Hybrid mesoporous silica nanoparticles templated with surfactant polyion complex (SPIC) micelles for pH-triggered drug release

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Introduction

Mesoporous silica particles (MS) are suitable for drug delivery systems (DDS) due to their high specific surface area, tunable mesoporous structure, or chemical stability in aqueous environments. The loading and release of therapeutic agents are determinated by pore diameter. Recent DDS advancements aim to incorporate additional release control mechanisms - chemical, physical, or biological stimuli - to enhance treatment effectiveness while minimizing side effects. Traditionally, MS preparation involves sol-gel synthesis with surfactants as structure-directing agents (SDA). However, this often yields non-functional materials requiring post-synthesis pore grafting and further functionalization.

To obtain such functionalized MS in one-pot synthesis under mild and eco-compatible conditions, thus addressing the requirements of more sustainable industrial processes, polyion complex micelles (PIC) have been developed and used as both structuring and functionalizing agents. PIC micelles dynamically assemble *via* electrostatic complexation between a double hydrophilic block copolymer (comprising a neutral and a polyelectrolyte block) and a partner with the opposite charge. For instance, PIC micelles were assembled from a neutral-ionisable poly(ethylene oxide)-b-poly(acrylic acid) copolymer (PEO-b-PAA) complexed with polycationic oligochitosan at pH 4.5 to 7, forming micelles with a hydrated PAA/oligochitosan complex core and a PEO corona [1].

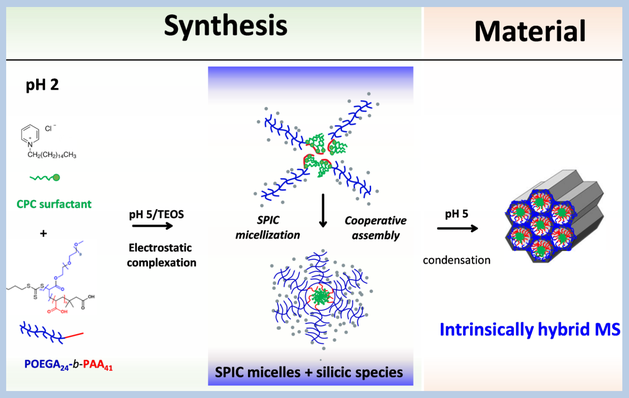
Herein, we attempted the electrostatic complexation of an antibacterial cationic surfactant, cetylpyridinium chloride (CPC), with a double hydrophilic block copolymer, containing a neutral comb block of poly(oligo(ethylene glycol)methyl ether acrylate) (PEOGA) and a weak polyacid block (poly(acrylic acid), PAA) [$PEOGA_{24}$-b-PAA_{41}], leading **to surfactant polyion complex (SPIC) micelles**. These SPIC micelles were subsequently employed as a new SDA for the eco-friendly and straightforward sol-gel synthesis of hybrid MS particles intrinsically functionalised with encapsulated CPC. This surfactant can form micelles itself and its an active against a variety of oral bacteria, including cariogenic and acidogenic *Streptococcus mutans*, which are major contributors to the degradation of dental and restorative materials (composites, titanium and its alloys). Interactions between CPC molecules and $PEOGA_{24}$-b-PAA_{41} were comprehensively investigated in terms of SDA properties, performing sol-gel synthesis at pH 5, 7 and 11 with and without copolymer. Optimized hybrid MS particles were evaluated in terms of pH-induced release of CPC from structure at pH of 3, 4.2 and 7.4.

Materials and Methods

Materials:

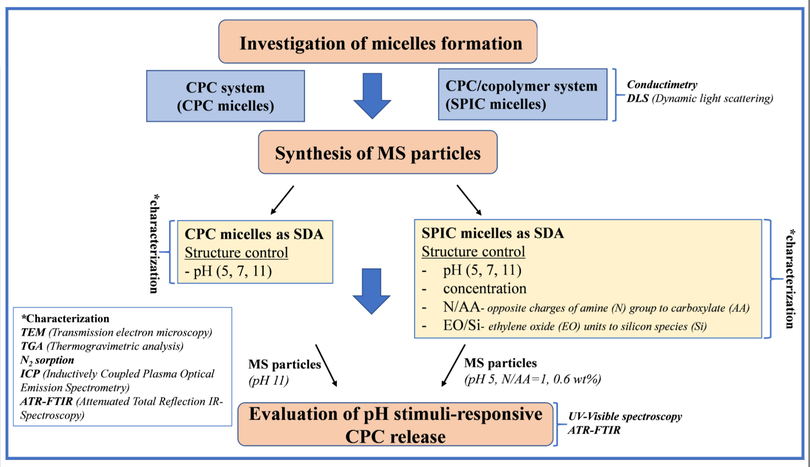
- **cationic surfactant:** cetyl-pyridinium chloride (CPC) (broad-spectrum antimicriobal activity)
- **copolymer: $POEGA_{24}$-b-PAA_{41}** (neutral comb block/ weak polyacid block)

Synthesis of hybrid MS nanoparticles templated with SPIC micelles



Surfactant-polyion complex (SPIC) micelles, formed by interaction of a cationic antibacterial surfactant with the weak polyacid block of a copolymer, serve as a SDA for pH-sensitive hybrid MS nanoparticles. During the sol-gel condensation of silica, H-bonding between the ether oxygen of the neutral PEO corona and the silicic species leads to the formation of an ordered hybrid MS material with the copolymer neutral block anchored in the silica walls. Simultaneously, the electrostatic PAA/CPC complex generates the mesopores.

FLOW OF EXPERIMENTS



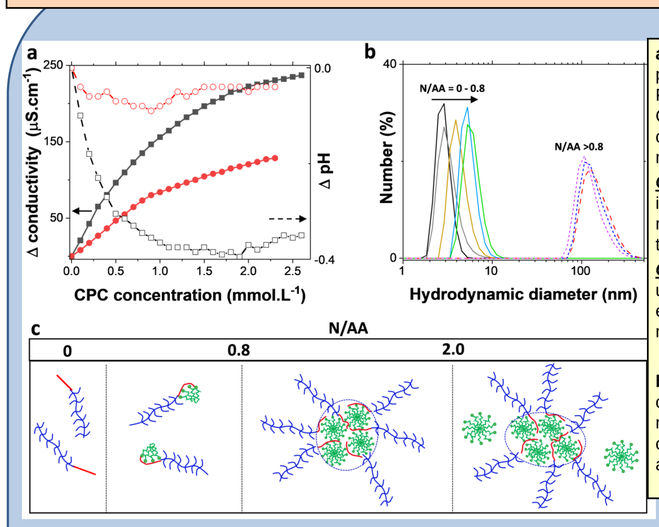
pH - Stimuli Release Mechanism - release of antibacterial compound from hybrid MS is determine by a local drop of pH, mimicking the metabolic activity of acidogenic (acid-producing) and aciduric (acid-tolerating) bacteria, such as S. Mutans.

→ ***Incubation of selected hybrid MS particles in 0.15M NaCl* at pH 3 and 7.4 up to 50 h and measurement of UV-Visible absorbance of the supernatants.***

**pH of saliva is typically between 6.2-7.6, with a salinity of 0.12M (±0.08) NaCl*

Results and Discussion

❑ Micelles formation: interactions between CPC and $PEOGA_{24}$-b-PAA_{41}



a) The conductometry/pHmetry results indicate a progressive interaction of CPC with $PEOGA_{24}$-b-PAA_{41} up to a critical aggregation concentration of CPC at ~1 mM (N/AA≈1) above which stable colloids formed by complexation between CPC micelles and the copolymer appear.

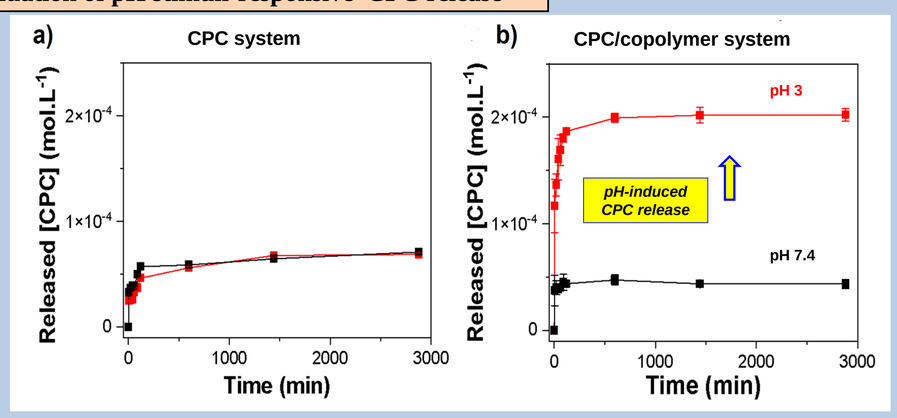
CPC system: ~1mM change in conductivity slope indicates CPC molecules self-assemble into CPC micelelles by hydrophobic interactions, decreasing the molar conductivity.

CPC/$PEOGA_{24}$-b-PAA_{41} system: decrease in pH until N/AA=1.1 (corr. to CPC=1.1 mM) indicates electrostatic complexation with CPC forming SPIC micelles.

b) The CPC-copolymer complex colloids are colloidally stable in solution while new CPC molecules are added up to another critical conc. of 2mM (N/AA≈2) above which free CPC micelles accumulate in solution.

a) Conductivity (filled symbols) and pH (open symbols) for CPC (red) and CPC/ $PEOGA_{24}$-b-PAA_{41} (black) systems as a function of CPC concentration (pH 5).
b) Hydrodynamic diameter distributions averaged in number, CPC/$PEOGA_{24}$-b-PAA_{41} system as a function of CPC concentration (pH 7): N/AA ratios of 0 (black line), 0.3 (grey), 0.5 (yellow), 0.6 (blue), 0.8 (green), 0.9 (dotted red), 1 (dotted blue) and 1.3 (dotted pink line).
c) Schematic description of the aggregation process by interaction between CPC and $PEOGA_{24}$-b-PAA_{41} at pH ≥ 5 as a function of the molar ratio N/AA.

❑ Evaluation of pH stimuli-responsive CPC release



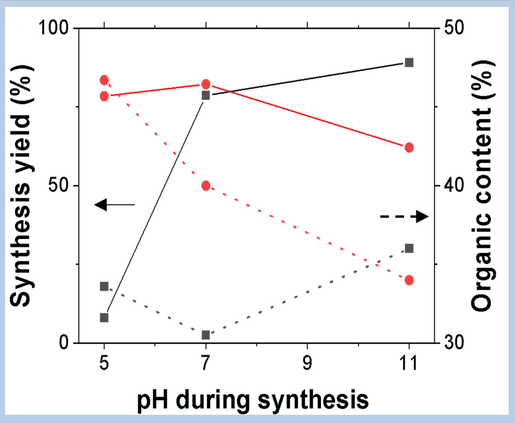
a) Control (CPC system): *hybrid silica templated with CPC micelles at pH 11 (the pore order on the longest range)*
b) Sample (CPC/copolymer system): *MS nanoparticles templated with SPIC micelles at pH 5*

CPC release profiles at pH 7.4 - both types of samples exhibit a limited release, stabilizing ~5.10^{-5}M CPC after 10h monitoring (desorption of loosely bound CPC molecules favoured by the change in the ionic strength of the solution).

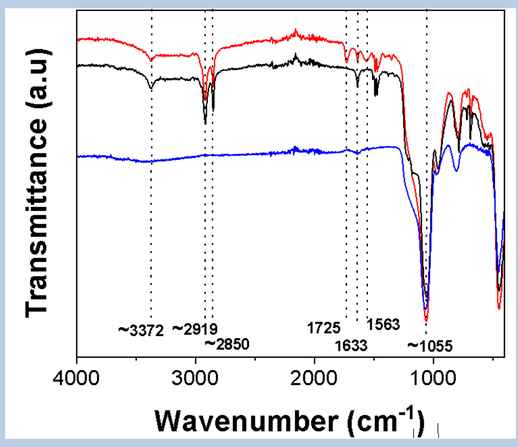
CPC release profiles at pH 3 - strongly depended on the type of hybrid MS particles

- **CPC system: CPC** release profile similar to profile at pH 7.4 (quickly stabilising around 5.10^{-5}M CPC). Absence of response attributed to the persistent electrostatic interactions of cationic CPC with negatively charged silica at pH 3. This system is unable to act as a smart delivery platform within the range of pH values found in biofilms, despite the good structural order and loading with CPC.
- **CPC/copolymer system:** CPC release profiles under the tested acidic conditions followed first-order rates Release concentrations of 2.10^{-4} M was exceeded within the first 5 minutes before stabilising ~2.10^{-4} M after 10h. The selective release of CPC from this system is attributed to the protonation of PAA grafted at the mesopore surface.

❑ Structural control of mesoporous silica particles: Effect of the pH



*Silica templated by SPIC micelles (red lines), (N/AA=1), **CPC micelles (black lines)**, synthesis yield (solid lines), organic content (dootted lines)*

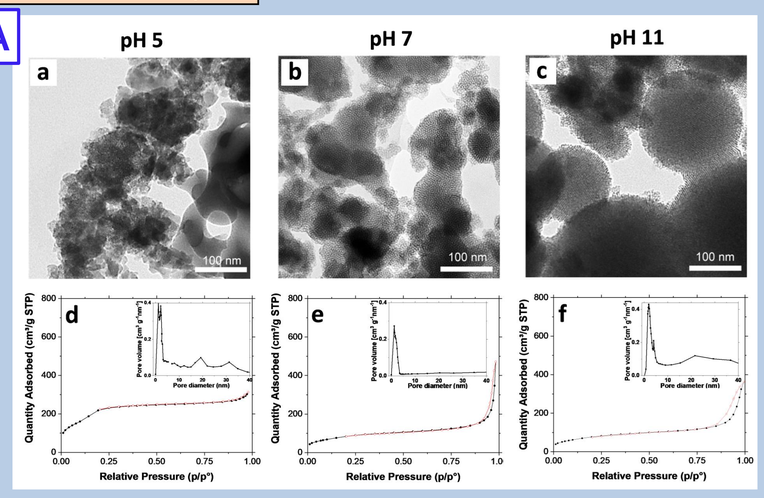


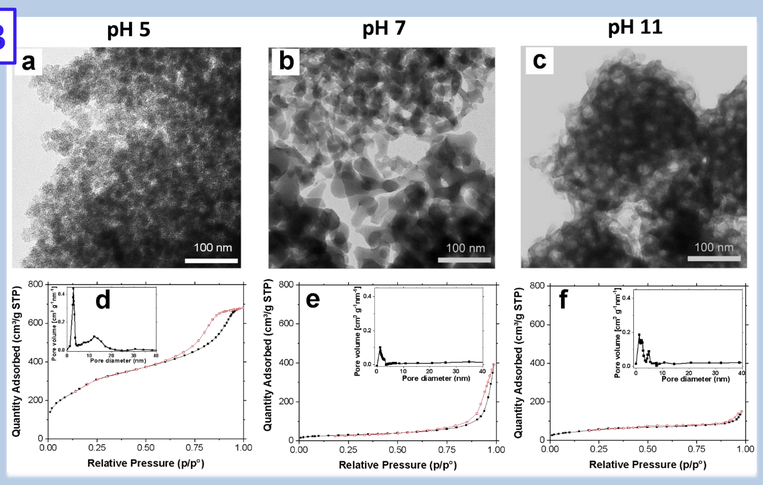
ATR-FTIR spectra of hybrid MS materials obtained using (black line) CPC micelles at pH=11 or (red and blue line) SPIC micelles at pH=5 as SDA; either (black and red line) before and (blue line) after calcination.

Silica in both materials:
~1060 cm^{-1} - Si-O-Si asymmetric stretching
960 cm^{-1} - Si-OH asymmetric bending

CPC in both materials:
~2914-2845 cm^{-1} - alkyl C-H stretching
~1633 cm^{-1} - aromatic C=C stretching
~783 cm^{-1} - cis C=C-H out of plane bending/rocking
~690 cm^{-1} - monosubstituted aromatic ring

Copolymer only in the SPIC micelles templated material:
1720 cm^{-1} - ester
1690 cm^{-1} - carboxylic acid
1560 cm^{-1} - carboxylate groups





pH has a influence on silica condensation kinetics, it affect the pore structure of the material depending on the micelle type used as SDA:

A) CPC micelles act as SDA of silica under neutral and alkaline conditions, leading to homogeneous pore size distributions of micropores (or small mesopores) with pH dependent phase types and order.
pH 5 *- poorly organized material, a mixture of non-porous and porous particles with disorganized micropores*
pH 7 *- a homogeneous distribution of micropores within particles, with mostly a worm-like organization with short range*
pH 11 *- a more ordered structure than at pH 7, particle size bigger than 100 nm.*

B) SPIC micelles- micellization process is favoured by deprotonation of the PAA block (pH ≥ 4.5) while H-bonding interactions of silica with the micelle corona (composed of PEOGA) are favoured at low pH. Materials obtained under neutral and alkaline conditions did not contain SPIC micelles, thus SPIC micelles are unable to act as silica SDA under these conditions.
pH 5 - *mesopores with a short-range worm-like organization, particles size less than 100 nm*

Summary

Surfactant based drugs can be incorporated directly into functional hybrid mesoporous silica nanomaterials with excellent stability under physiological conditions. By mimicking the pH conditions of biofilm microenvironments, the pH-triggered release of antibacterial CPC has demonstrated the potential of these mesoporous hybrids for the development of smart antibacterial drug delivery systems.

Reference

[1] Ecodesign of Ordered Mesoporous Materials Obtained with Switchable Micellar AssembliesN. Baccile, J. Reboul, B. Blanc, B. Coq, P. Lacroix-Desmazes, M. In and C. Gérardin, Angew. Chemie - Int. Ed., 2008, 47, 8433–8437.

Acknowledgements

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