

Formulation of Next-Generation Multicompartment Microcapsules by Reversible Electrostatic Attraction

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Abstract: The combination of several active substances into one carrier is often limited due to solubility, stability and phase-separation issues. These issues have been addressed by an innovative capsule design, in which nanocapsules are assembled on the microcapsule surface by electrostatic forces to form a pH-responsive hierarchical capsule@capsule system. Here, melamine-formaldehyde (MF) microcapsules with a negative surface charge were synthesized and coated with a novel MF-polyethyleneimine (PEI) copolymer to achieve a

positive charge of $\zeta = +28$ mV. This novel coating procedure allows the electrostatic assembly of negatively charged poly-L-lactide (PLLA, $\zeta = -19$ mV) and poly-(lactide-co-glycolide) (PLGA, $\zeta = -56$ mV) nanocapsules on the microcapsule surface. Assembly studies at pH 7 gave a partial surface coverage of PLLA nanocapsules and full surface coverage for PLGA nanocapsules. The pH-responsive adsorption and desorption of nanocapsules was shown at pH 7 and pH 3.

Introduction

Computer-assisted field of product optimization will soon become a fast-growing branch of industry yielding in large diversity of smart and programmable materials with multiple integrated functions.^[1,2] Nano- and microtechnology plays an increasingly important role in this development. Micro- and nanoparticles with sophisticated architecture,^[3] which can store and protect a component of interest and release it with a defined rate on demand, is an essential tool for smart combination and integration of functions into a broad range of materials. In this regard, formulation of next generation of multifunctional microcarriers is an important topic in both, scientific community and industry.^[4–6] Until now, the application fields of multicompartment microcarriers were mainly limited to

bioscience and medicine due to the high production costs and restrictions in formulation that make flexible combination of two or more components in one carrier system technically challenging.^[7,8] Hierarchical multicompartment microcarrier set-up containing two liquid functional components separated in different prefabricated compartments assembled into one carrier system was identified as the most promising approach for the fabrication of the “next generation of carriers with increased complexity”.^[9] This serves as the motivation to create a facile and versatile toolbox technology platform suitable for a broad range of technical applications. A hierarchical electrostatically assembled nanocapsule@microcapsule structure was targeted here for flexible combination of diverse active ingredients in one carrier system (Figure 1). The composition and the release from each compartment can be optimized separately and the overall release out of the assembled multi-

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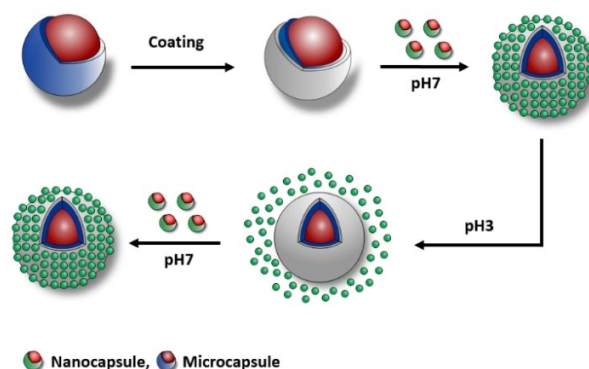


Figure 1. Flow chart of multicompartment microcapsule synthesis and pH-responsive disassembly. A novel coating for microcapsules was applied to change the surface potential from negative to positive. Nanocapsules with a negative surface charge were added to positively charged multilayered capsule to form a multicompartment microcapsule structure.

compartment carrier system can thus be comparatively easily programmed.

Moreover, the microcapsules can serve as docking unit for the pH-induced controlled and successive attachment or detachment of the nanoparticles, which could potentially lead to the generation of even more complex programmable and dynamic active component loading/release profiles.

Herein we present a new microcapsule coating procedure, which allows for permanent and pH-stable modification of a broad range of microparticle/microcapsule surfaces with primary amine groups, which hold positive charge in acidic and medium basic pH. As the surface charge of the resulting coated microcapsules is positive within the broad pH range, such coating enables flexible choice of the underlying microcapsule material and the complementary nanocapsule system, as their pH-dependent surface charge properties do not have to be meticulously matched. The control over the nanocapsule density on the microcapsule surface at a chosen pH can be thus achieved via variation of the surface properties of the nanocapsules alone. This substantially broadens the operational pH window of such systems and allows for easier matching to the broader range of the application scenarios. The same behavior could not be achieved by other microcapsule surface modification procedures, such as, for example, adsorption of strong polyelectrolytes, as it would tend to desorb from many surfaces in the lower pH region, which would make the nanocapsule (re) deposition process not completely reversible. Herein, we demonstrate that combination of micro- and nanocapsules through electrostatics-driven self-assembly by utilization of the new coating is viable.

Microcapsules made from melamine formaldehyde (MF) resins and nanocapsules made from poly-L-lactide (PLLA) and poly-(lactide-co-glycolide) (PLGA) were synthesized in separate steps. The assembly of micro- and nanocapsules was achieved through a new patent-registered polyethyleneimine (PEI)/MF coating for microcapsules, which allows for simple and irreversible changing of the negative charge of the microcapsule surface ($\zeta = -17$ mV) to a positive surface charge ($\zeta = +28$ mV) at pH 7.^[10]

The control over the nanocapsules density on the microcapsule surface at pH 7 is realized by variation of the copolymer composition of nanocapsules correlating with their surface charge; PLLA ($\zeta = -19$ mV) or PLGA ($\zeta = -56$ mV).^[11] The release profiles of the core material out of the nanocapsules and microcapsules is out of the scope of the present publication. Eucalyptus oil was chosen as model core material for both, microcapsules and nanocapsules, as it has application in perfume industry and known to naturally possess antibacterial properties.

Electrostatic capsule@capsule assembly and detachment process can be precisely controlled by changes of the pH value. The system was designed to form stable capsule@capsule structures at neutral pH, while the lowering to pH 3 leads to full detachment of nanocapsules. This process could be repeated by successive addition of nanocapsules.

This pH-responsive multicompartament capsules are of immense interest for the development of novel multifunctional

and programmable systems due to their modularity and flexibility in a seamless integration of different functions. Various types of nanocapsules and microcapsules, loaded with different cargos can be synthesized separately and further combined through electrostatic forces in a target-oriented manner.

Results and Discussion

Preparation and characterization of MF microcapsules with negative surface charge

Microcapsules loaded with eucalyptus oil were synthesized through an acid catalyzed polycondensation of MF resins.^[12] MF resins are highly accepted in industry for microencapsulation due to the strong affinity of polycondensation intermediates to a broad range of interfaces. This affinity is the precondition for the deposition of the solid and densely crosslinked layers of melamine resin onto the surface of dispersed particles and oil droplets resulting in their efficient microencapsulation. Eucalyptus oil serves as the model core material from the class of essential oils and natural biocides^[13] with the properties profile typical for this class of compounds. The oil was colored with sudan III for easier tracking.

The successful formation of the microcapsule shell was observed with an optical microscope (Figure 2A). The microcapsules are spherical with the mean capsule diameter (D_{50}) of 123 ± 21 μm determined by laser diffraction, which was in agreement with the optical microscopy observations. The big size of microcapsules was necessary to ensure easy, fast and complete separation of the capsules from the aqueous medium, in which further experiments with nanoparticles deposition were performed.

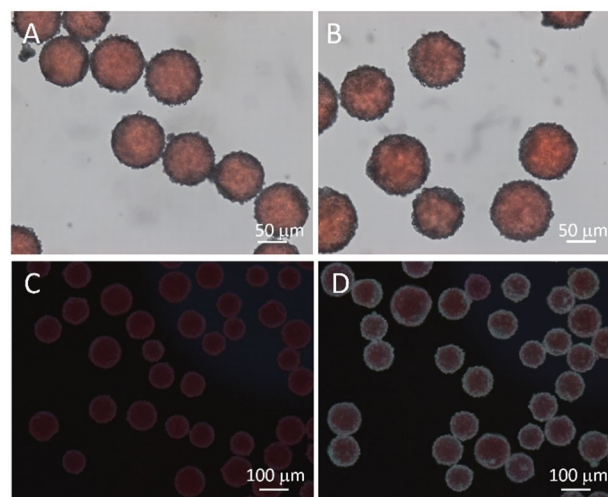


Figure 2. A) Spherical sudan III colored MF and B) MF-PEI-coated microcapsules in optical microscopy. C) MF- and D) MF-PEI-coated microcapsules in fluorescence microscopy. The MF-PEI coating leads to no change in capsule morphology, but successful deposition is confirmed by a blue fluorescent signal emitted by the capsule shell.

The MF microcapsules with smaller diameters are generally known to be very stable towards isolation and drying.^[14] The prepared herein rather big microcapsules lack the mechanical stability due to the comparatively high thickness and corresponding strong shrinkage of MF resin upon condensation, which results in partial cracking of the microcapsules upon isolation and drying. To obtain the microcapsules with better mechanical stability and thus enable handling of the microcapsules in dry state, the MF prepolymer precipitation procedure was repeated. Scanning electron microscopy (SEM) images (Figure 3A) of dry capsules confirmed the expected core-shell morphology of microcapsules with the total shell thickness of 1.2 μm after the second MF deposition.

After successful synthesis of stable microcapsules loaded with eucalyptus oil, the surface charge of the capsule was investigated. Because the available procedures for measurement of surface potential (laser doppler electrophoresis and streaming potential) are limited to maximum capsule size of 10 μm , the surface charge was measured indirectly. For this purpose, in a separate experiment, pure MF prepolymer was condensed in exactly the same manner as in the microencapsulation procedure with the only difference that no core material was added to the vessel. In this way MF condensed and precipitated in the form of microparticles with the average size (D_{50}) of 3.5 μm and its electrophoretic mobility was analyzed. The zeta potential of MF polymer, which corresponds to the capsule shell material, was negative and equal to $\zeta = -17$ mV at pH 7.

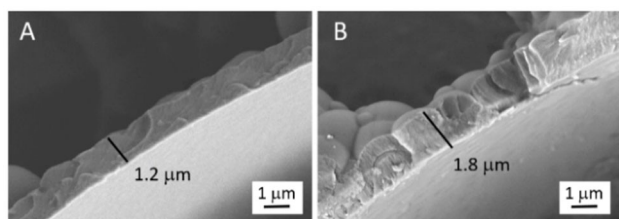
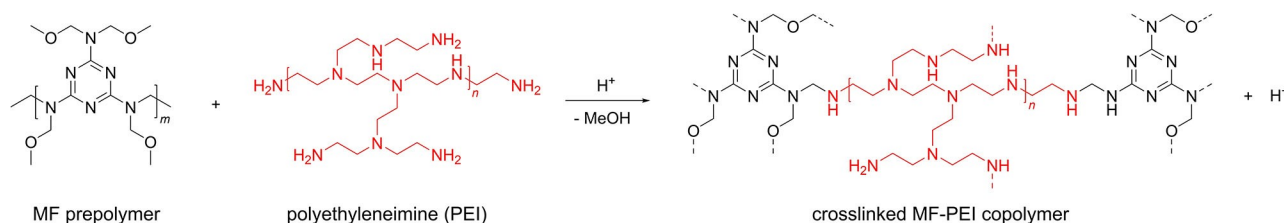


Figure 3. SEM images of A) MF- and B) MF-PEI-coated microcapsule shells after breakage. The capsules give a core shell morphology with thicknesses of 1.2 and 1.8 μm .



Scheme 1. Scheme of acid-catalyzed polycondensation of a MF prepolymer with branched PEI yielding a three dimensional copolymer for microcapsule coating. The remaining surface groups are predominantly free amine groups, which are responsible for the positive zeta potential.

Deposition of microcapsule coating with a positive surface charge

In the past, several organic and inorganic micron-sized particles and droplets were coated with MF resins.^[15–17] Thus, the MF prepolymer as described above can be used as capsule shell material as well as a coating with negative surface charge at neutral pH. The targeted capsule@capsule structure relies on positively charged microcapsules and negatively charged nanocapsules. Therefore, the MF prepolymer was copolymerized in-situ with polyethyleneimine (PEI) resulting in a new crosslinked coating material that has free primary amine groups on the microcapsule surface (Scheme 1). The copolymerization of MF precondensates with 12 wt% PEI (in relation to MF resin solid content) resulted in the novel polymeric water-born coating,^[10] which combines the properties of the MF (deposition on the broad range of surfaces and formation of chemically stable crosslinked films) and PEI (primary amine groups). As amine groups of PEI are reactive towards formaldehyde groups present in MF, it integrates into the crosslinked film structure and acts as the functional reactive building block.

The MF-PEI polymer was coated on pre-synthesized eucalyptus oil-loaded microcapsules with the same acid-catalyzed polycondensation procedure as described for microencapsulation. Optical microscopy showed no change in microcapsule morphology after deposition of the positively charged layer (Figure 2B). The mean particle size (D_{50}) of MF-PEI-coated microcapsules gave 128 ± 22 μm as determined by laser diffraction method. The proof for the successful deposition of MF-PEI coating on the microcapsule surface was provided by capsule shell thickness measurements and fluorescence microscopy. The new copolymer coating showed an increase in the shell thickness from 1.2 to 1.8 μm , as confirmed by SEM (Figure 3B).

Pure MF capsules do not exhibit any fluorescence signal, whereas the new MF-PEI copolymer has autofluorescent properties meaning that it emits a fluorescent signal without any addition of dyes when excited with UV light (Figure 2D). The new autofluorescent MF-PEI polymers had $\lambda_{\text{ex}} = 360$ nm and a $\lambda_{\text{em}} = 490$ nm (further detailed information on the fluorescent behavior will be provided in a following paper). So far, the origin of this effect cannot be explained but the blue colored emission of MF-PEI coating proves that the deposition as well as the copolymerization between MF and PEI successfully occurred.

For the same reasons as described in the chapter above, the zeta potential of coated microcapsules was measured indirectly. The MF-PEI coating was condensed and precipitated in the form of microparticles with the average size (D_{50}) of 1.6 μm and its electrophoretic mobility was investigated. The zeta potential of MF-PEI polymer, which corresponds to the capsule coating was positive and equal to $\zeta = 28$ mV. Additionally, a trinitrobenzene sulfonic acid (TNBSA) assay was performed with MF- and MF-PEI-coated microcapsules to prove the existence of free amine groups on the microcapsules surface.

TNBSA is known to give yellow complex^[18] with free primary amines. For this analytical procedure uncolored MF and MF-PEI capsules were synthesized under same conditions (without sudan III). The MF-PEI-coated microcapsules gave a clear yellow color that is characteristic for the complex between TNBSA and free primary amine groups, while the pure MF capsules kept almost white in color (Figure 4).

Microfluidic preparation and characterization of different types of nanocapsules with negative surface potential

The formation of negatively charged PLLA and PLGA nanocapsules loaded with eucalyptus oil was achieved through the emulsification/solvent evaporation process, performed in a continuous flow. Sodium dodecyl sulfate (SDS) was used here as stabilizer of emulsion droplets/nanocapsules. The continuous production of nanocapsules in microfluidic systems is favored due to stable process conditions, high reproducibility, the reduced formation time of nanocapsules and high production scale can be achieved.

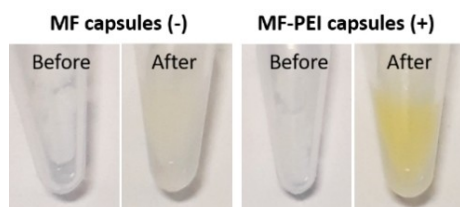


Figure 4. Left: White MF microcapsules and right: MF-PEI-coated microcapsules before and after addition of TNBSA. The yellow color of the MF-PEI-coated capsules verifies the presence of free amine groups on the surface. The eucalyptus-oil-filled microcapsules were synthesized without addition of sudan III.

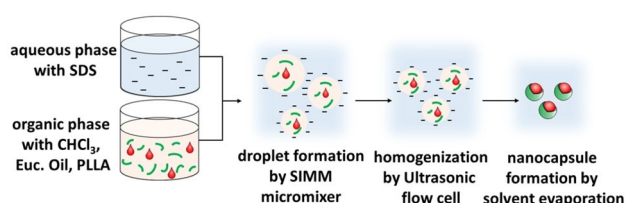


Figure 5. Formation of polymeric nanocapsules by emulsification/solvent evaporation. The organic phase is dispersed in the aqueous phase by SIMM V4 micro mixer with a modified 50 μm outlet. Droplets are homogenized by ultrasonic flow, and chloroform was evaporated by FFMR at 58 $^{\circ}\text{C}$.

Both types of nanocapsules, PLLA and PLGA, were prepared according to the process shown schematically in Figure 5. The first step of droplet formation was performed by a slit interdigital micro mixer having 50 μm pinhole in the outlet channel resulting in macro-emulsion droplets with the size up to 20 μm . Further size reduction and homogenization was done by an ultrasonic flow cell that induces cavitation and shear forces to the emulsion. Droplets with a diameter of around 1 μm , which consisted of chloroform, eucalyptus oil and PLLA or PLGA, were formed this way. The evaporation of chloroform took place in the pre-heated falling film micro reactor at 58 $^{\circ}\text{C}$ and with nitrogen as carrier gas.^[19] Upon evaporation of solvent, the used polymer precipitated at the interface of the droplets and formed the nanocapsules shell with eucalyptus oil as a core. PLLA and PLGA nanocapsules showed homogeneous size distribution with an average size of 115 ± 21 and 145 ± 21 nm, respectively.

To effectively assemble nanocapsules onto microcapsule surface through electrostatic attraction, it is very important that the charged groups are present on the surface of both capsules. Small and mobile SDS molecules present at high concentrations in the PLLA/PLGA nanocapsule dispersions will spontaneously deposit on the surface of MF microcapsules, thus hindering the interactions with negatively charged nanocapsules. Through repetitive centrifugation/redispersion in the demineralized water, the excess of SDS molecules was washed out and only very few amount of SDS remains that is attached to nanocapsules surface. After washing cycles, the zeta potential of PLLA and PLGA nanocapsules corresponds to -19 and -56 mV. As compared to PLLA nanocapsules, the zeta potential for PLGA nanocapsules is higher, which is due to the higher amount of carboxylic groups present in the PLGA polymer.

The PLLA/PLGA system presents a robust nanoencapsulation process. As both polymers are soluble in chloroform and insoluble in the chosen model core material (eucalyptus oil), the capsule fabrication procedure is almost independent of the chosen wall building block component. Thus, the surface charge of the resulting capsules at a chosen pH can be controlled simply by the choice of the polymer.

Formation of multicompartament microcapsules

The focus of the present study is the formation of multicompartament microcapsules with hierarchical structure through electrostatic attraction. Therefore, PLLA and PLGA nanocapsules with different strength of negative surface charge were mixed with positively charged MF-PEI microcapsules at neutral pH (pH 7).

Without addition of nanocapsules, the positively charged MF microcapsule surface shows some inequalities in scanning electron microscopy (SEM) but no adsorption of nanoparticles (Figure 6).

When synthesized PLLA nanocapsules with a surface potential of -19 mV were added at pH 7, the nanocapsules assembled on microcapsules' surface with an even distribution and regular gaps between single PLLA capsules (Figure 7A).

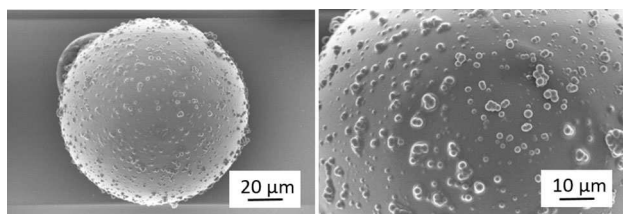


Figure 6. SEM images of spherical MF-PEI-coated microcapsules with some inhomogeneity at the surface.

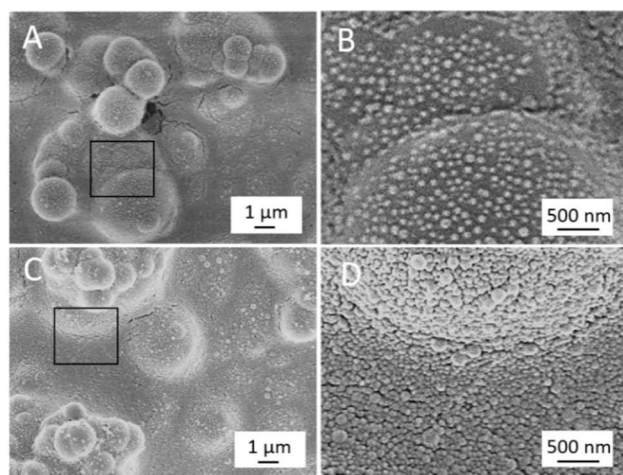


Figure 7. SEM images of microcapsules with adsorbed A), B) PLLA and C), D) PLGA nanocapsules at pH 7.

However, no adsorption occurred when PLLA capsules were added to negatively charged MF microcapsules (data not shown).

The PLGA nanocapsules with more negative surface potential of -56 mV resulted in almost full coverage of microcapsule surface (Figure 7B). Both types of negatively charged nanocapsules are electrostatically attracted to the positively charged microcapsule surface. The main factor that is responsible for the assembling density seems to be the surface charge of nanocapsules.

The formation of multicompartiment microcapsules with negatively charged nanocapsules on the surface of positively charged microcapsules have been successfully demonstrated. Based on the presented multicompartiment capsule@capsule approach, we assume that numerous encapsulated hydrophobic materials can be attached to MF microcapsules surface and even more complex systems can be generated.

This structural set-up with separated encapsulation of hydrophobic components is a versatile process, easy to apply and adjustable for any kind of application.

Successive adsorption/ desorption of PLGA nanocapsules

The surface potential of nano- and microcapsules strongly depends on the pH value of the dispersion medium and is

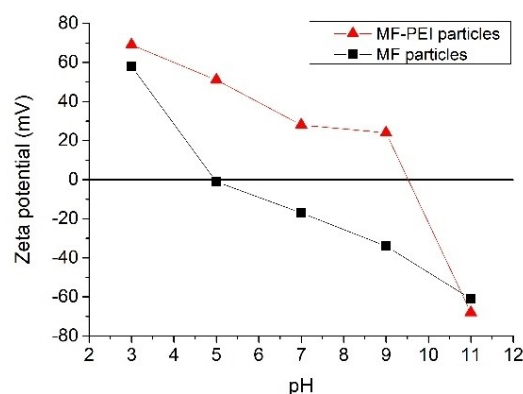


Figure 8. Zeta potential measurements of MF and MF-PEI particles as a function of pH value. The MF polymer exhibits negative surface potential from strongly basic pH up to pH 5, whereas the MF-PEI polymer shows a positive surface charge over broad pH range ($< \text{pH } 10$).

usually determined at pH 7. The presented capsule@capsule assembly was designed by the surface charges so that at pH 7 a strong electrostatic force acts between the MF-PEI microcapsules and PLLA/PLGA nanocapsules. By lowering the pH, the attraction will change significantly due to the protonation of used amine and carboxylic groups. Zeta potential measurement of MF-PEI particles between pH 3 and pH 11 exhibits a positive charge of the amine groups over a wide pH range (pH 3–9) and thus a good operating window for the assembly of negatively charged nanocapsules (Figure 8). It is known from the literature that the surface of PLLA^[20] and PLGA^[21] nanocapsules shows a negative potential at pH 7, whereas at pH 3 the carboxyl groups are no longer deprotonated ($\text{p}K_a$ 4–5),^[22] so that the negative charge decreases significantly. For the formation of stable PLGA nanocapsules, we used SDS as anionic surfactant, and although the zeta potential measurements at pH 3 showed a negative charge of the nanocapsules (-40 mV), which is mainly due to the presence of sulphate groups, a complete desorption of PLGA nanocapsules in the PLGA@MF-PEI capsule assembly at pH 3 can be observed. The obtained results demonstrate that the covalently bonded carboxyl groups are mainly responsible for the adsorption of PLGA nanocapsules onto the MF-PEI microcapsules. The physically adsorbed SDS molecules most probably interact with the positive charges of microcapsule, but are not responsible for the assembly of nanocapsules.

If the pH value is now set back to pH 7 and fresh PLGA nanocapsules are added, the capsule@capsule assembly is formed again. SEM images of the different states are shown in Figures S1–S4 in the Supporting Information. The pH is a high potential stimulus for successive assembly processes which allows a potentially infinite number of adsorption/ desorption cycles. Furthermore, it is assumed that the presented solution can be transferred to other oppositely charged systems such as positive charged nanocapsules and negative charged microcapsules since the MF polymer also works as coating for microcapsules yielding a negative surface potential over broad pH range (Figure 8).

Conclusion

This study presents the design and fabrication of stimuli-responsive multicompartment microcapsules for the delivery of hydrophobic, active substances. A novel, hierarchical capsule@capsule structure was targeted and formed through electrostatic assembly of PLLA or PLGA nanocapsules on a MF microcapsule surface. Investigations by SEM confirmed the formation of the capsule@capsule structures caused by the electrostatic attraction of oppositely charged capsule wall materials. The density of the nanocapsules on the microcapsule surface increased with the increasing gap in zeta potential. PLGA nanocapsules gave full surface coverage, whereas PLLA nanocapsules gave partial surface coverage on MF microcapsules. The attraction between nano- and microcapsules strongly depends on pH value; this was used as stimulus for the successive adsorption/desorption of nanocapsules. For PLGA nanocapsules, a fully successive adsorption at pH 7 and desorption at pH 3 was demonstrated.

In contrast to known procedures for complex capsule synthesis, this novel and facile approach allows the free combination of diverse available capsules with different loading materials within one multicompartment microcapsule structure.

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Conflict of Interest

The authors declare no conflict of interest.

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