Microfluidic Assembly of Janus-Like Dimer Capsules

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Ⓢ *Supporting Information*

ABSTRACT: We describe the microfluidic assembly of soft dimer capsules by the fusion of individual capsules with distinct properties. Microscale aqueous droplets bearing the biopolymer chitosan are generated in situ within a chip and, as they travel downsteam, pairs of droplets are made to undergo controlled cross-linking and coalescence (due to a channel expansion) to form stable dimers. These dimers are very much like Janus particles: the size, shape, and functionality of each individual lobe within the dimer can be precisely controlled. Dimers with one lobe much shorter than the other resemble a bowling pin in their overall morphology, while dimers

with nearly equal-sized lobes are akin to a snowman. To illustrate the diverse functionalities possible, we have prepared dimers wherein one lobe encapsulates paramagnetic Fe_2O_3 nanoparticles. The resulting dimers undergo controlled rotation in an external rotating magnetic field, much like a magnetic stir bar. The overall approach described here is simple and versatile: it can be easily adapted in numerous ways to produce soft structures with designed properties.
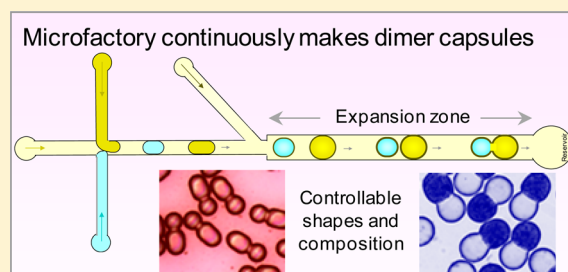
◼ INTRODUCTION

The promise of microfluidic and "lab-on-a-chip" systems is predicated on their ability to miniaturize operations that occur at the macroscale.[1] In particular, a microfluidic chip could be envisioned as a "microfactory"[2] that takes in soluble chemical precursors, builds solid "parts" out of them, and further assembles these parts into a complete object with a specified function. Ideally, such a "microfactory" would operate in a continuous mode without requiring manual intervention. The throughput of completed objects would then be controlled simply by the flow rates of fluids moving through the microfluidic channels. This throughput could then be enhanced by parallel operation of numerous chips. We explored the above concept in a previous study where we used a microfluidic chip to create flexible magnetic chains of microparticles.[3] However, the process used to make the chains required manual intervention to block and unblock the end of a channel at precise junctures. In the present study, we have developed a scheme that enables continuous synthesis of "dimer capsules", which are two individual biopolymer capsules fused into one stable structure (see Figure 1). Our method leverages both the fluid dynamics at the microscale (to induce droplet coalescence within a microchannel) as well as the chemistry of biopolymer cross-linking (to fix the dimer structure).

The dimer structures we create are reminiscent of Janus microparticles, which have attracted much attention recently.[4−6] Janus particles are those having one-half with a certain physical or chemical property while the other half has a different property.[7] They derive their name from the Roman god of gates and doors, Janus, who is depicted with two fused

heads, each facing in the opposite direction. Most Janus particles synthesized thus far are spherical in nature and in turn have two distinct hemispherical halves.[5,8] Various microfluidic-assisted synthesis methods have been explored for the synthesis of spherical Janus particles.[9−14] For example, the laminar coflow of two adjacent fluid streams in a microchannel can be broken up into discrete droplets by an immiscible phase, and the resulting droplets can be rapidly photopolymerized in situ to give Janus particles.[9,11] In addition to single particles with distinct halves, other researchers have used bulk routes to create dimers of distinct colloidal particles (micro- or nanoscale) and shown that such dimers can have a Janus-like morphology.[15−19] The widespread interest in Janus particles has arisen due to their multifunctional nature: potential applications for these particles have been demonstrated or envisioned in a variety of areas, including targeted drug delivery, emulsion stabilization, etc.[5,6]

Our approach to synthesize Janus-like dimers is quite different from those in previous studies. We use a microfluidic chip to generate aqueous droplets bearing the biopolymer chitosan. Two droplet generators are employed to produce alternating droplets of distinct composition (see Figure 1).[20] These pairs of droplets are then induced to meet and coalesce downstream by means of an expansion region in the channel.[21,22] At the same time, the droplets are also contacted by a continuous flow of glutaraldehyde (GA), which is a known
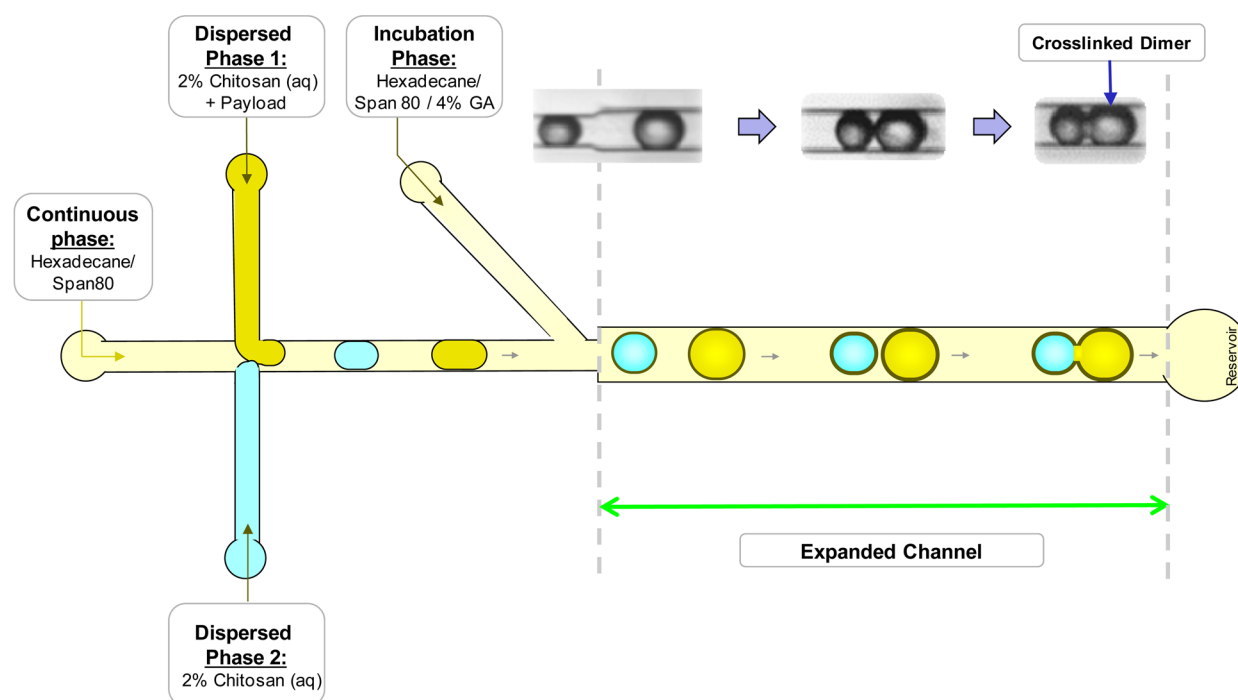
Figure 1. Schematic of the microfluidic setup for generating Janus-like dimer capsules. In the cross-channel geometry, two aqueous dispersed phases are contacted by an oily continuous phase. The dispersed phases are aqueous solutions of the biopolymer chitosan (with appropriate payloads). At the T-junction, alternating droplets of the dispersed phases are formed. Dispersed phase 1 flows at a higher flow rate Q_1 and thus generates a larger droplet compared to dispersed phase 2 (flow rate Q_2). As the droplets move down the channel, they are met by a flow of the incubation phase, which contains the cross-linker GA. Subsequently, the droplets enter an expanded channel region, with the expansion inducing the droplets to meet. The droplets are partially cross-linked by GA when they begin to coalesce, and the result is that they merge to form a cross-linked dimer. Photographs of the droplets merging into a dimer are shown at the top of the figure. Note that the two lobes of the dimer retain their distinct identity (no mixing of their internal contents) and are connected by a neck region. Ultimately, the dimers are collected in the reservoir at the end of the channel. The entire process of dimer formation is shown in Movie 1 (SI).

cross-linker for chitosan.[3] The GA converts the droplets into solid capsules and also arrests their coalescence; in effect, the capsules are connected by a neck region to form a stable dimer with each half of the dimer retaining its distinct identity. The entire process of dimer formation is completed within 30 s, with the final structures collected continuously at the channel outlet. Our study illustrates how a "microfactory" can be engineered to accomplish a series of steps: droplet formation, fluidic assembly, and chemical linkage, all of which take place on-chip without any manual interruption or manipulation. Two external handles are available to tune the morphology of the dimers: the flow rates of each stream, and the channel geometry, specifically the expansion ratio between the expanded and main channels. Stable dimers are obtained only for a subset of these variables, and we will present these results in terms of a "phase diagram" for dimer formation. Overall, our method offers a simple, continuous way to create Janus-like microparticles from commercially available precursors.

■ RESULTS AND DISCUSSION

The microfluidic chip used in our study has the design shown in Figure 1. Droplets are generated by contacting an aqueous dispersed phase and an oily continuous phase at a T-junction. Two dispersed phases are used in a cross geometry to produce alternating droplets with different composition and sizes.[20,21] Both dispersed phases contain 2 wt % of the amino-polysaccharide chitosan dissolved in 0.2 M acetic acid. Different materials such as magnetic or metallic nanoparticles or fluorescent dyes can be included in the dispersed phases to

provide distinct functional properties to each of the droplets. By controlling the flow rates of the dispersed phases, we can dictate the sizes of the droplets.[20,21] For our purpose, it is essential that the droplets' sizes be different, and more specifically, we ensure that within each pair of droplets, the leading droplet is larger than the trailing one. The larger droplet radius is designated as R_1, and the flow rate of its dispersed phase is Q_1; similarly, the smaller droplet corresponds to a radius R_2 and a flow rate Q_2.

To convert the chitosan-bearing droplets into stable capsules, a stream of 4 wt % glutaraldehyde (GA) dissolved in oil is introduced downstream. GA is a bifunctional molecule that cross-links the free amines on chitosan. Given enough contact time, the cross-linking by GA will result in a shell around each droplet.[3] However, in the present case, we induce the droplets to pair up (partially coalesce) before they are fully cross-linked. This is done by introducing an expansion zone in the downstream portion of the channel.[21,22] As pairs of droplets travel down the expanded channel, they both slow down, but the leading droplet is slowed more than the trailing one.[22,23] As a result, the droplets (which are semicross-linked at this stage) meet and partially coalesce within this zone. Simultaneously, the GA continues to cross-link the chitosan and thereby the overall merged structure is fixed into a doublet or dimer. Note that there is negligible mixing between the two halves (lobes) of the dimer because the individual droplets are rapidly "frozen" (by GA cross-linking) midway through the coalescence event. Thus, dimers can be created with tunable lobes containing distinct functional materials. The dimers are then collected in

the reservoir at the end of the channel. Movie 1 (see Supporting Information (SI)) reveals the entire sequence of events from start to finish. The total on-chip residence time for the two droplets from their generation to collection as a dimer in the reservoir is approximately 30 s. With typical flow rates (0.15 to 0.35 μL/min for the dispersed phases and 1.5 to 2 μL/min for the continuous phase), we generate on average 1 dimer every 1.4 s. From the reservoir, the dimers are pipetted into a collection vial containing 2 wt % GA and 2 wt % of the detergent Span 80, where they are further cross-linked for 30 min. The dimers are then sequentially washed in hexadecane and ethanol, and then redispersed in water, where they remain stable and free of aggregation.

We now discuss the conditions for stable dimer formation. Note that the two droplets initially have elongated plug shapes because their volume is larger than can be accommodated in a sphere that spans the initial width of the channel.[1,3] However, once the droplets reach the wider expansion zone, they relax into more spherical shapes, which is the one that minimizes surface energy.[1,3] In the absence of GA cross-linking, the two droplets will meet and then fuse into a larger structure. One factor in stable dimer formation is the concentration of GA because it controls the kinetics of cross-linking. The cross-linking has to be rapid enough to fix the dimer shape before the droplets can fuse. This is why it is necessary to use 4 wt % GA (a relatively high concentration). We originally tested 2 wt % GA, but in this case the GA-induced cross-linking was too slow to prevent partial droplet fusion (see Figure 4 below).

Two other key variables are involved in dimer formation, and these are (a) the ratio of the initial droplet sizes (R_1/R_2) measured in the expanded channels and (b) the extent of channel expansion. Note that R_1 corresponds to the larger droplet and so $R_1/R_2 > 1$ in all our experiments. The channel expands from an initial width W_1 to a higher width W_2 and we define a channel expansion parameter as $CEP = (W_2 − W_1)/W_1$. Figure 2 is a plot of CEP versus R_1/R_2 and it shows the conditions that correspond to stable dimer formation (indicated by green circles, collectively encompassed by the dashed oval) as well as the conditions that do not lead to stable dimers (indicated by red diamonds and blue triangles). Figure 2 is thus a "phase diagram" for dimer formation. We consider the three cases below.

First, the red diamonds in Figure 2 correspond to the case where R_1/R_2 is not much greater than 1 and the CEP is low. In this case, successive droplets simply do not meet in the expansion zone, and therefore no dimer is formed. To understand this, we elaborate on the reason why channel expansion forces the droplets to meet. Before entering the expansion zone, the plug-like droplets fill up the entire channel and both droplets travel at the same velocity (if there was no expansion, the droplets would never meet). As the droplets move from the normal to the expanded channel, they slow down by the law of continuity.[24] Moreover, in the expansion zone, the inset in Figure 1 shows that the larger leading droplet (radius R_1) spans the channel whereas the trailing droplet (radius R_2) travels along the center line but occupies only a portion of the channel. For plane Poiseuille flow in the laminar regime,[24] it is known that the fluid velocity assumes a parabolic profile, with a maximum v_{max} at the center line, and zero velocity (no-slip condition) at the channel walls. The mean velocity for this flow profile is $2/3v_{max}$. Thus, a droplet that spans the channel will have a velocity $\approx 2/3v_{max}$, whereas a very small droplet that is close to the center line will have a higher

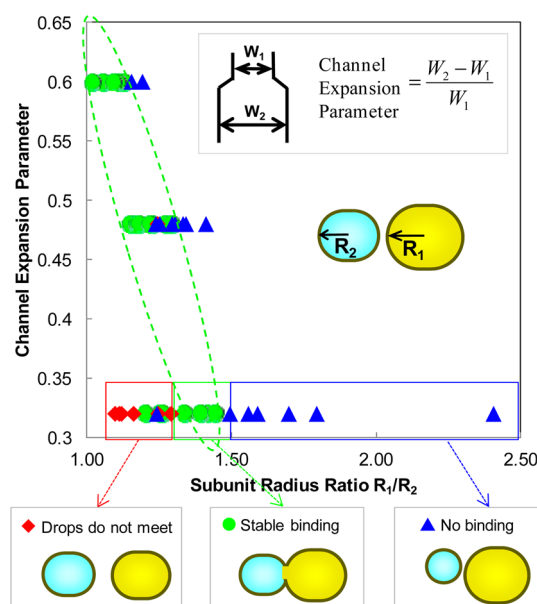**Figure 2.** "Phase diagram" for dimer formation. This is a plot of the channel expansion parameter (CEP) as a function of the radius ratio R_1/R_2 between the two droplets that form the dimer. The plot shows that stable dimers are formed only for a subset of the conditions studied, which are depicted by green circles. Under these conditions, the droplets meet in the expansion channel and bind to form stable dimers. By contrast, for the conditions marked by red diamonds (typically at low R_1/R_2), the droplets are too similar in size and do not meet in the expansion channel. On the other hand, for the conditions marked by blue triangles (typically at high R_1/R_2), the droplets meet in the expansion channel but do not bind.

velocity that is $\approx v_{max}$. More generally, the smaller trailing droplet will have a higher velocity than the larger one ahead of it, and this allows the two to catch up.[22,23] However, if R_1 and R_2 are very close, the velocity difference is not enough to ensure that the droplets will be able to catch up within the length of the expanded channel. This explains why no dimers are formed for the conditions marked by the yellow diamonds.

Next, we consider the conditions marked by the blue triangles in Figure 2, which correspond to high R_1/R_2 at each CEP. In these cases, the leading droplet (R_1) is much larger than the trailing one (R_2). We observe that the droplets meet in the expansion zone, but do not merge. The reasons for this are not completely clear. One factor is that the smaller droplet experiences hydrodynamic forces that cause it to meet its counterpart at an angle and not along the center line of the channel, as depicted in the schematic for the blue triangles in Figure 2. This is what we observe in experiments, and it has been reported by others as well.[23] We speculate that such off-center contact is not conducive to merging of droplets. (An equivalent viewpoint is that the hydrodynamic forces undo the droplet−droplet chemical bonds induced by GA.) All in all, we observe stable dimers for moderate values of R_1/R_2 (not too low or high) at each CEP and these conditions are marked by the green circles. As shown by the inset in Figure 1, a stable dimer typically has a neck region between the two adjacent lobes.

Other factors to consider in dimer formation are the lengths of the microfluidic channel segments. In our design (Figure 1), the expansion channel is placed close to the GA inlet stream. This is done to ensure that the droplets do not get substantially cross-linked by GA before they meet. That is, dimerization can

only occur for droplets that have not been fully converted into capsules. In addition, the expansion channel must be of sufficient length to provide enough time for the dimer to fully form.[22] That is, after the droplets first meet, the film between the droplets has to drain completely for the droplets to merge and cross-link into a dimer.[25,26] For this, our experiments show that the droplet pair has to remain in contact for about 13 s in the expansion channel before merging is completed (see Movie 1, SI). Note that this time is rather large compared to the time for film drainage in previous droplet coalescence studies, which have been reported to be on the order of 10^{-2} s.[25,26] Evidently, the present case is more complex as it involves a combination of droplet merging as well as chemical cross-linking of each droplet and also of the neck region between the droplets. The cross-linking reaction is expected to reduce the mobility of the fluid between the two droplets and thus reduce the film drainage rate,[27] which could explain why the merging process takes a longer time in our case.

Figure 3 shows the morphology of dimers corresponding to different sizes of the expansion channel (with the main channel
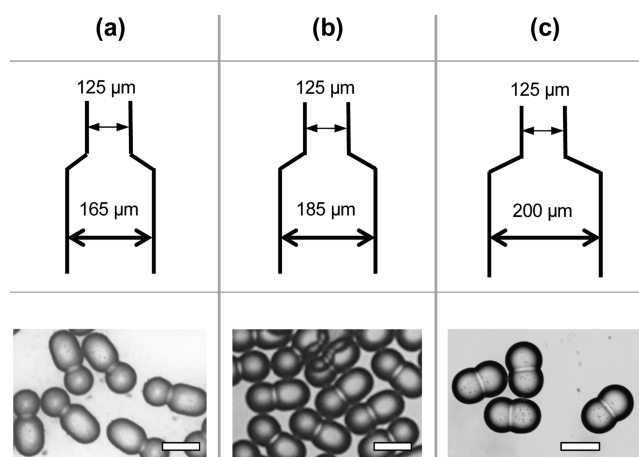

Figure 3. Dimers of different morphologies by adjusting the channel geometry and dispersed flow rates. Three different sizes of the expansion channel: (a) 165 μm, (b) 185 μm, and (c) 200 μm were tested, with the main channel maintained at 125 μm. In (a) the dimers assume a "bowling-pin" morphology, with one lobe elongated and the other spherical. In (c) the dimers take on a "snowman" morphology with two nearly spherical lobes. In (b) the morphology is intermediate between the other two. Scale bar represents 200 μm.

maintained at 125 μm). For an expansion channel size of 165 μm (the smallest tested), we found that among each pair of droplets, the larger leading one remains plug-shaped in the expansion channel while the smaller trailing one relaxes to a spherical shape. Dimers formed from such pairs of droplets have an elongated shape reminiscent of a "bowling pin" (Figure 3a). Note that the bowling pins have a short spherical lobe attached to a longer plug-shaped lobe. If the expansion channel is made wider (185 or 200 μm), then both the leading and trailing droplets relax to spherical shapes in the expansion channel. The resulting dimers have a rounder morphology, and the shape in Figure 3c is reminiscent of a "snowman".[28] In this case, the two lobes of the dimers have nearly equal lengths.

In addition to creating dimers of various morphologies, we are interested in engineering the functional properties of these dimers. As an initial demonstration, we incorporate magnetic nanoparticles (MNPs) into one lobe of our dimer to create

Janus-like dimers with an overall magnetic moment. Specifically, we combined 0.5 wt % of the MNPs with the 2 wt % chitosan solution and used this mixture as the dispersed phase for one inlet, whereas the other inlet was just the 2 wt % chitosan solution. Optical micrographs of the resulting snowman-shaped magnetic dimers are shown in Figure 4a.
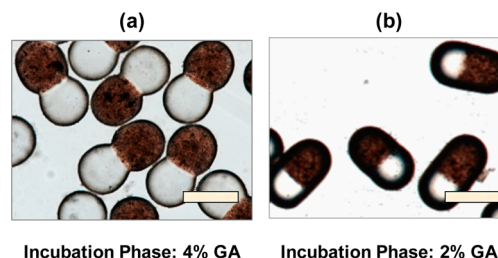

Figure 4. Magnetic dimers with MNPs in one lobe. The lobe with MNPs shows a dark color relative to the other lobe. These Janus-like dimers were created by using two dispersed phaes, one of chitosan +MNPs and the other of chitosan alone. The dimers in (a) were formed with 4% GA as the incubation phase: in this case, the contents of the lobes are well-separated. On the other hand, the dimers in (b) were formed with 2% GA as the incubation phase. At this lower concentration of the GA cross-linker, the contents of the two lobes undergo partial mixing and there is no neck region separating the lobes. Scale bar represents 200 μm.

The MNP-bearing lobe has a dark brown color, whereas the other lobe is colorless. Note the clear separation between the two lobes, which shows that the inner contents of the two lobes do not mix during dimer formation. Such dimers were produced using 4 wt % GA as the cross-linker. If the GA concentration was reduced to 2 wt %, we obtained the dimers shown in Figure 4b. As noted earlier, at this lower GA, cross-linking is not rapid enough to prevent the droplets from partially fusing. Thus, some fusion of the MNP-bearing droplet and the bare droplet occurs in this case, as seen from the dark brown color pervading through most of the pill-shaped dimers in Figure 4b. Also, these dimers have no intervening "neck" region between their respective lobes.

The magnetic response of the anisotropic (Janus-like) dimers in Figure 4a was tested by placing a Petri dish containing the dimers in water on a standard magnetic stir plate. As shown by Movie 2 (SI), the rotating magnetic field produced by the stir plate causes the dimers to rotate, much like a microscale magnetic stir bar. This occurs because the dimer acquires a magnetic moment due to the MNPs being localized in one lobe. Note also that the axis of rotation is located within the MNP-bearing lobe, i.e., it is eccentric with respect to the whole particle.[29] The rotation of the dimer induces significant convective mixing in the surrounding fluid close to the dimer. This is shown in the second segment of Movie 2, where we placed a dimer in a suspension of polystyrene microbeads (0.1% w/v) that each have a diameter of 6−8 μm. The rotation of the dimer is seen to cause local mixing of the beads. This suggests the possibility of using magnetic dimers for the micromixing of fluids within microscale and lab-on-a-chip devices.[29]

■ CONCLUSIONS

We have demonstrated the continuous micromanufacturing of Janus-like dimer capsules on a microfluidic chip. Our method involves generating alternating droplets of distinct composition

(both based on the biopolymer chitosan) and inducing pairs of droplets to meet downstream by means of an expansion region in the channel. At the same time, a flow of cross-linker (GA) converts the droplet pair into a stable dimer while also arresting their coalescence. The overall process starting from soluble precursors and culminating in stable dimers takes about 30 s and occurs continuously on-chip without external manual control. Each lobe of the dimer retains its distinct identity giving the overall structure a Janus-like architecture. As a demonstration of the utility of this approach, we create dimers that have a net magnetic moment by including MNPs in one lobe: these dimers rotate when placed on a magnetic stir plate. Overall, we have put forward a new microfluidic method for creating Janus-like structures without the use of templates and without resorting to photopolymerization. An attractive feature of this method is the ability to easily tailor the functional properties of our dimers by incorporating nanoparticles or other moieties into one or both lobes. The resulting dimers may be explored for application in areas such as drug delivery, microrobotics, micromixing, and sensors.

■ MATERIALS AND METHODS

Materials and Chemicals. Chitosan (medium molecular weight, 190−310K; degree of deacetylation ∼80%), the nonionic detergent, sorbitan-monooleate (Span 80), hexadecane, and glutaraldehyde solution (grade I, 70% in water), were obtained from Sigma-Aldrich. Magnetic γ-Fe_2O_3 nanoparticles (average surface area ≈42 m^2 g^{-1}) were purchased from Alfa Aesar. Polystyrene beads of diameter 6−8 μm were purchased from Spherotech. All materials were used as received.

Solution Preparation. Two weight percent chitosan was dissolved in a 0.2 M acetic acid solution, from here on referred to as the dispersed phase. For the preparation of magnetic dimers, 0.5 wt % of the γ-Fe_2O_3 nanoparticles were added into the 2 wt % chitosan solution to create a second dispersed phase. The continuous phase was prepared by dissolving 2 wt % of Span 80 in hexadecane. Finally, the incubation phase was a solution in hexadecane containing 0.2 wt % of Span 80 and 4 wt % of glutaraldehyde. The above mixture was vortexed and sonicated for 30 min before use.

Image Analysis. Bright-field optical images of dimer capsules and Movie 2 were taken with a Nikon Eclipse LV-100 Profilometer Microscope. Capsule sizes (length and radius) were determined using the Nikon Microscope software. Movie 1 showing the dimer formation process was taken using an inverted fluorescent microscope (Nikon Eclipse TE2000s).

Chip Fabrication. Microfluidic chips were fabricated from poly(methyl methacrylate) (PMMA) as described previously.[3,30] PMMA sheets (FF grade; 4″ × 4″ × 1/16″) were purchased from Piedmont Plastics. Microchannels were fabricated by direct mechanical milling onto a PMMA substrate using a 125-μm-diameter end mill (Performance Micro Tool, TR-2-0050-S) on a Roland MDX-650 CNC milling machine with a depth of 90 μm. Holes for the needle interface and access reservoir were drilled into the substrate plate using a 650 μm drill bit and a 2 mm diameter drill bit, respectively. The machined PMMA plate was then sequentially cleaned by deionized (DI) water and isopropyl alcohol, then sonicated for at least 1 h to remove milling debris, followed by a 24 h conservation in a 40 °C vacuum oven to remove the residual solvents. After the vacuum drying, both the processed PMMA and a raw PMMA chip were oxidized by an 8 min exposure to ultraviolet (UV) light in the presence of ozone. The oxidized PMMA wafers were immediately mated together and thermo-bonded at 85 °C using a Carver AutoFour hot press under a pressure of 3.45 MPa for 15 min. The world-to-chip interfaces were established by inserting hypodermic stainless steel needles into the 650 μm diameter mating holes. Precision syringe pumps (PHD 2000, Harvard Apparatus) were used to control the infusion of fluids into the chip.

Chip design for dimer formation is described in Figure 1 and the accompanying text. In addition to the elements shown in Figure 1, one optional element was used in some cases to further facilitate droplet formation. This was to introduce a geometric constriction in the shape of a toothcomb structure to the channel at the end of the expanded region and prior to collection in the reservoir.[31−33] The constriction segment ensured that any capsule pairs that did not merge in the straight channel would merge in this region before leaving the outlet. Note that the toothcomb was not an essential element in the design: dimers could be formed without the toothcomb, as shown for example in Movie 1 (SI). However, the constriction is a helpful element for coalescence, as noted by other researchers.[31−33]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Movies demonstrating the formation of dimer capsules and the rotation of magnetic dimers. This information is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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