[31-33] following a change in pH or ion concentration.

Theoretical considerations

Fluid dynamics in microfluidics

Droplet formation in a MFFD takes place, as mentioned above, due to a Rayleigh-Plateau hydrodynamic instability under the action of interfacial tension. This results in an unstable jet that breaks down into smaller segments that acquire a spherical shape due to surface area minimization.[34] Two dimensionless parameters can be used to describe the formation of droplets from a horizontal flowing jet: the Reynolds number, Re, and the capillary number, Ca;

$$\mathrm{Re} = \frac{\rho v l}{\eta} \qquad [1]$$

$$\mathrm{Ca} = \frac{\eta v}{\sigma} \qquad [2]$$

where ρ, v, η, l, and σ are the density, mean velocity, viscosity, characteristic length of the fluid (the jet diameter) and interfacial tension respectively.[34] To pinch off a droplet, the inertial force on the droplet must overcome the surface tension forces. At low capillary numbers, i.e. at low viscous drag, the Weber number, We which describes the balance between inertial and surface tension become increasingly important in describing the droplet formation:

$$\mathrm{We} = \frac{\rho v^2 l}{\sigma} = \mathrm{Re} \times \mathrm{Ca} \qquad [3]$$

Fickian diffusion through the capsule wall

It is well established that Fick's 2nd law of diffusion can be used to estimate the diffusion constant of a molecule due to a concentration gradient:

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial r^2} \qquad [4]$$

where t, c and r are the time, concentration of encapsulated fluorescent dextran and the radius of the sphere respectively. An analytical solution, [5], describing the total amount diffusing from a spherical object was derived by Crank[35] [5] under the assumption that the system has a uniform initial concentration, C1, and that the surface concentration is maintained constant at C0 throughout the experiments.

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp\left(-\frac{Dn^2\pi^2 t}{r^2}\right) \qquad [5]$$

where M_t is the amount that has diffused after time t, M_∞ is the amount that has diffused after equilibrium. Equation [5] assumes a solid sphere, but Kräger et al.[36] have shown that

Equation 5 can be used for a capsule by rescaling the capsule into a solid sphere with the same volume-to-surface-area ratio.

Experimental

Material

Dissolving pulp (Domsjö Dissolving Plus), containing 93% cellulose and having a degree of polymerization of about 780, was provided by Aditya Birla Domsjö Fabriker AB, Sweden. N,N-dimethylacetamide, lithium chloride, isopropanol, octane, polydimethylsiloxane, 1-chloro-acetic acid, monopotassium phosphate and fluorescein-isothiocyanate (FITC)-labelled dextran with a molecular weight of 4 kDa were all purchased from Sigma-Aldrich and were used as received without further purification.

Preparation of cellulose solutions

The cellulose was dissolved in a mixture of 5 wt% LiCl in DMAC according to an earlier described protocol.[37] Before adding cellulose to the solvent mixture, which is highly hygroscopic, the solvent was heated to 105 °C for 30 min to completely remove traces of water. If water is still present in the solvent, it hinders the dissolution of cellulose[38] and promotes the formation of polymer aggregates.[39] Different amounts of oven-dried fibres were added to reach different cellulose concentrations, using a total final volume of 100 mL. The solution was then re-heated to approximately 80 °C to further remove traces of water (emanating from the hygroscopic cellulose) and to promote the dissolution of the cellulose.

Preparation of carboxymethylated cellulose fibres

According to a method earlier described by Wågberg et al.[40], fibres were carboxymethylated with 1-chloro-acetic acid to a total charge density of 350 µmol charges/g fibres (µeq./g) as measured by conductometric titration[41]. The reference fibres had a total charge density of 29 µeq./g, mainly due to residual traces of charged hemicelluloses.

Methods

Pendant drop

The interfacial energy between the continuous silicone oil and the dissolved cellulose was measured by a pendant drop experiment,[42] where a drop of silicone oil was injected into the cellulose solution and the curvature of the droplet was measured and the interfacial tension was calculated using the Young-Laplace equation.

Viscosity

The viscosity of the cellulose solution was determined by a "Brookfield DV-II + Pro" viscometer for the 0.5 wt%, 0.7 wt% and 1 wt% cellulose solutions at 20 °C using a concentric cylinder set-up (Spindle S-18) at low shear rates.

Preparation of cellulose capsules using microfluidics

Cellulose capsules were prepared with a MFFD schematically described in Figure 1.[16] The device was constructed from cylindrical and square glass capillary tubes where three fluids were injected through tapered channels and the immiscible fluids were pinched off as droplets, forming octane-filled cellulose droplets. As shown in Figure 1, the interfacial zone in the MFFD consisted of two cylindrical tubes placed in a larger square tube, where the left-hand inner tube was the inlet for the inner fluid (octane) with viscosity of 0.54 mPa·s and the second tube acted as a collection tube and outlet for the droplets which was formed. The other two inlets, i.e. for the middle and continuous fluids (cellulose and silicone oil) with viscosities of 40 and 101 mPa·s, were formed by placing the two cylindrical tubes inside the square tube as shown in Figure 1. The fluids were injected into the MFFD using syringe pumps with Teflon tubing connecting the inlets and syringes, at flow rates of 10, 60 and 2000 µl/hr for the inner oil, the middle cellulose solution and the continuous oil respectively. The middle fluid, i.e. the cellulose solution, consequently focused the inner octane oil, creating a thread of oil in cellulose. This thread of oil was then focused into the collection tube by the continuous silicone oil. Initially, in the collection tube, there was a thread of oil inside a thread of cellulose which, as a result of hydrodynamic instability, was then broken up to form a double emulsion of oil in cellulose solution in oil. This process was monitored by a Phantom V 5.0 high speed camera.

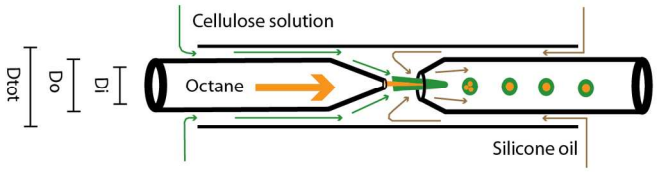

Figure 1. Schematic description of the used MFFD, showing inlet locations, fluids and flow directions of the three fluids. The capillary tube inner diameter, outer diameter and total inner width of the microfluidic flow focusing device was Di = 580 µm, Do = 1000 µm and Dtot = 1050 µm respectively.

Conversion into solid capsules

The dissolved cellulose capsules were regenerated/precipitated by the removal of the cellulose solvent (LiCl-DMAc) through an addition of isopropanol creating a gel-like capsule consisting of cellulose in isopropanol (Figure 2). The isopropanol was injected into the microfluidic channels after the double emulsion preparation step and, as the isopropanol diffused into contact with the cellulose solution, the cellulose was immediately regenerated creating a gel-like cellulose capsule around the octane phase. The capsules were then carefully solvent-exchanged into water by the addition of acetone and water for at least three days for each solvent. The water-containing capsules were then used for further experiments or freeze-dried through liquid nitrogen cooling and sublimation in a Coolsafe™ freeze dryer operating at -98 °C and a pressure below 0.06 Pa.

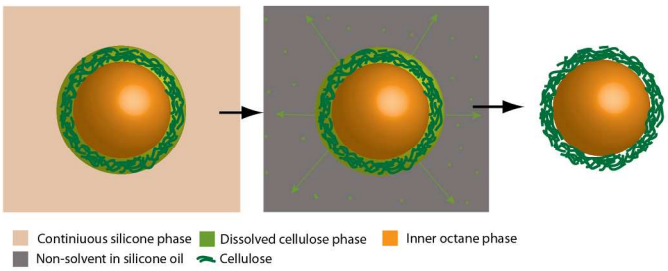

Figure 2. Schematic illustration of the formation of a regenerated cellulose capsule from the double emulsion. The non-solvent in the present experiment was isopropanol.

Determination of diffusion across the capsule wall

To study the amount of substance permeating from a capsule loaded with a model drug, a 4 kDa dextran was used. The capsules were loaded by incubation in a phosphate buffer at pH 7.4 containing 15 mg/ml FITC-labelled dextran. Approximately 30 cellulose capsules (20 µl) were then transferred to a Petri dish followed by the addition of 5 ml of FITC-free phosphate buffer. The intensity of the fluorescent dye inside five different capsules was then continuously observed with a LSM 510 Meta confocal laser-scanning microscope until equilibrium was reached.

To estimate the diffusion constant of the dextran diffusing through the cellulose capsules, an analytical solution [5] of Fick's second law [4], earlier derived by Crank,[43] was fitted to the experimental data after rescaling the radii of the cellulose capsules to solid spheres of the same surface-area-to-mass ratio as the hollow capsules.[36] The fit was performed using a Matlab routine which finds the best least squares approximation for the diffusion constant, D. For computational reasons, only the first ten terms of the summation in [5] were considered.

Determination of the influence of pH on capsule swelling

Swelling experiments were performed at pH levels of 3, 7.4, 10 and 12. The pH was monitored by a pH meter and regulated by the addition of HCl or NaOH at a 10 mM background concentration of NaCl. After at least 24 hours at the desired pH, the inner and outer diameters of at least ten capsules were measured by light microscopy. After each pH, the spheres were carefully washed for at least five days prior to the next pH experiment.

Results

Cellulose capsules prepared with aid of MFFD

The rate of formation of the inner oil droplets was higher than the rate of cellulose droplet formation; at least three octane droplets were captured inside each cellulose droplet. These three or more droplets of octane later coalesced and formed a single larger octane droplet inside the cellulose shell. At a distance of approximately 1 mm into the collection tube, the thread of cellulose solution broke into spheres with encapsulated octane drops (Figure 3). The rate of production of cellulose droplets was approximately 40 s^{-1}.

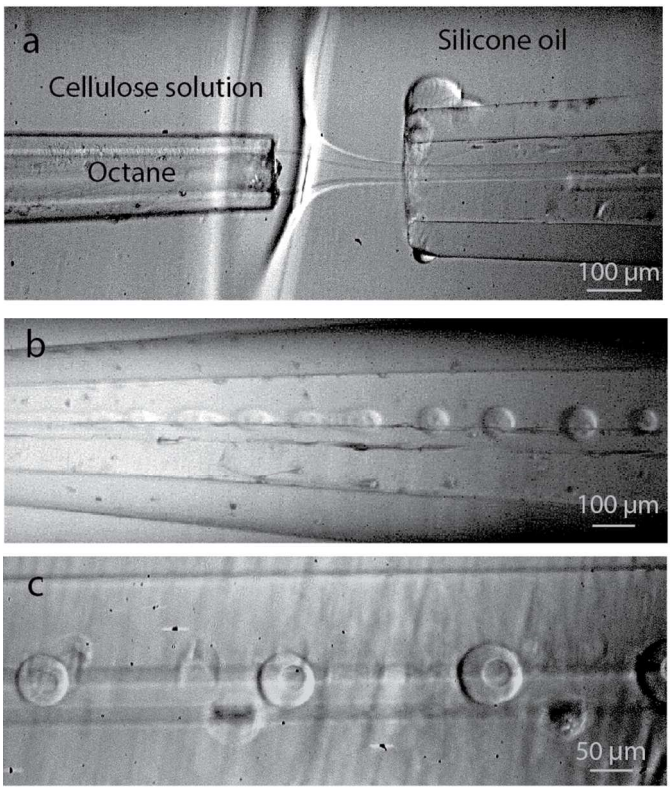

Figure 3. Photomicrographs from a MFFD experiment with octane, cellulose and silicone oil. (a) The inner liquid (octane) is injected from the tapered cylinder on the left (diameter ≈ 50 µm) and is focused by the middle fluid (a 0.7 wt% cellulose solution) entering from the left in the outer square tube. (b) These two fluids (a) are focused into the inner tapered tube on the right (diameter ≈ 150 µm), i.e. the collection tube, by the continuous fluid (silicone oil) entering from the right in the square outer tube.(c) Magnification of a part of the collection tube seen in (b).

The length of the thread in the collection tube could be controlled by the flow rate of the middle fluid; the higher the rate, the longer the thread. The flow rate of the middle fluid was therefore optimized (60 µl/h) so that the break-up of the middle fluid occurred approximately 1 mm down-stream in the collection tube (Figure 3b). Photomicrographs of the regenerated cellulose capsules in isopropanol are shown in Figure 4. For freeze-drying, the capsule wall requires a certain mechanical integrity not to collapse. This is also demonstrated in Figure 5 where representative cellulose capsules prepared from 0.5 and 0.7 wt% cellulose solutions are shown and, as clearly can be seen, the capsule prepared from the lower concentration is collapsed. The higher cellulose concentration evidently allowed for a solvent exchange of the inner oil to water, and freeze drying without collapse.

The outer radius of the intact cellulose capsules, i.e. those prepared from 0.7 wt% cellulose solution was in the range of 32–62 µm, with an average outer radius of 44 µm, and the inner radius was in the range of 21–41 µm, with an average inner radius of 29 µm (Figure 6).

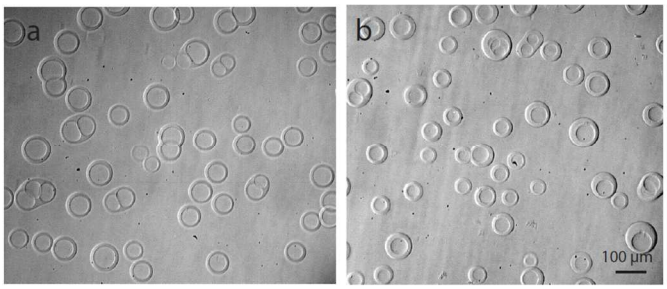

Figure 4. Photomicrographs of the MFFD-prepared cellulose capsules after the addition of isopropanol; (a) capsules prepared from 0.5 wt% cellulose concentration, (b) cellulose capsules prepared from 0.7 wt% cellulose solution.

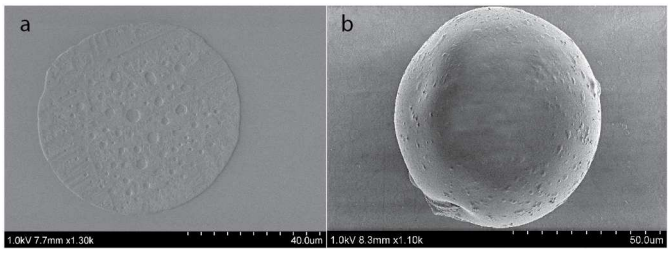

Figure 5.SEM micrographs of (a) a collapsed cellulose capsule prepared from a 0.5 wt% cellulose solution, (b) an intact cellulose capsule prepared from a 0.7 wt% cellulose solution. The cellulose capsule on the left collapsed since the low cellulose concentration in the capsule did not support the spherical geometry, shown in Figure 4, throughout the freeze drying process whereas the capsule prepared at the higher concentration remained intact.

In the case of the capsules that could be dried without collapsing, i.e. at 0.7 wt% cellulose, the values of Re [1] and Ca [2] were $1.3 \cdot 10^{-2}$ and 0.6 respectively for the cellulose solution phase and $4.5 \cdot 10^{-2}$ and 3.2 respectively for the continuous silicone oil phase. When the cellulose concentration was increased from 0.7% to 1%, i.e. when the viscosity of the cellulose solution phase was increased from 40 mPa·s to 156 mPa·s, which corresponds to Re and Ca numbers of $3.4 \cdot 10^{-3}$ and 2.4, no droplet formation was observed within a reasonable distance from the exit of the tube. Furthermore, the Weber number of the cellulose solution [3], describing the ratio of inertial forces to surface forces, was $8.0 \cdot 10^{-3}$ for droplet formation with a cellulose viscosity of 40 mPa·s.

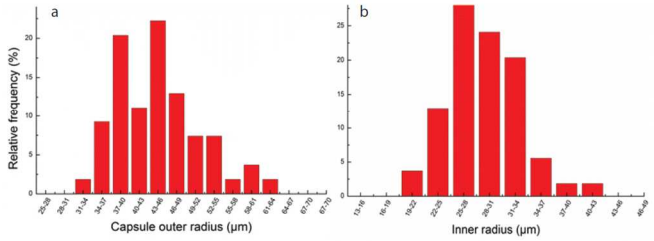

Figure 6. Distribution of (a) outer, and (b) inner radius of intact capsules prepared from a 0.7% cellulose solution.

Release of encapsulated dextran and determination of its diffusion constant

Dried capsules were loaded with FITC-labelled dextran (4 kDa). Figure 7 shows the release as a function of time when capsules were placed in a 0.01 M phosphate buffer at pH 7.4. The solid circles represent experimental data and the dashed line the best fit of Equation 5 to the experimental data, estimating the diffusion constant to be $6.5 \cdot 10^{-14}$ m^2/s. As can be seen, it took approximately two hours for the dextran to be released from the cellulose capsules and to reach equilibrium with the surrounding solution.

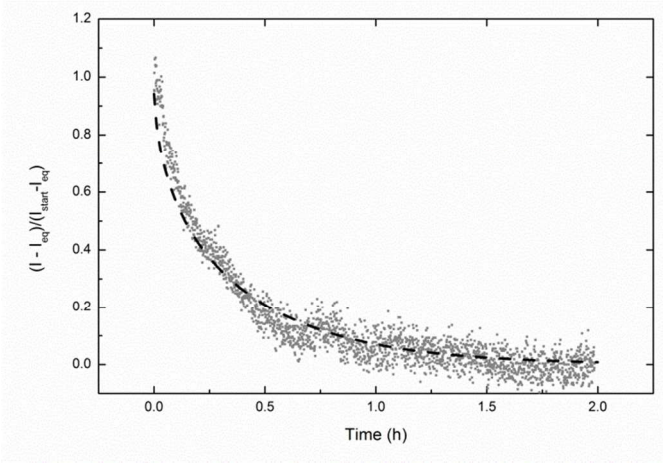

Figure 7. Normalized intensity of 4 kDa FITC-labelled dextran, in the centre of a capsule, as a function of time when placed in 0.01 M phosphate buffer at pH 7.4. Closed circles represent experimental data and the dashed line represents the intensity calculated according to eq. 5 using the diffusion constant ($D=6.5 \cdot 10^{-14}$ m^2/s) to best fit the experimental data.

pH-responsive carboxymethylated cellulose capsules

Since regenerated cellulose capsules in the wet state showed a gel-like behaviour, it was considered interesting to investigate the influence of pH on capsule size. In Figure 8, the effect of pH on swelling is shown for capsules made from untreated cellulose, having a charge density of 29 µeq./g, and from carboxymethylated cellulose with a charge density of 350 µeq./g. The relative wall volume of capsules made from modified cellulose increased when the solution pH was increased from pH 3 to pH 10, i.e. a volume change driven by the deprotonation of carboxyl groups and the thereby introduced an osmotic pressure within the capsule wall. The capsules made from untreated cellulose with low amounts of carboxyl groups showed, as expected no significant pH-dependence. When the pH was further increased to pH 12, the wall volume decreased, as an effect of the high counter ion concentration, to approximately the same level as at pH 3, as could be expected from earlier results and theoretical estimates.[31]

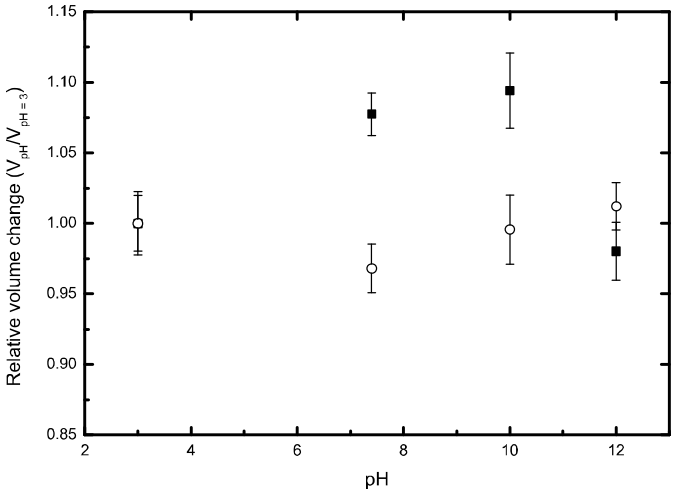

Figure 8. Relative capsule volume as a function of pH for capsules prepared from carboxymethylated cellulose pulp (solid squares) and native cellulose capsules (open circles). Error bars indicate 95% confidence limits.

Discussion

Using a MFFD, cellulose capsules were prepared with outer and inner radii ranging from 32–62 µm and 21–41 µm, respectively. The size distribution was narrow compared to the results of many other types of emulsification technique.[44, 45] It is suggested that the droplet formation took place too far down the collection tube to produce capsules with a narrow size distribution and by decreasing the jet length, a situation known to produce more monodisperse microspheres[16] it would most probably be possible to produce capsules with a more narrow size distribution. In order to decrease the jet length, the capillary number should typically be below 0.2.[46] This can be achieved either by lowering the viscosity or by decreasing the flow velocity of the cellulose phase. However, when the cellulose concentration in the current system was 0.5 wt%, i.e, with a viscosity of 15.5 mPa·s instead of 40 mPa·s, the capsules collapsed during the freeze-drying process (Figure 5), probably due to the poor mechanical strength of the cellulose capsule wall. An alternative way to reduce the flow velocity is to change the device geometry or decrease the flow rates of the fluids. This approach was attempted, but no significant improvement in monodispersity was achieved. As clearly shown here, cellulose capsules can nevertheless be prepared by MFFD to create a double emulsion of oil and dissolved cellulose that later can be precipitated to produce non-collapsed cellulose capsules. However, additional work is needed to fully optimize the properties of the fabricated capsules.

The dimensionless numbers, Re, Ca and We are of great importance for the design of the MFFD, and cellulose capsule formation can presumably be achieved as long as the previously reported dimensionless numbers are the same or similar to the numbers used in this study. If these numbers are kept constant one could in theory change the geometry of the MFFD, and consequently the size of the fabricated capsules to any desirable size.

The capsules that could withstand the solvent exchange are expected to be stable over time since cellulose is chemically stable and has a low solubility in most solvents. For the preservation of non-collapsed capsules we believe that the critical step is when the continuous phase is exchanged into water. This since the cellulose capsule-wall structure formed at low cellulose concentration could not withstand the osmotic swelling-forces during water uptake when exchanging the continuous phase into water. The expansion and increased water pressure inside the capsule resulted in frequent capsule failure. This phenomenon was qualitatively observed by microscope as sudden and rapid propulsions of capsules, indicating a rapid and local release of the interior fluid.

The cellulose capsules could be loaded with drugs and be used for extended release. Using a model drug, 4 kDa dextran molecules, the release was monitored over approximately two hours and the diffusion constant over the cellulose wall was calculated to be $6.5 \cdot 10^{-14}$ m^2/s. This value can be compared with the diffusion of dextran in a cellulose fibre wall, $8.4 \cdot 10^{-12}$ m^2/s for a 10 kDa polymer.[47] The diffusion of the slightly shorter dextran molecule used in our system is thus approximately two orders of magnitude slower than that the previously reported for wood fibres. This indicates that the capsule wall structure is less porous and consequently a better encapsulation material.

Capsules were also functionalized by chemical modification by incorporating carboxymethyl groups on the cellulose polymer. This increase in charge density enhanced the swelling/shrinking capacity of the capsules (Figure 8). An increase in pH increases the degree of dissociation of the carboxyl groups and hence the charge density. This increases the osmotic pressure inside the capsule and induces swelling. When the pH is increased from 10 to 12, the ionic strength is also increased, and this counteracts the swelling and, therefore, decreases the osmotic pressure. This swelling behaviour, driven by the degree of dissociation of the carboxyl groups suggests that the swelling is reversible. Furthermore, since the diffusion coefficient increases exponentially with decreasing polymer volume fraction,[48] i.e. when the capsule swells, the observed swelling of the capsules is interesting for controlled–release applications. This, however, emphasizes the need for further development on how to further tailor the capsules for pH-induced controlled release or on the development of stimuli-responsive capsules for a more advanced substance-release strategy.

Conclusions

A double emulsion of octane inside a dissolved native cellulose phase in silicone oil has been prepared using a microfluidic flow focusing device. The cellulose shell could then be precipitated at an optimum cellulose concentration of 0.7 wt% to form a hydrogel cellulose capsule by an addition of a non-solvent, in this case water, to the cellulose oil phase. The so prepared capsules could withstand the osmotic pressure without collapsing when the inner encapsulated oil phase was exchanged for water. The capsules were also sufficiently mechanically stable to withstand freeze drying. The average outer and inner radii of the capsules were 44 µm and 29 µm, respectively. A FITC-labelled 4 kDa dextran model drug was encapsulated in the capsule and continuously released from the capsule over a period of approximately two hours. The diffusion of the dextran was further characterized by fitting the data to Fick's second law, giving a diffusion constant of $6.5 \cdot 10^{-14}$ m^2/s. The cellulose could also be modified by carboxymethylation to induce a pH responsivity of the prepared capsules and the capsule wall volume then increased by about 10% when the pH was raised from pH 3 to pH 10.

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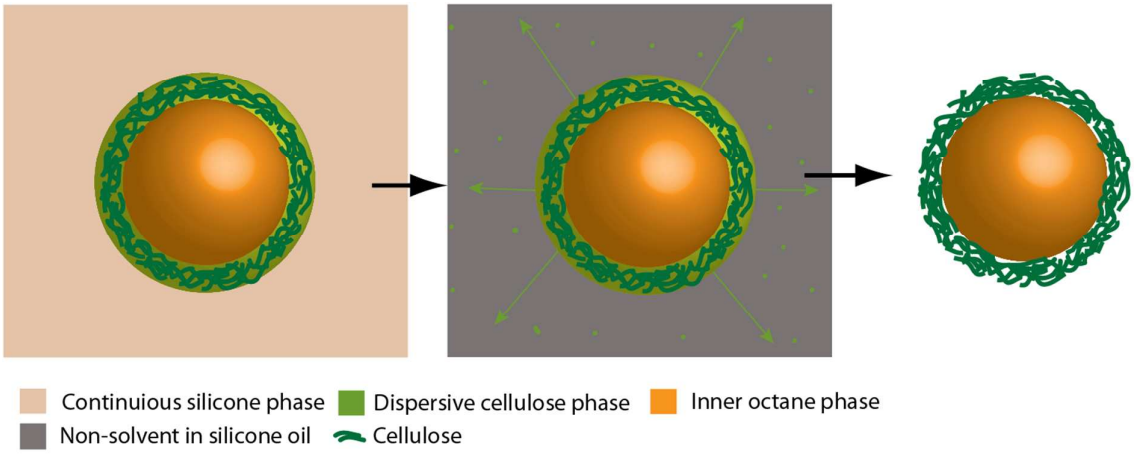
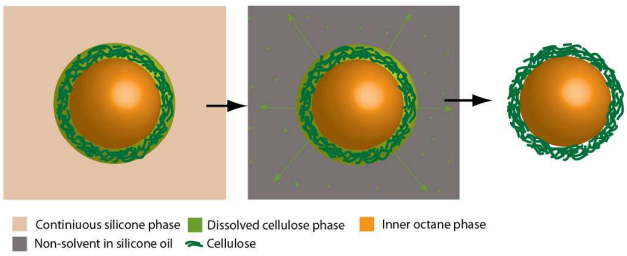


Schematic illustration of the formation of a regenerated cellulose capsule from the double emulsion. The non-solvent in the present experiment was isopropanol.



Schematic illustration of the formation of a regenerated cellulose capsule from the double emulsion using microfluidic flow focusing and isopropanol as precipitating solvent.