ARTICLES

Chitosan-TPP microcapsules for controlled drug release

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Microcápsulas de Chitosan-TPP para liberación controlada de fármacos

Microcàpsules de quitosà-TPP per alliberament controlat de fàrmacs

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ABSTRACT

Production of chitosan/sodium tripolyphosphate (CS/TPP) microcapsules via spray drying involves atomizing an emulsion containing CS, TPP, acetic acid (AcOH), and folic acid (FA) into fine droplets exposed to high-temperature, low-pressure gas flow. Solvent evaporation within the drying chamber leads to solid particle formation. Spray drying is valuable for creating solid CS/TPP microcapsules. Precise equipment parameter adjustments, like inlet temperature and gas flow rate, enable the study of microcapsule morphology, size, and properties. This adaptability allows for customization to specific pH dissolution ranges. The production method's impact on CS/TPP microcapsules was studied by modifying spray drier parameters, including inlet temperature and aspirator pressure, to enhance understanding of their behavior in solution under varied production conditions.

In chitosan delivery systems, various approaches can encapsulate drug agents like folic acid, an analog to the cancer treatment drug methotrexate. Agents can be added to the chitosan solution pre-crosslinking, incorporated into gelation-inducing agents pre-mixing with chitosan, or included in the crosslinking mixture. Experiments were conducted to assess CS/TPP microcapsules' behavior when encapsulating agents like folic acid. Release profiles were analyzed to understand their drug delivery capabilities and potential as controlled release carriers.

Keywords: CS/TPP complexes, spray dryer, microcapsules.

RESUMEN

La producción de microcápsulas de quitosano/tripolifosfato de sodio (CS/TPP) mediante secado por aspersión implica atomizar una emulsión que contiene CS, TPP, ácido acético (AcOH) y ácido fólico (FA) en finas gotas expuestas a un flujo de gas a alta temperatura y baja presión. . La evaporación del disolvente dentro de la cámara de secado conduce a la formación de partículas sólidas. El secado por aspersión es valioso para crear microcápsulas sólidas de CS/TPP. Los ajustes precisos de los parámetros del equipo, como la temperatura de entrada y el caudal de gas, permiten el estudio de la morfología, el tamaño y las propiedades de las microcápsulas. Esta adaptabilidad permite la personalización a rangos de disolución de pH específicos. El impacto del método de producción en las microcápsulas de CS/TPP se estudió modificando los parámetros del secador por aspersión, incluida la temperatura de entrada y la presión del aspirador, para mejorar la comprensión de su comportamiento en solución en diversas condiciones de producción.

En los sistemas de administración de quitosano, varios enfoques pueden encapsular agentes farmacológicos como el ácido fólico, un análogo del medicamento para el tratamiento del cáncer metotrexato. Se pueden

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agregar agentes de reticulación previa a la solución de quitosano, incorporarse a agentes inductores de gelificación premezclados con quitosano o incluirse en la mezcla de reticulación. Se realizaron experimentos para evaluar el comportamiento de las microcápsulas de CS/TPP al encapsular agentes como el ácido fólico. Se analizaron los perfiles de liberación para comprender sus capacidades de administración de medicamentos y su potencial como portadores de liberación controlada.

Paraules clau: Complejos CS / TPP, secadora por pulverización, microcápsulas.

RESUM

La producció de microcàpsules de quitosà/tripolifosfat de sodi (CS/TPP) mitjançant l'assecat per aerosol implica atomitzar una emulsió que conté CS, TPP, àcid acètic (AcOH) i àcid fòlic (FA) en gotes fines exposades a un flux de gas a baixa pressió i alta temperatura. . L'evaporació del dissolvent dins de la cambra d'assecat condueix a la formació de partícules sòlides. L'assecat per aerosol és valuós per crear microcàpsules sòlides de CS/TPP. Els ajustaments precisos dels paràmetres de l'equip, com la temperatura d'entrada i el cabal de gas, permeten l'estudi de la morfologia, la mida i les propietats de la microcàpsula. Aquesta adaptabilitat permet la personalització a intervals de dissolució de pH específics. L'impacte del mètode de producció en les microcàpsules CS/TPP es va estudiar modificant els paràmetres de l'assecador de polvorització, inclosa la temperatura d'entrada i la pressió de l'aspirador, per millorar la comprensió del seu comportament en solució en condicions de producció variades.

En els sistemes de lliurament de quitosà, diversos enfocaments poden encapsular agents farmacèutics com l'àcid fòlic, un anàleg del medicament per al tractament del càncer metotrexat. Els agents es poden afegir a la solució de reticulació prèvia de quitosà, incorporar-se als agents inductors de gelificació que es barregen prèviament amb quitosà o incloure'ls a la barreja de reticulació. Es van realitzar experiments per avaluar el comportament de les microcàpsules CS/TPP quan s'encapsulen agents com l'àcid fòlic. Es van analitzar els perfils d'alliberament per entendre les seves capacitats de lliurament de fàrmacs i el seu potencial com a portadors d'alliberament controlat.

Paraules clau: Complexos CS/TPP, assecador de polvorització, microcàpsules.

INTRODUCTION

During the process of spray drying, the combination of heat and the low humidity in the drying gas causes the droplets to reduce in size and solidify, resulting in the formation of microcapsules[1]. Within the drying chamber, the drying gas follows a cyclonic pattern, which aids in separating solid particles from the remaining droplets and drying gas. These solid particles are gathered in a cyclone or a similar separation device, while the drying gas is expelled from the system[2].

Spray drying is a valuable method for creating solid CS/TPP microcapsules. By carefully adjusting equipment parameters like inlet temperature and gas flow rate, we have the capability to control the characteristics of the generated microcapsules[3]. This flexibility allows us to customize CS/TPP microcapsules to meet the specific requirements of our research. Consequently, we investigate how the production process impacts the morphology, size, and residual moisture content of CS/TPP microcapsules by modifying the parameters of the spray dryer, such as inlet temperature and aspirator pressure. We also conducted an in-depth examination of the emulsion composition for CS/TPP microcapsule production. Our goal in studying these aspects was to deepen our comprehension of how CS/TPP microcapsules behave in solution under varying production conditions and their potential to validate the hypotheses of this thesis.

Chitosan is a natural, biocompatible, biodegradable polymer and in the realm of chitosan delivery systems, multiple methods are available for encapsulating drug agents such as folic acid, an analog of methotrexate used in cancer treatment. These agents can be introduced into the chitosan solution before the addition of crosslinking-inducing agents, integrated into gelation-inducing agents before mixing with the chitosan solution, or incorporated into the crosslinking mixture solution containing both chitosan and gelation-inducing agents[4,5,6]. The choice of method depends on the properties of the chitosan delivery system and the specific drug agent to be encapsulated. Furthermore, we conducted experiments to investigate how CS/TPP microcapsules behave in solution when they encapsulate agents like folic acid. We analyzed the release profiles to gain insights into their drug delivery capabilities and assess their potential as effective carriers for controlled release applications.

MATERIALS AND METHODS

Chitosan was purchased from Across Organics. Chemical reagents such as hydrochloric acid, acetic anhydride, oxalic acid, potassium hydroxide, sodium hydroxide, Sodium tripolyphosphate, and glacial acetic acid were purchased from Sigma Aldrich Co. in St Louis, USA. Folic acid (FA) was obtained from BDH Chemicals in England. All chemical reagents were used as purchased without any further purification. Synthetic dry air with 99.5% purity was purchased from Carburos Metálicos, S.A. in Spain. Ultrapure water from Millipore in the USA was used throughout the experiment.

Preparation of CS/TPP emulsions and characterization

To prepare chitosan and TPP solutions, chitosan was first dissolved in an acetic acid (AcOH) solution until the final pH of 6.2 for complete dissolution (Chitosan pKa 6.5). While TPP was dissolved in water (pH above 8 due to TPP speciation). Both solutions were kept

under magnetic stirring until complete dissolution. The emulsions were mixed by slowly adding the TPP solution to the CS solution under constant magnetic stirring (500 rpm, Yellow line MAG HS7, IKA, Germany) at room temperature for 30 minutes before spraying. Initially, different formulations were studied to evaluate morphology, size, size dispersion, and crosslinking degree of CS/TPP. Additionally, the capacity of the microcapsules in encapsulating compounds, like folic acid, was evaluated.

Spray dryer equipment and microcapsule production

CS/TPP microcapsules were generated using a B-290 Mini BÜCHI® Spray Dryer, utilizing 100 mL of emulsions. The key technical parameters affecting morphology and size were the inlet temperature (ranging from 150 to 180 °C), aspirator pump flow rate (varying from 20 to 32 $x10^3$ L/h), and feed flow rate (0.42 L/h). The spray chamber maintained an air flow of 357 L/h at 0.23 bar, with a nozzle featuring an inner diameter of 2 mm and an outer diameter of 4 mm.

For subsequent experiments comparing compositions, we used the optimal spray dryer conditions: an inlet temperature of 170 °C, an aspirator pump flow rate of 28 $x10^3$ L/h, and a feed flow rate of 0.42 L/h. The resulting microcapsules were stored in amber glass containers at room temperature.

Morphology characterization

The morphology, size, and composition of the microcapsules were analyzed using an environmental scanning electron microscope (ESEM) FEI Quanta 600. The microcapsules were transferred onto a carbon tape and coated with a ~27 nm Au layer (30 mA, 90 s) in a sputter coater (Quorum Q150T S plus). The diameter of the microcapsules was manually measured in the SEM images using ImageJ software (version 1.53e) to determine their size distribution.

FTIR analysis

The crosslinking degree of the microcapsules was analyzed using infrared spectroscopy with a Jasco FT/IR-6700 Infrared Spectrometer equipped with an attenuated total reflection (ATR) PRO ONE accessory and a diamond crystal kit or a Ge crystal kit. The microcapsule samples were directly placed on the surface of the optic lenses without any prior treatment. The FTIR spectra were recorded in transmittance mode with a resolution of 4 cm^{-1} by accumulating 32 scans from 4000 to 400 cm^{-1}.

Microcapsule performance at different pH solutions

To explore microcapsule behavior in various environments, we dispersed them in solutions with pH levels spanning from 4.5 to 8.5, simulating the pH range commonly encountered in different tissue-origin solid tumors. pH was controlled by adding 0.001M HCl or 0.001M NaOH. Additionally, we examined microcapsules in buffer solutions: sodium phosphate buffer, representing a physiological simulation, and lactic/lactate buffer, emulating a cancer extracellular environment.

pH analysis

We evaluated the morphology of the microcapsules in solution at 0 and 60 minutes (time enough for most of drugs to distribute in the body with high efficiency) using an optical microscope, and we measured the change in pH of the solution by adding 100 mg of microcapsules to 10 mL of solution. We used a Thermo Scientific™ Orion™ 3-Star Benchtop pH Meter to take pH measurements every 30 seconds.

Zeta potential measurements

The size and zeta potential (ZP) of the microcapsules were measured using a Malvern Zetasizer Ultra instrument (Malvern Panalytica) at a temperature of 25.0 ± 0.5 °C. The size measurement was performed using a dynamic light scattering (DLS) technique, and the ZP measurement was conducted using Laser Doppler Anemometry (LDA). The microcapsules were analyzed in suspension immediately after preparation to avoid any changes in their size or charges due to Ostwald ripening or particle growth. For each experiment, the mean of three measurements was calculated.

Folic acid profile release from the microcapsules

To assess folic acid release, 100 mg of microcapsules were mixed with 10 mL of buffer solutions, stirred at 300 rpm at room temperature, and sampled every 10 minutes for 30 minutes, maintaining a consistent 5% v/v of the total solution volume. The filtrate (filtered using a 200 nm pore size filter) was then analyzed using HPLC-DAD Shimadzu LC-40C with a C18 column (Kromasil 100-5 phenyl®, 300X4.6 mm, 5 µm) from Agilent Technology. The HPLC analyses ran isocratically at 1.5 mL/min at room temperature, with detection at 290 nm. Calibration curves were established for low (0.2-1 ppm, $R^2 = 0.9991$, $y = 77.622x + 7198.9$) and high concentrations (1-5 ppm, $R^2 = 0.9993$, $y = 104031x + 12488$). Folic acid's retention time was determined during the analysis.

RESULTS

Microcapsule morphology dependent on composition

Some preliminary microcapsules were produced by using an emulsion with 0.4, 0.6, and 0.8 %w/v CS mixed with and without TPP and FA, in order to observe morphology and size dependency on composition, microcapsules are shown in **Figure 1**. The parameters of the spray drier were the same in all experiments, inlet temperature 170 °C, aspirator 29.75 m^3/h, and feeding rate 6 mL/min. The microcapsules are mostly collapsed. In general, microcapsules look more collapsed with lower content on CS, which might be due to the drying process.

In the spray-drying process, each droplet typically forms one microcapsule, with its size determined by the initial droplet size and solid content. However,

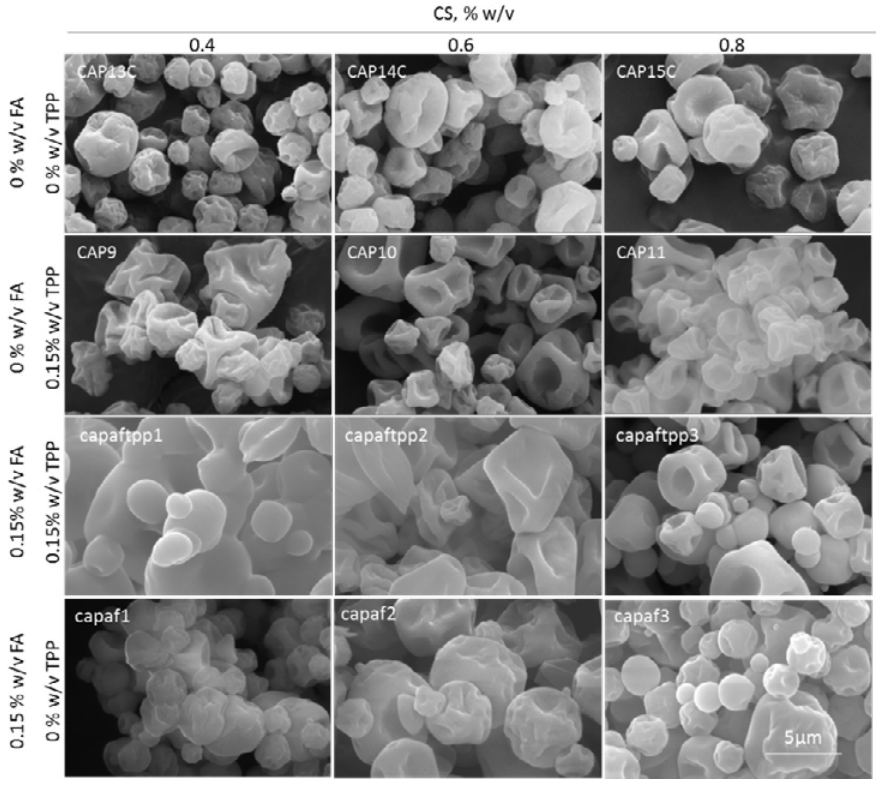

Figure 1. *Microcapsules produced by SD at different CS and TPP composition.*

droplet formation lacks precise control, resulting in microcapsules having a wide size range. This variance occurs due to droplets breaking into smaller fragments during drying, primarily when the solution is dilute.

During microcapsule shell formation, moisture rapidly migrates from the droplet interior to maintain surface moisture saturation and minimize surface energy. As water and AcOH (acetic acid) evaporate from the droplet surface, it becomes fully moistened, leading to reduced droplet size and maximum drying speed. Faster evaporation leads to quicker critical supersatura-

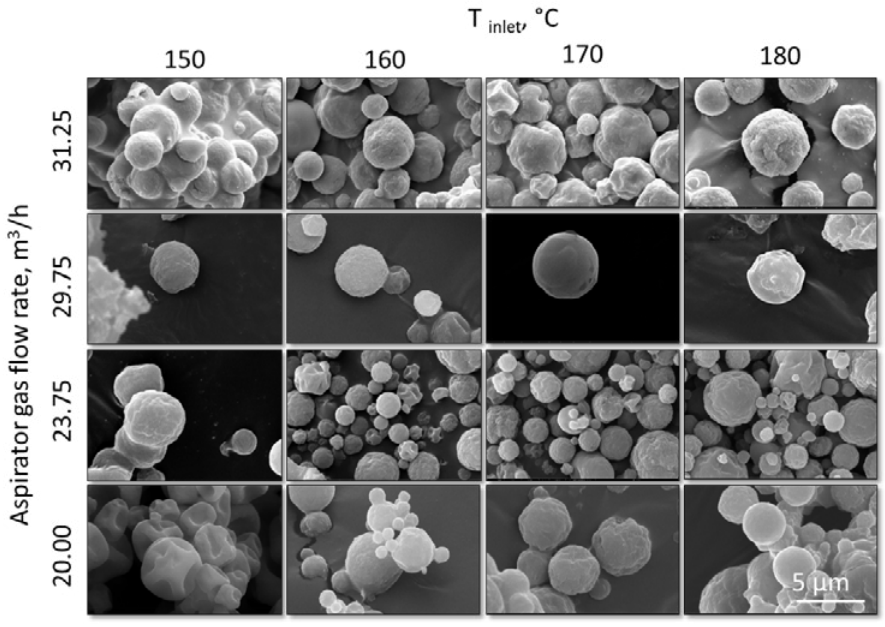

Figure 2. *SEM images of CS/TPP microcapsules C18 (0.80 %w/v CS/0.64 %w/v TPP) at different aspirator gas flow rates and inlet temperatures.*

tion, initiating early shell development, often forming a corrugated shell.

Subsequently, the droplet's surface can't maintain moisture saturation, causing vapor within the shell to diffuse outward through pores or molecular gaps. The drying rate slows as the shell thickens, with a consistent diffusion time across all experiments due to an aspiration rate of 29.75 m^3/h. Therefore, the drying process depends on emulsion drop interactions, with shell thickness influenced by solid content and raw material feed rate[2,3].

Microcapsule morphology

Various spray-drying setups were used to study the impact of inlet temperature and aspirator gas flow rate on microcapsule characteristics. The chosen emulsion composition (0.80%w/v CS and 0.64%w/v TPP) was processed at a constant flow rate of 6 mL/min.

The inlet temperature is a crucial spray dryer parameter, affecting drying capacity, solvent evaporation rate, crystallization, porosity, and drug loading. Higher temperatures lead to faster drying, increased porosity, and uniform morphology. Conversely, lower temperatures and high gas flow rates retain more moisture and extend drying time, ensuring well-dried microcapsules[3,7].

We created microcapsules with varying CS and TPP ratios to assess crosslinking. We focused on the CS concentration yielding spherical microcapsules and compared them to emulsions with the same ratios but lower mass content. Spray drying conditions were 180°C, flow rate 6mL/min, and aspirator gas flow rate 31.25 m^3/h, as displayed in Figure 3.

Microcapsules with more TPP than CS had a globular shape with a regularly rough surface, enhancing roughness as TPP increased. In contrast, microcapsules with more CS than TPP showed collapsed shapes with mixed rough and flat surfaces. Spherical microcapsules achieved maximum structural stability through uniform diffusion of CS, TPP, and solvents (water and AcOH) within the droplets.

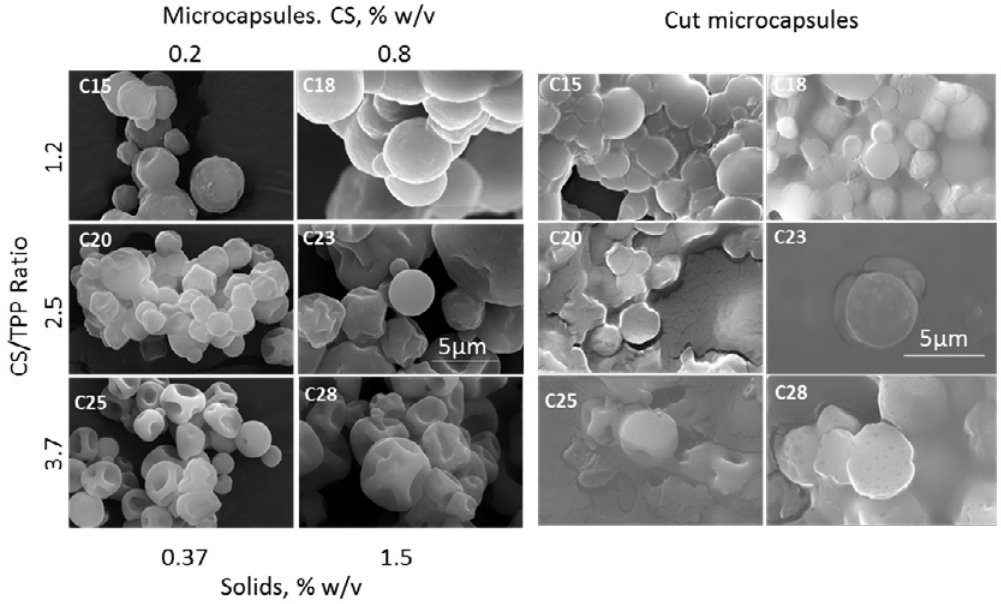

Figure 3. *SEM images of CS/TPP microcapsules obtained by SD at 1.2, 2.5 and 3.7 CS/TPP ratio.*

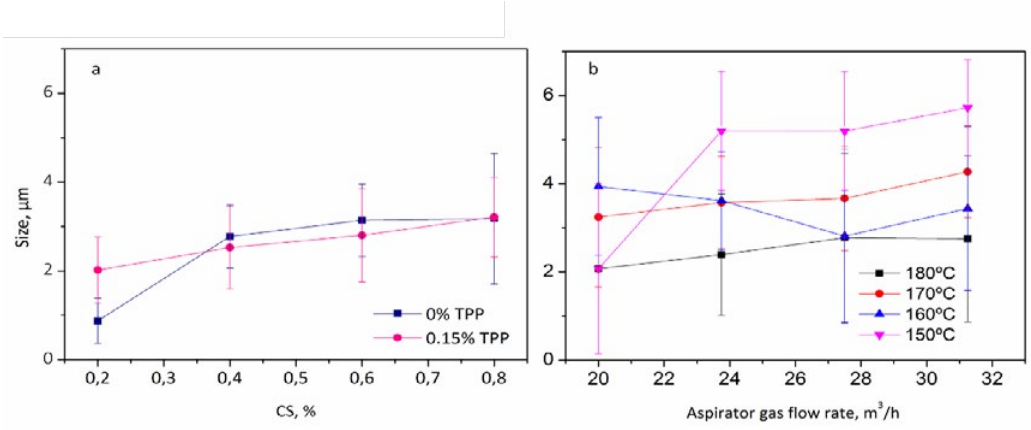

Figure 4. *Comparison of the size diameter momentum (average of standard deviation of 100 microcapsules SD) of CS/TPP and CS microcapsules obtained by spray drier at different a) CS concentration of the solutions and b) SD conditions.*

The collapsed microcapsules morphology might be attributed to the faster diffusion of the CS and TPP solids to the shell and the lowest migration of liquids outside of the microcapsule. However, if the drying process is too fast, and there is no chance for CS and TPP to diffuse, a hollow structure of the microcapsules will be formed as in C28 microcapsule[2,3].

Microcapsules' size and size distribution

The size distribution of microcapsules, produced from emulsions with different ratios of CS to TPP, but under the same spray-drying conditions (inlet temperature: 170°C, aspirator gas flow rate: 29.75 m^3/h, pump rate: 6 mL/min) is shown in **Figure 4a**. As expected, the microcapsules' size is directly proportional to the CS concentration. However, at low CS concentrations (0.2% w/v), the size is drastically affected by the TPP concentration. This may be due to the lower compactness of the net and crosslinking degree at higher TPP concentrations, resulting in a higher size distribution.

Microcapsules produced at different spray drier conditions but same composition (**Figure 4b**), as expected, are larger at lower inlet temperatures due to the higher moisture content during the drying process. Additionally, microcapsules produced at lower aspirator gas flow rates remain in the spray drier chamber for a longer period, hindering the evaporation process. However, despite our efforts to study the composition and spray drier parameters, it was not possible to obtain microcapsules with a narrower size distribution. The mean size of the microcapsules remains consistent in both plots in **Figure 4**, regardless of the emulsion concentration and spray drier conditions.

Evaluation of microcapsule crosslinking degree

The crosslinking degree is a crucial factor in microcapsules to be used for drug delivery applications as it determines the point at which the resulting structure is dissolved into the solution to release the load. In order to analyze this parameter, we compared the FTIR spectra of raw CS and TPP, CS/TPP coacervated, and C18 microcapsules, as shown in **Figure 5**. To obtain the FTIR spectra of the emulsion, we subtracted the background signal from the water.

Typically, the FTIR bands of CS and TPP overlap when the compounds are mixed, but new bands or elongations appear when a new bond is formed, as seen at 1410 and 1560 cm^{-1}, which elongate due to electrostatic interaction between CS and TPP. This elongation is caused by the stretching movement between the -C-N- and -N-H of the chitosan, due to the presence of the electrostatic interaction of the phosphorus compound from TPP. This electrostatic interaction promotes crosslinking between the CS chains' ($-NH_3^+$ group) and TPP molecules' (-OH group) to form a net. The net's density depends on the quantity of TPP per CS chain[8].

Microcapsule morphology in simulated physiological media

Chitosan, a weakly basic polymer, becomes positively charged when its amino groups protonate under acidic conditions. This charge increase at low pH enhances electrostatic repulsion between chitosan chains, reducing aggregation and stabilizing CS microcapsules.

In contrast, CS/TPP microcapsules are less pH-sensitive due to TPP acting as a crosslinker. TPP's negative

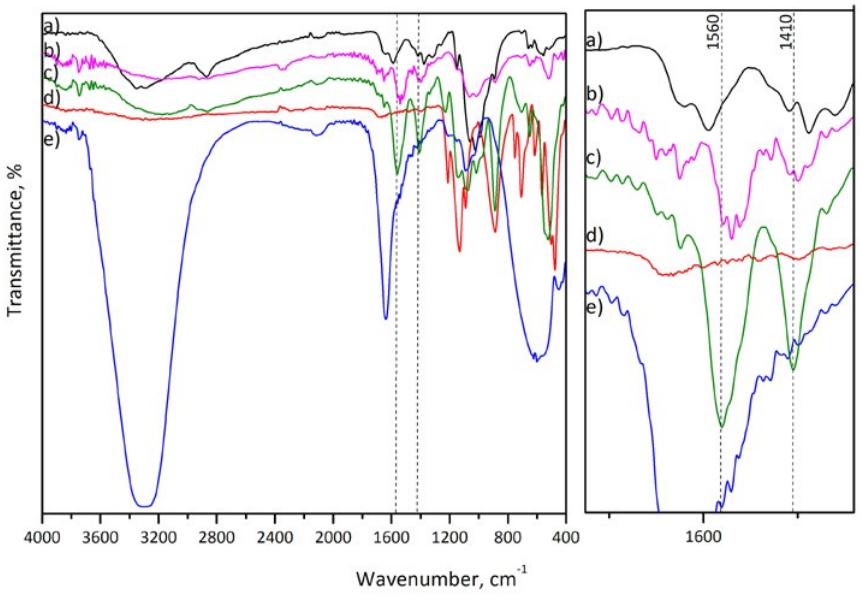

Figure 5. *FTIR spectra of different components involved in the production of CS/TPP microcapsules. The spectra of a) CS, b) coacervated with composition C18 without water background, c) microcapsule with composition C18, d) TPP, and e) coacervated with composition C18 with water background.*

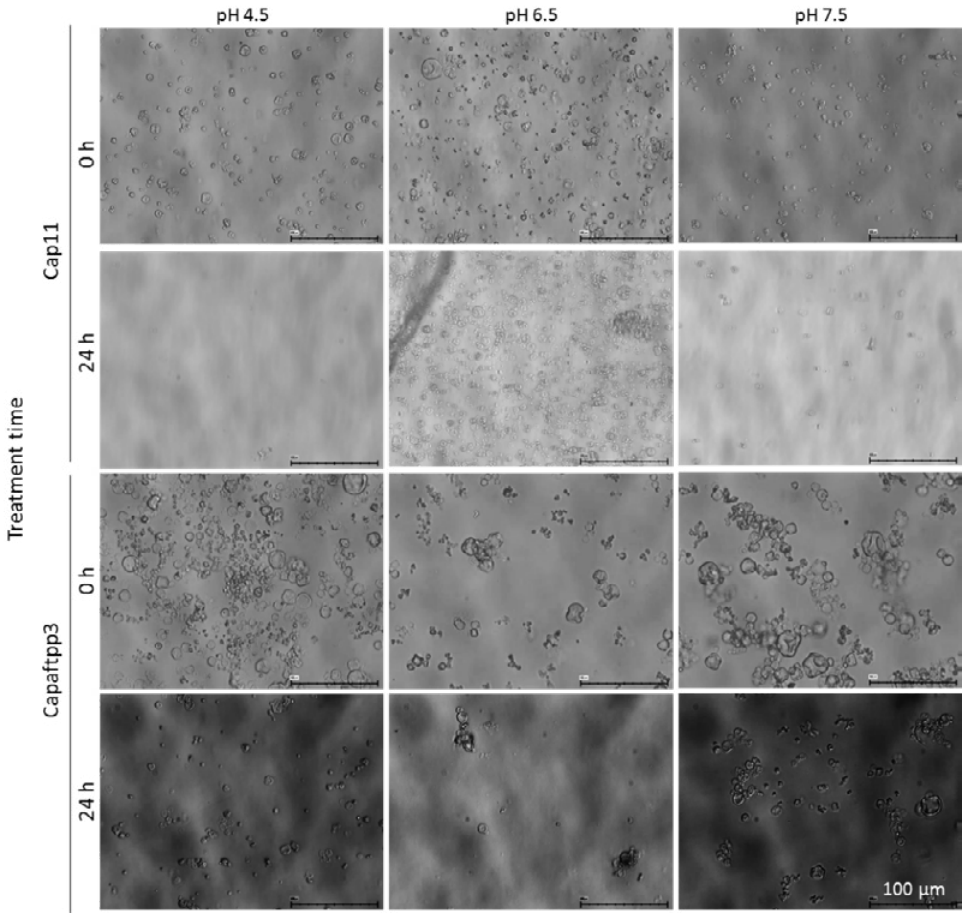

Figure 6. *Optical images of microcapsules captured at different exposure times and pH values.*

charge reacts with chitosan's positive amino groups, forming a network of crosslinked polymer chains. This crosslinking enhances stability across a broad pH range.

We created crosslinked microcapsules containing folic acid (FA) for release profile and integrity assessment. The microcapsules were submerged at pH 4.5, 6.5, and 7.5 and observed under a 40X optical microscope at 0 and 24 hours. In **Figure 6**, cap11 microcapsules remained unswollen, while capaftpp3 microcapsules swelled after 24 hours. This swelling resulted from the ionization of -OH groups in the presence of protons, generating charges within the polymer networks, leading to electrostatic repulsion forces.

Zeta potential measurement dependent on the pH of the solution

The behavior of microcapsules in solution is influenced by factors such as pH and surface charge[9]. In our study, it was observed that microcapsules tended to aggregate and precipitate, indicating poor stability in dispersions below 30 mV. Zeta potential (**Figure 7a**) and pH measurements (**Figure 7b**) were performed with sample capaftpp3 (**A**): 0.684 %v/v AcOH, 0.8 %w/v CS, 0.15 %w/v TPP, 0.015 %w/v FA, and cap11 (**B**): 0.684 %v/v AcOH, 0.8 %w/v CS, 0.15 %w/v TPP. As can be seen in **Figure 7a,** the reference microcapsules in **Figure 7a**(**B**) exhibited a lower value of zeta potential, indicating an increase in electrostatic attraction and sedimentation tendency. Conversely, microcapsules containing FA in **Figure 7a**(**A**) showed a higher zeta potential value, indicating a greater surface charge due to FA and enhanced electrostatic repulsion. This suggests improved dispersion stability.

In other words, the surface charge of CS/TPP microcapsules is pH dependent as shown in **Figure 7a**(**A-B**)**.** At low pH values, the chitosan molecules on the microcapsule surface remain partially protonated, resulting in a net positive charge, leading to greater electrostatic repulsion and higher zeta potential. This increased stability can be attributed to the continued protonation of the CS chain. Therefore, FA distribution on the microcapsule surface was evident through the increased surface charge at low pH. The zeta potential was directly correlated with CS concentration, indicating that higher CS concentration resulted in an increased zeta potential.

At neutral pH, the surface charge of CS/TPP microcapsules is close to zero due to the balance between the positive charge from chitosan and the negative charge from TPP phosphate groups.

Above neutral pH, the surface charge of CS/TPP microcapsules becomes increasingly negative due to the deprotonation of TPP hydroxyl groups, leading to a decrease in the positive charge. This shift towards

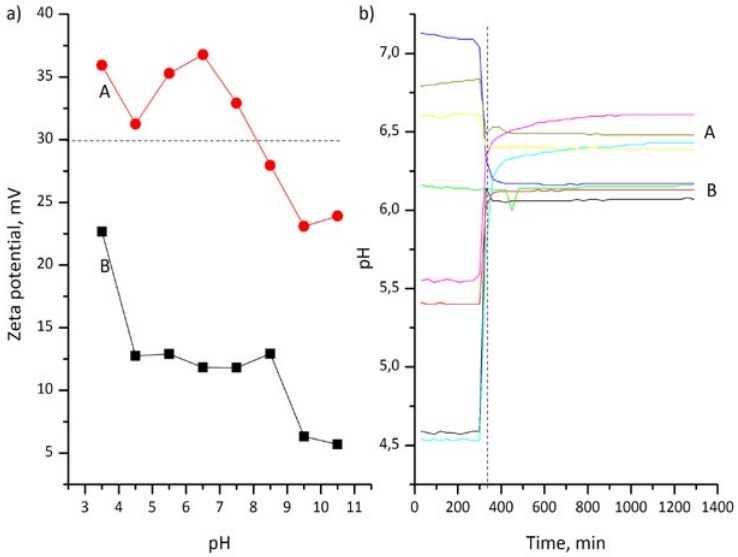

Figure 7. *Estimation of CS/TPP microcapsules stability in various pH solutions and the proton exchange compared to reference and FA microcapsules. a) zeta potential analysis and b) pH measurement of samples in contact with different pH solutions where A: sample capaftpp3 and B: sample 11.*

a negative surface charge enhances the stability and dispersion of the microcapsules, reducing aggregation tendencies and improving colloidal stability.

Controlling the surface charge through pH adjustment is a crucial feature for the targeted delivery of microcapsules to specific tissues or cells, enhancing efficacy and minimizing unwanted side effects[9]. This pH-dependent surface charge has significant implications for microcapsule behavior in different environments and their potential applications in drug delivery[10]. Microcapsules with FA were found to have a higher tendency to attach to proteins for medical purposes while remaining dispersed[11].

As shown in **Figure 7b**, the microcapsules containing FA in **Figure 7b**(**A**) are able to release more protons to the medium than the reference microcapsules in **Figure 7b**(**B**).

We performed DLS measurements in different pH and salt solutions to enhance microcapsule dispersion. Unfortunately, the results remained unsatisfactory and showed no improvement compared to previous findings. The size measurements did not align with SEM

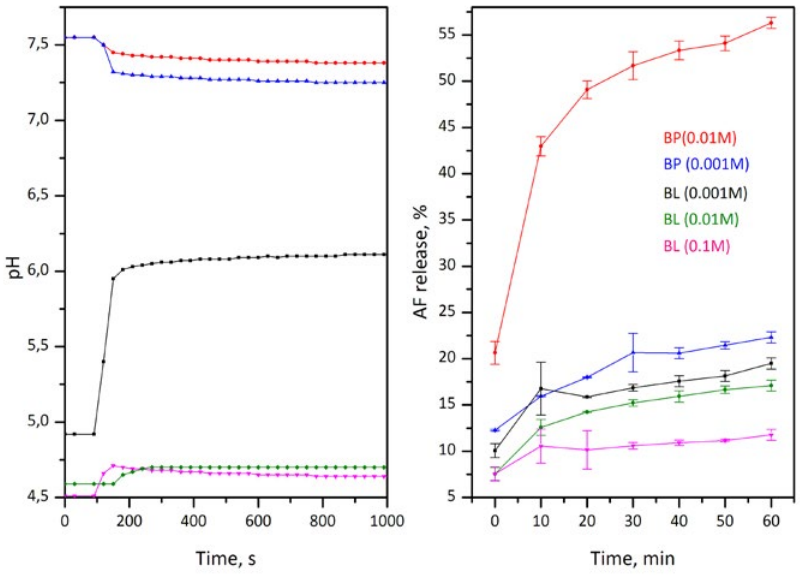

Figure 8. *a) Buffer effect on microcapsule (CapAFTPP3) containing FA, and b) release profile of folic acid (FA) in phosphate buffer (PB) and lactate buffer (LB).*

images, likely because large aggregates existed beyond the equipment's detection limit. Strong electrostatic interactions on the microcapsules hindered their dispersion in various solution compositions.

Release profile of folic acid

The release profile of FA shown in **Figure 8**, from crosslinked microcapsules in phosphate buffer solution, shows that over 20 %w/v FA is released from the microcapsules at 0 min, indicating that FA is not fully incorporated into the microcapsules. However, over 60 min, there is an increasing tendency to donate protons to the media, suggesting that the cationic FA is becoming more susceptible to being released into the phosphate buffer solution. In contrast, when the microcapsule is exposed to buffer lactate for 60 min, the microcapsules show a tendency to trap protons from the media and remain swollen, while FA remains attached to the CS/TPP crosslinked chains. This indicates that FA is more effectively attached to the microcapsules in the presence of the buffer lactate, resulting in a lower release rate compared to the phosphate buffer solution.

These results are interesting as they reveal the potential of CS/TPP microcapsules containing folic acid. Chitosan effectively retains folic acid under low pH conditions, which are typically found in aggressive tumor environments[12]. This property makes the microcapsules suitable for efficiently targeting cancer cells[13]. Additionally, the microcapsules in the proximity of cancer cells can release other anticancer drugs without experiencing chemical deactivation, making them promising candidates for pharmaceutical applications.

CONCLUSION

Spray drying yielded microcapsules with a wide size range (0.8 µm to 50 µm). Adjustments in parameters like nozzle size, atmospheric gas, and pressure can help reduce this size distribution. Lower air inlet temperatures led to denser membranes, higher moisture content, reduced fluidity, and increased agglomeration, while temperatures above 170 °C caused excessive vaporization, potentially leading to membrane cracks and microcapsule integrity issues.

CS/TPP microcapsules with the TPP crosslinker exhibited stability across a broad pH range above 4.5. In contrast, chitosan capsules were more pH-sensitive, dissolving at low pH values due to protonation of their amino groups, which increased polymer chain repulsion and solubility. The physical cross-linking of CS chains contributed to microcapsule structural integrity below pH 6.5.

The surface charge of CS/TPP microcapsules was pH-dependent, with higher zeta potential at lower pH values, indicating enhanced surface charge and dispersion stability. The presence of cationic FA on the microcapsule surface further increased the surface charge, improving dispersion stability. FA release experiments in phosphate buffer solution showed a higher release rate, while lactate buffer solution led to a lower release rate. This suggests that FA release was influenced by pH, with the microcapsules retaining their swollen state in lactate buffer, trapping protons, and delaying FA release.

STATEMENT

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