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High-Throughput Platform for Synthesis of Melamine-Formaldehyde Microcapsules

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ABSTRACT: The synthesis of microcapsules via in situ polymerization is a labor-intensive and time-consuming process, where many composition and process factors affect the microcapsule formation and its morphology. Herein, we report a novel combinatorial technique for the preparation of melamine-formaldehyde microcapsules, using a custom-made and automated high-throughput platform (HTP). After performing validation experiments for ensuring the accuracy and reproducibility of the novel platform, a design of experiment study was performed. The influence of different encapsulation parameters was investigated, such as the effect of the surfactant, surfactant type, surfactant concentration and core/shell ratio. As a result, this HTP-platform is suitable to be used for the synthesis of different types of microcapsules in an automated and controlled way, allowing the screening of different reaction parameters in a shorter time compared to the manual synthetic techniques.

KEYWORDS: *microcapsules, melamine-formaldehyde, high-throughput*

INTRODUCTION

Melamine-formaldehyde (MF) microcapsules have been extensively used during the last decades because of their low price, easily controlled preparation, high compatibility, and good thermal and chemical stability.[1] Among the materials inside the core, solvents and plasticizers,[2] fragrance oils,[1a,3] phase change materials,[1b,c,4] additives,[5] and reactive materials for self-healing applications[6] have been protected by the brittle rigid MF shell. A well-known microencapsulation approach is based on an oil-in-water (o/w) emulsion and an in situ polymerization process. For this, a pre-reacted MF polymer is incorporated to the emulsion and the polymerization reaction occurs in the continuous phase, leading to a prepolymer that grows and is then deposited on the surface of the droplets containing the dispersed core material. After cross-linking in a fairly acidic media with temperature, the solid shell is formed.[7]

A large number of experimental parameters[8] are involved in the synthesis of MF microcapsules and their influence on the final properties of the microcapsules has been the source of inspiration for quite a high number of publications during the last 17 years (Figure 1). However, the optimization of existing processes was mostly performed via a trial-and-error approach. The vast majority of publications that are related to MF microcapsules relied on the experimental screening or characterization,[9] very often evaluating the same factors and with merely descriptive conclusions about a particular system. Sometimes, the significance of the paper was related to the use of an original type of core[10] as a result of the foreseen

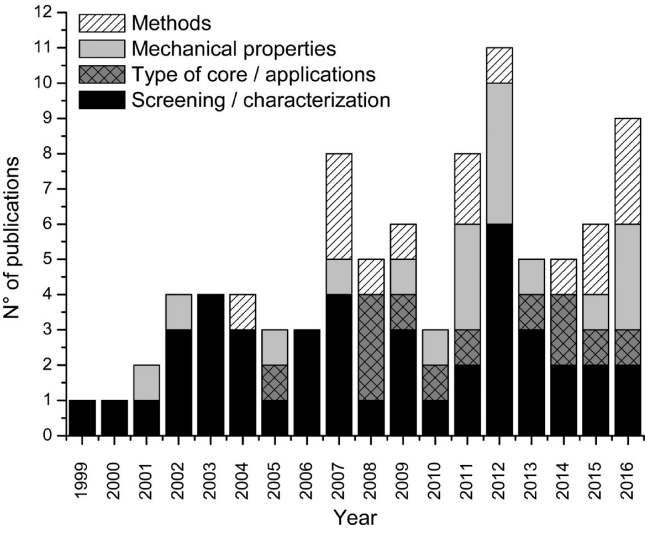

Figure 1. Historical evolution of publications in peer-reviewed journal papers related to MF microcapsules in the last 15 years, classified by topic. Source: Scifinder and Sciencedirect.

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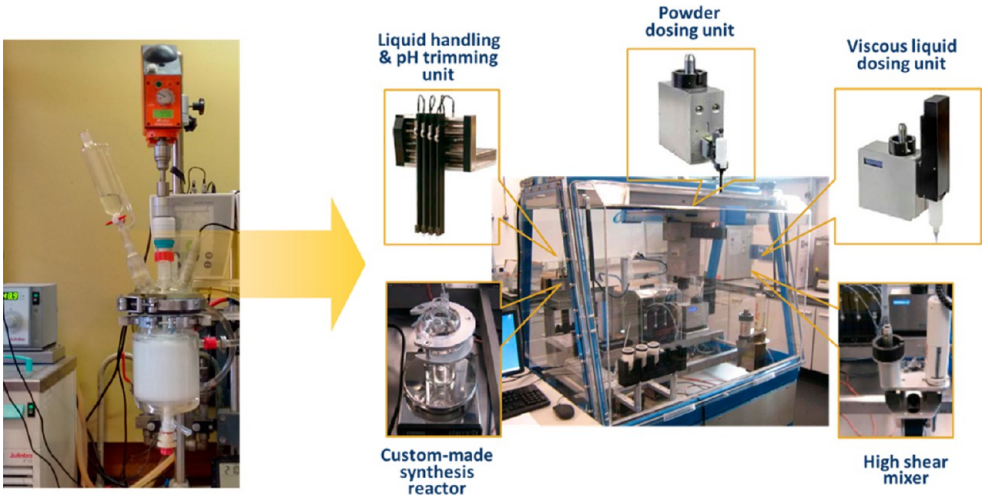

Figure 2. Lab-scale microcapsule synthesis set up (left) vs developed automated microcapsule synthesis platform (right).

applications of the microcapsule system.[5b,6d,e,11] In other cases,[12] the mechanical properties were the key factor for applications related to pressure-sensitive applications such as carriers for fragrances, or self-healing materials.[1b,6e,11c,13] However, the most relevant works report improved or more controlled processes for specific needs[2c,d,14] or novel preparation methods.[15]

Despite the particularities of each individual system, it is surprising to observe the numerous efforts that are still systematically performed to elucidate the links between the capsules properties (e.g., morphology, size, core content, shell properties, dispersion, etc.) and the interconnected experimental parameters involved during the preparation, such as pH, temperature, reaction time, surfactant type and concentration, stirring rate, core/shell ratio, and heating gradient.

The aim of this research is to present a combinatorial approach to enhance the efficiency of the investigation of a variety of synthesis and process parameters for the preparation of MF microcapsules containing cyclohexane, selected as a standard hydrophobic solvent for the core. The utilization of a unique high-throughput platform with automated multiple synthesis modules aims to allow for speeding up the number of syntheses while reducing the error-prone manual procedures. Besides, the applied design of experiment (DoE) protocol will provide a more complete and comprehensive overview of the links between different sets of parameters, often in a nonlinear way.

Combinatorial chemistry is already known for decades and commonly applied in several domains, such as pharmacology[16] (e.g., controlled drug delivery), biotechnology,[17] polymer research[18] and catalysis.[19] The field of polymer research seems to be perfectly suited for parallel and combinatorial methods because of many parameters can be varied during synthesis and processing. It will be shown for the first time that combinatorial techniques, parallel experimentation and high-throughput methods provide a very promising approach to speed up the large-scale preparation and investigation of polymeric microcapsules, more specifically MF microcapsules. In this way, a large variety of parameters can be screened simultaneously, resulting in new structure/property relationships, involving numerous important parameters, such as morphology, cross-link density, particle size, hardness, stiffness, and other application-specific properties.

Nowadays, numerous suppliers of high-throughput technologies offer standardized automated synthesis platforms to enhance the discovery, research and development of new chemistries, building blocks, molecules, (bio)polymers, etc. Despite the intensive search to encapsulate various ingredients, such as reactive components, catalysts, corrosion inhibitors, etc., and because of the complexity of the process, more particularly the in situ polymerization process, a high-throughput encapsulation platform has never been reported in literature. In this context, such a unique in-house built dedicated high-throughput platform for synthesizing microcapsules was developed. Figure 2 shows how the manual lab scale setup was transferred into a high-throughput synthesis platform.

It is expected that the use of these combinatorial approaches can significantly reduce the time-to-market for new types of polymeric microcapsules in comparison to traditional approaches and allow for a much more detailed understanding of different systems from the macro- to the nanoscopic scale.

EXPERIMENTAL SECTION

Materials. All the chemicals were purchased from Sigma-Aldrich. Melamine 99% (CAS No. 108-78-1), formaldehyde 37 wt% (CAS No. 50-00-0), triethanolamine 99% (CAS No. 102-71-6), cyclohexane 99% (CAS No. 110-82-7), polystyrene maleic anhydride (CAS No. 31959-78-1), sodium carbonate (CAS No. 497-19-8), sodium dodecyl sulfate, 99% (CAS No. 151-21-3), polyvinylalcohol 78% hydrolyzed, MW = 6000 (CAS No. 9002-89-5), 1-octanol (CAS No. 11-87-5), sulfuric acid (CAS No. 7664-93-9), acetic acid (CAS No. 64-19-7), and magnesium chloride, 99% (CAS No. 7791-18-6) were used as supplied.

Manual Synthesis of MF Microcapsules. The procedure was adapted from Yuan et al.[6d] and modified. The precondensate prepolymer was prepared by mixing 12 g of melamine and 25 mL of formaldehyde solution (37%). pH was adjusted to 9 by adding triethanolamine. The mixture was heated up in an oil bath at 70 °C for 30 min, until it became transparent. In parallel, the emulsion was prepared by mixing cyclohexane with 200 mL of aqueous solution of surfactant. Microcapsules with two different amounts of core content were prepared. Cyclohexane was added according to a core/shell ratio of either 2.82 or 4.23. The pH of the emulsion was slowly

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decreased to 5 by dropwise addition of acetic acid (12 wt %), while the mixture was homogenized at a speed of 7000 rpm with an Ultra Turrax (IKA) device. One or two drops of 1-octanol were added to control the foaming. Finally, the stable emulsion was transferred to a reactor with mechanical agitation with a four-bladed stirrer at 400 rpm. 200 mL of water was added at this stage. The pre-reacted prepolymer was slowly added to the reactor, leading to a sharp pH increase that was controlled by the addition of acetic acid solution, during the incorporation. After completing the addition of the precondensate, 10.65 g of magnesium chloride hexahydrate (dissolved in 20 mL of water) was slowly added to the reactor. The final pH was adjusted to 5. The reactor was heated from room temperature to 50 °C and the microcapsule slurry was collected after 1 h. Microcapsules were kept in the slurry form until usage. For characterization, microcapsules were filtered with filter paper, washed with distilled water, and dried overnight in a vacuum oven at 40 °C.

Automated Synthesis of MF Microcapsules. In the first step of the microcapsule preparation, the MF prepolymer was prepared, adding 25 g of formaldehyde (37 wt %) and 12 g of melamine in a reactor (R1).

Meanwhile, in another reactor (R2), the emulsion was prepared. In a 100 mL reactor 8.74 or 13.1 g of cyclohexane was added to an aqueous solution (29.1 or 43.6 g) containing emulsifier and high-shear mixed at 11000 rpm. The pH was adjusted to 5.

Six grams of the prepared precondensate solution (R1) was slowly added to the emulsion (R2) and pH adjusted to 5 with an acetic acid solution. Additionally, 42.4 or 38.9 g of demi-water[1] was added together with 1.6 g of the $MgCl_2 \cdot 2H_2O$ solution and finally pH trimmed to 5, prior to the poly condensation reaction at 50 °C for 1 h.

All these synthetic steps were performed on a modified Swing module (Chemspeed AG), consisting of controllable heated magnetic stirring plates (CAT), 6 independent 100 mL reactors, pH trimming module (4-channel liquid handling module, Chemspeed AG), overhead gravimetric dispensing of powders and liquids (SDU, GDU-V, and 4-channel liquid handling module, Chemspeed AG) and a high-shear mixing tool (KINEMATICA). Every step in the processing of microcapsules was thoroughly examined. A specific reactor concept, combined with an in-house written generic software were developed, allowing to synthesize microcapsules autonomically in a miniaturized fashion without any further human intervention. Furthermore, this unique high-throughput synthesis platform was designed in such a way that the number of syntheses per day could be doubled compared to the manual experimentation procedure. The fact that many parameters, such as pH, the heating/cooling ramp and/or -temperature, the magnetic as well as high-shear mixing speed and/or -time, the reaction time of each step and not to mention the numerous possibilities on the composition side, could be examined, an upfront selection of the parameters of interest is required. Once the selection and the boundaries are determined, a well-defined DoE could be setup. This HTP platform enables to perform, monitor and register each action of the in situ microencapsulation process in an objective manner.

Characterization of MF Microcapsules. The morphology of the MF microcapsules was visualized using scanning electron microscopy (SEM) (Phenom FEI, Table-top SEM).

For the core content calculation, a weighted amount of dry microcapsules was extracted in acetone at 60 °C in a Soxhlet apparatus for 24 h. Extracted samples were fully dried for 24 h at 60 °C. Core content was calculated by knowing the initial weight of the vacuum-dried capsules (W_i) and the final weight of the empty dried shells (W_f) as follows:

$$\text{core content } \% = ((W_i - W_f)/W_i) \times 100$$

Design of Experiments (DoE). On basis of previous optimization studies, the benchmark microcapsule was chosen as the one prepared at pH 5 with 2.5 wt % PSMA surfactant with a core/shell weight ratio of 2.82. The DoE was set up according to the benchmark sample by varying the most important parameters (Table 1). It was aimed to screen 3 different surfactants, that is, poly(vinyl alcohol) (PVA), sodium dodecyl sulfate (SDS), and polystyrene maleic anhydride (PSMA), at different concentrations (2.5 and 5 wt %). The surfactants were tested both pure and in combinations. The samples were coded according to the first two letters of the surfactant used in each case. The weight ratio of core/shell was also varied at different ratios, 2.82 and 4.23. A D-optimal design was selected and resulted in 24 experiments.

Table 1. Design of Experiments (DoE) Showing the Variables Used in the High-Throughput Platform

	Levels		
parameter	level 1	level 2	level 3
pH (3−5.5)	fixed (pH = 5)		
high shear (RPM) (11000−20000)	fixed (11000 rpm)		
ratio core/shell (1.41−4.23) (no. 2)	2.82	4.23	
no. of surfactants (no. 3)	PVA	SDS	PSMA
range of surfactant, % (0.5−5) (no. 2)	2.5	5	
ratio surfactants (no. 2)	100/0	50/50	

RESULTS AND DISCUSSION

Initially, a reproducibility study was performed by repeating the high-throughput experiments of the benchmark (depicted as PS1 in Figure 6). As shown in Figure 3, according to the SEM measurements, all 4 experiments resulted in microcapsules with similar average sizes around 100 ± 15 μm. Core contents of the capsules showed a range from 49.1% to 60.8% with an average core content of 55.7% ± 5.2%.

As the platform was proven to give reproducible results with the benchmark microcapsule, microcapsules with different variables were synthesized, both manually and in an automated way. For each set of reaction that was performed, all the variables were kept the same. The only difference was the stirring rate during the homogenization, that is being 11000 rpm in case of the automated syntheses and 7000 rpm in case of manual reactions as a result of the used experimental setup. This difference has an effect on the microcapsule size as observed in the SEM pictures in Figure 4a and 4b. The pictures a and b refer to the benchmark experiments performed via the HTP platform and manual experiments with core contents of 60.8% and 85.1%, respectively. It is clearly seen that well-shaped microcapsules were formed via both synthetic techniques with rather high core contents. Manual synthesis led to higher core content as a result of the lower stirring rate during homogenization, which resulted in larger droplets and eventually in larger microcapsules. As the amount of shell is the same in both cases, larger-sized microcapsules contain more cyclohexane. It is observed that MF particles deposit on the surface of the microcapsules, leading to a rough surface.

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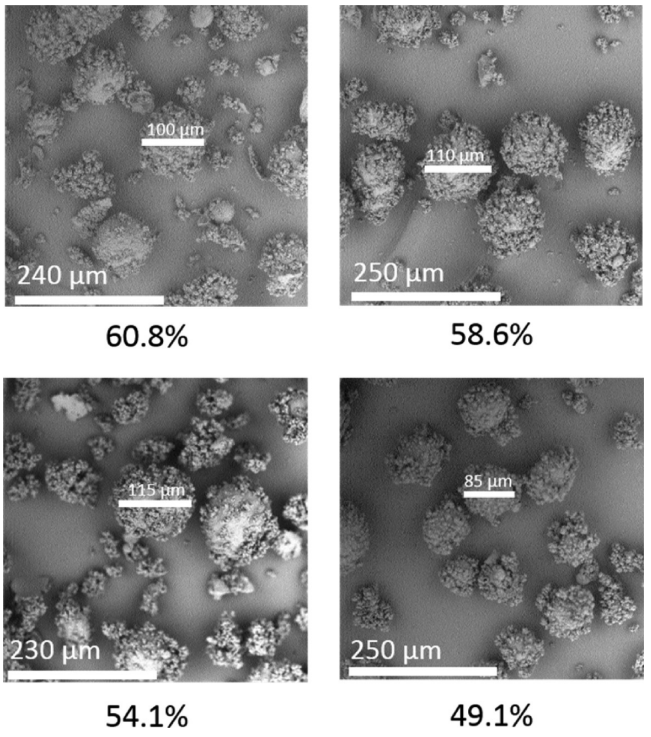

Figure 3. Reproducibility experiments of the benchmark microcapsule, synthesized via the high-throughput platform. The numbers are showing the measured core content of each batch.

Nevertheless, both samples are very similar in morphology showing that both synthetic approaches are in agreement.

Pictures **c** and **d** refer to the reactions synthesized by PVA as the surfactant with 2.5 wt % concentration and with a core/shell weight ratio of 2.82. In both cases it is observed that there is a formation of very small highly deformed and agglomerated capsule-like structures, showing that PVA is not a good surfactant under the reaction conditions used. In case of the automated synthesis these structures are more deformed, again most probably because of the higher homogenization rate. In some of the previous MF microcapsule studies, PVA has been used as a stabilizer in addition to another surfactant, providing repulsive forces between the droplets as well as increasing the viscosity of the continuous phase.[20] During the reactions,

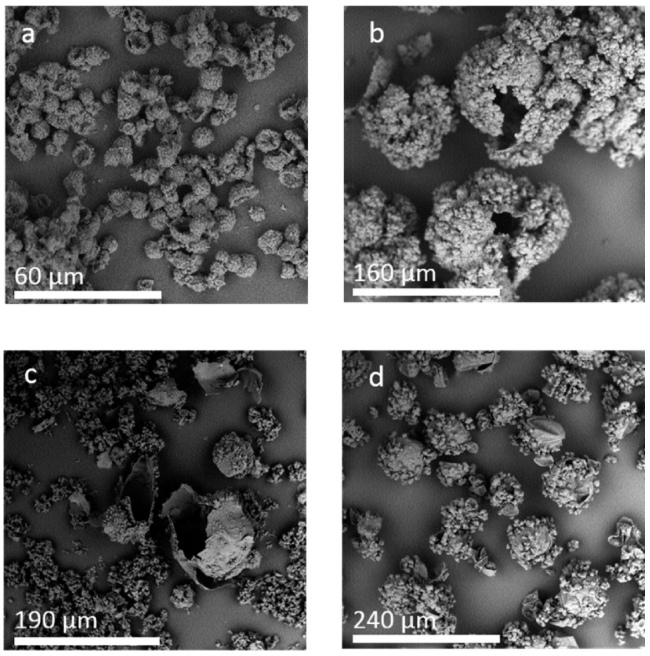

Figure 5. Microcapsules with different surfactants at pH = 4, core/shell = 2.82, 2.5% surfactant at different scales: (a) PSMA, (b) SDS, (c) PVA, and (d) PSMA/PVA (50/50 by weight).

performed at a pH of 4, of the microcapsules with PSMA (e and f, weight core/shell = 2.82), automated reactions led to small-size deformed microcapsule-like structures, while manual reactions resulted in agglomerated microcapsules with a core content of 61.1%. In this case, it seems that manual synthesis works better than the automated system. This might be ascribed to the difficult control of foaming at low pH where a lot of acid has to be added to decrease the pH. Reactions performed using 5 wt % SDS (g and h) are both very similar in structure, that is, agglomerated tiny particles resulting in no microcapsule formation. Despite some differences in morphology, the pairs of samples synthesized in a manual or automated fashion with the same reaction conditions are in agreement.

As both the reproducibility and the comparison experiments were in agreement and the high-throughput platform was shown to be accurate and reliable, a design of experiments (DoE) study was planned. The important parameters that affect

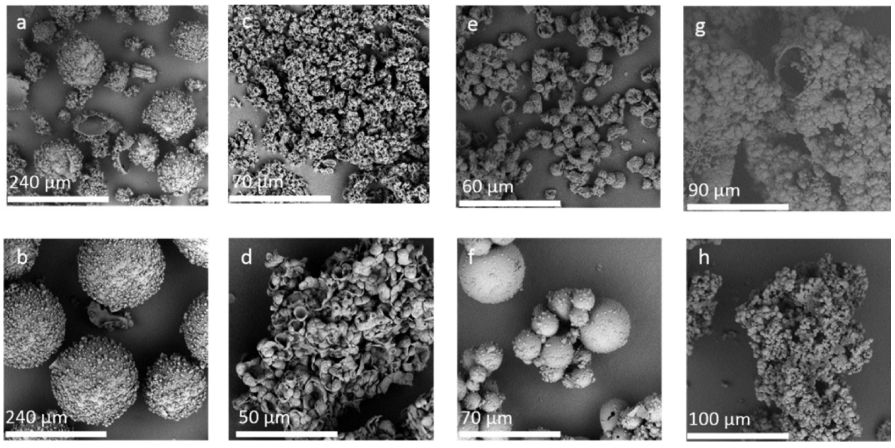

Figure 4. Comparison of microcapsules with 2.82 core/shell ratio synthesized by the HTP platform (top ones) and by manual synthesis (bottom ones): (a, b) PSMA2.5%, (c, d) PVA 2.5%, (e, f) PSMA 2.5%, pH = 4, and (g, h) SDS 5%.

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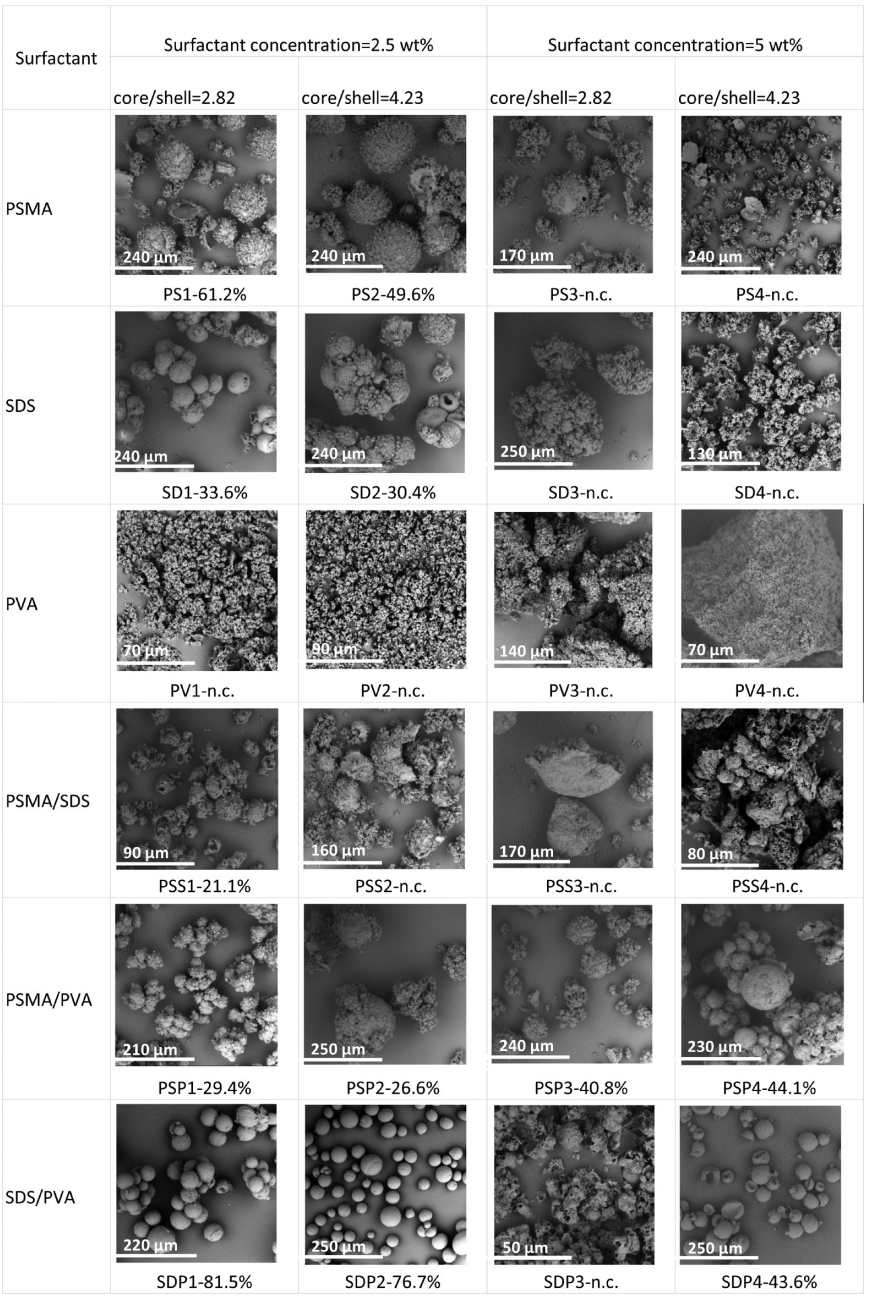

Figure 6. Overview of the DoE performed via the HTP platform, with resulting microcapsule SEM images. Sample codes and core contents are mentioned under every image (n.c. = no core content). Scales: 50−250 μm.

the microcapsule formation can be listed as pH and temperature of the encapsulation medium, type and concentration of the surfactant and core/shell ratio. Temperature (50 °C) and the stirring rate (11000 rpm) were kept fixed for the DoE. On the other hand, as shown before, the type of surfactant has a very significant role in the formation of microcapsules and their morphology and the core content. As a result, three different surfactants were selected, namely, PSMA, SDS, and PVA. Pure surfactants were used, as well as 50/50 weight mixtures with 2.5 and 5 wt % concentrations. Another parameter that was changed included the core/shell ratio.

To check the effect of pH, manual and automated experiments were executed at different pH values, ranging from 4 to 5.3. The pH above 5 was difficult to control and a rapid increase was observed, blocking the encapsulation process. Figure 5 shows the set of microcapsules produced in the automated system with pH 4, a core/shell weight ratio of 2.82 and a surfactant concentration of 2.5% for PSMA, SDS, PVA, and PSMA/PVA mixture (50/50 by weight) to see the effect of different surfactants at pH 4. The synthesis by making use of PSMA as surfactant was already discussed above. As explained before, in the HTP system it is more difficult to lower pH of the encapsulation medium in a controlled way due to foaming. The reactor dimensions are limited and fine-tuning of acid addition/stirring has to be done. When SDS was used, again capsule-like but broken particles were observed. PVA at low pH does not work unless it is used together with PSMA as shown in Figure 5d. In that case, microcapsule formation with a core content of 26.6% was observed. Although lower pH seemed to work according to the previously published

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research[5b,6d] it was decided to use a pH of 5 for the DoE because of the limitation of pH control at more acidic conditions.

All experimental results of the DoE are shown in Figure 6. The main factors affecting the capsules' size are the homogenization rate (constant) and the surfactant amount. However, the surfactant type not only influences the size, but the morphology as well.

The first row shows the 4 experiments with PSMA as surfactant. As shown by the SEM analyses, both PS1 and PS2 consist of nicely formed microcapsules but bigger capsules are detected in PS2 due to increased cyclohexane amount resulting in a core content of 49.6%. Despite the higher amount of cyclohexane, thecore content did not increase compared to PS1, leading to the assumption that shell thickness was bigger in case of PS2. PS3 and PS4 synthesized with 5 wt % PSMA did not result in the formation of microcapsules with all the tested core/shell ratio, which can be ascribed to the insufficient control during encapsulation because of extensive foaming.

The second row of microcapsules was synthesized by using SDS. SD1, which was synthesized by 2.82 core/shell ratio and 2.5 wt % SDS concentration, resulted in smaller size microcapsules compared to PS1 with an average size of 80−90 μm. When higher core/shell ratio was used (SD2), the surface of the microcapsules became rougher and agglomeration occurred while the core contents were similar. When SDS concentration was increased to 5 wt % (SD3 and SD4) neither experiments ended up in the formation of microcapsules, meaning that high concentrations of SDS are not favored. The third row is composed of experiments done with PVA as surfactant. It is clear that PVA, if used alone, does not lead to any microcapsule formation in all 4 variations of syntheses.

The next 3 rows of experiments are composed of capsules prepared by mixed surfactants (50/50 by weight). Although 2.5 wt % PSMA and SDS at two different core/shell ratios resulted in microcapsules, no microcapsules were formed when their mixture was used. On the other hand, the experiments executed by mixing PSMA and PVA 50/50 by weight resulted in microcapsules with different morphologies and core contents. The first one, with 2.82 core/shell ratio and 2.5 wt % surfactant (PSP1), resulted in agglomerated small microcapsules with a core content of 29.4%. When the core/shell ratio was increased to 4.23 (PSP2), a similar core content (26.9%) was achieved with bigger microcapsules. Five wt % PSMA/PVA and 2.82 core/shell ratio resulted in microcapsules with a similar morphology to PS1 and PS2 but smaller in size. The core content ratio increased to 40.8% compared to the microcapsules obtained with 2.5 wt % concentration of the same mixture of surfactants. When the core/shell ratio was increased to 4.23, while keeping the surfactant concentration at 5%, microcapsules with a smoother surface were obtained, though some agglomeration was also detected. Core content in this case amounted to 44.1%.

A final set of experiments, performed by using a 2.5% SDS/PVA mixture, ended up in very smooth and nicely formed microcapsules, independently of the core/shell ratio, and with very high core contents (81.5 and 76.7). While some agglomeration was observed in case of SDP1, SDP2 resulted in perfectly shaped separate microcapsules with a particle size between 35 and 60 μm. Again, when the surfactant concentration was increased to 5%, the results were not as good in terms of encapsulation efficiency (no capsules were formed in SDP3), morphology, and core content. SDP4 showed shrunk microcapsules with smooth surface and much lower core content. These results confirm the added value of PVA when used together with SDS.

CONCLUSIONS

In this study, a unique custom-made high-throughput platform for the combinatorial synthesis of melamine-formaldehyde microcapsules was successfully achieved. This high-throughput encapsulation platform allows to perform experiments in parallel, while mimicking the synthetic procedure of a manual laboratory procedure with the advantages of consuming less raw materials under better controlled process conditions. SEM images of the design of experiments confirmed the successful design and performance of the HTP-platform. Although in few cases excessive foaming made it very challenging to control the synthesis, this combinatorial approach allowed us to find the ideal conditions for the melamine-formaldehyde microcapsule formation with the set of variants we have used. According to the SEM images, the best results were obtained when a 50/50 by weight SDS/PVA mixture as surfactant with a 2.5 wt % concentration was used, with core/shell ratios of 2.82 and 4.23. These experiments resulted in spherical and smooth microcapsules with high core contents.

This combinatorial approach of synthesizing melamine-formaldehyde microcapsules provides the opportunity for the application-oriented preparation of microcapsules in a totally automated and controlled way.

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Notes

The authors declare no competing financial interest.

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