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# Self-organized thermo-responsive hydroxypropyl cellulose nanoparticles for curcumin delivery

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ABSTRACT

A tunable temperature-responsive nanoparticulate system based on the ionic modifications of hydroxypropyl cellulose (HPC) was obtained. Two derivatives of HPC were successfully obtained and characterized: cationic (modified with trimethylammonium groups) and anionic (modified with styrenesulfonate groups). Due to the polycation-polyanion interactions they spontaneously self-assemble into nanoparticles in water. The size and surface charge of the nanoparticles can be controlled by the polycation/polyanion ratio. The resulting structures are spherical with diameters in the range from 150 to 250 nm, as confirmed by AFM, SEM, and DLS measurements. The size of the nanospheres increases in elevated temperatures. A model compound, curcumin, known for its anti-cancer and anti-inflammatory properties, was effectively entrapped inside nanospheres. Its release profile was found to be temperature-dependent.



## 1. Introduction

Polymer-based nanoparticles are widely exploited as versatile systems with many scientific and industrial applications, e.g., in electronics [1], optoelectronics [2], waste treatment [3], medical diagnostics [4], and drug delivery [5]. Recent advances in this field are focused on the development of more sophisticated, tunable systems [6]. At the same time, to be commercially useful, such nanoparticles have to be inexpensive and easy to obtain. Moreover, when used in environmental protection, medicine, or pharmacy, nanoparticles have to be non-toxic and biocompatible. For this reason polysaccharides are frequently chosen as starting materials in those applications.

Hydroxypropyl cellulose (HPC) is a semi-synthetic, biocompatible polysaccharide, commercially available and relatively inexpensive. It is used as a thickener, filler, anti-clumping agent, and emulsifier in many foods and constitutes a component of many pharmaceutical formulations. In pharmacy it is used mainly as an excipient in oral solid dosage forms, in which it acts as a disintegrant [7], and as a binder [8]. It is also an ingredient of so-called "artificial tears" used in the treatment of the dry eye syndrome (i.e., insufficient tear production), and to moisten contact lenses. An interesting feature of HPC structure is the presence of both hydrophobic and hydrophilic groups. As a result, HPC shows a lower critical solution temperature (LCST) at ca 42 °C [9]. At temperatures below the LCST, HPC is readily soluble in water, while above the LCST its solubility in water decreases drastically. There are two important consequences of this behavior: (1) above the LCST the nanospherical, metastable objects are formed in aqueous solutions of HPC [9] and (2) HPC-based systems

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tend to be thermo-responsive in nature [10]. These properties make this polymer a promising starting material for manufacturing a nanospherical system with interesting properties.

Few HPC-based nanoparticulate systems have been reported so far. Sun et al. [11] described the synthesis of HPC-acrylic acid nanospheres cross-linked with N,N′-methylene bisacrylamide. The authors propose that, due to the presence of the carboxylic groups, such system may be useful as a carrier of the cationic compounds (e.g., drugs). However, to purify the nanoparticles from the unreacted monomers and a cross-linker, a long dialysis is necessary, which could lead to the removal of the loaded, water-soluble substance. Thermosensitivity was not studied in this system, but chemical cross-linking may result in the loss of this property. Another approach was to add salt to the HPC aqueous solution at the concentration high enough to decrease polymer LCST value to room temperature [12]. This led to the formation of nanoparticles, which were then stabilized via chemical cross-linking, using divinyl sulfone in strongly basic medium (NaOH). Also in this case one week long dialysis was needed to purify the nanoparticulate system. Although the temperature of the synthesis influenced the size of the obtained structures, no thermo-sensitivity was reported for the nanoparticles. Thermo-responsive nanoparticulate system was synthesized based on the mixture of poly(N-isopropylacrylamide) and HPC by Hu et al. [13]. However, the ability of the particles to encapsulate drugs or other active compounds has not been tested.

Our approach was to obtain a new, stable nanoparticulate system based on ionic HPC derivatives, which would spontaneously self-assemble in water forming stable nanospheric aggregates. This way we attempted to achieve the system which would show thermo-responsiveness in the physiologically relevant range of temperatures and, at the same time, could be fabricated using a simple methodology. The main idea was to obtain two HPC derivatives, namely HPC modified with (1) cationic trimethylammonium groups and (2) with anionic styrenesulfonate groups. The polycation-polyanion interactions should lead to self-organization, leading to the formation of stable nanoparticles. Additionally, as the HPC derivatives could be mixed at different ratios, such a system would be tunable in respect to its surface charge and size. The nanoparticles were further tested as a carrier for curcumin, a natural polyphenol derived from turmeric (*Curcuma longa*), a dietary spice originating from southern Asia. It was shown that curcumin exhibits a wide range of potential therapeutic and prophylactic effects due to its antitumor [14], antioxidant [15], antiamyloid [16], and anti-inflammatory [17] properties. Unfortunately, curcumin exhibits low stability in aqueous solutions and is characterized by low bioavailability. Recently, the encapsulation of curcumin in microparticles composed of ethylcellulose or ethylcellulose/methylcellulose blends was proposed [18]. High loading (up to 49%), slow release *in vitro*, and good adhesion to the mucosal epithelia of the stomach was reported. We believe that the nanosized, thermo-responsive, stable and tunable nanocarrier we have developed would provide a better control over curcumin absorption and distribution, thereby improving its bioavailability.

## 2. Materials and methods

### 2.1. Materials

Curcumin (⩾94% curcuminoid content, ⩾80% curcumin) and hydroxypropyl cellulose (HPC) (average $M_w$ ~80,000, average $M_n$ ~10,000, powder, 20 mesh particle size – 99% through, the ratio of the number of hydroxyl groups of the glucose units to the number of hydroxypropyl units attached was 1:1 as verified by elementary analysis) N-acrylamidopropyl-N,N,N-trimethylammonium chloride (APTMAC, 75 wt.% solution in water, stabilized with 3000 ppm MEHQ) and sodium p-styrenesulfonate (SSS) (⩾90%) were purchased from Sigma–Aldrich. Spectroscopic grade ethanol, oleic acid (p.a.) and acetic acid (p.a.) were purchased from POCH, Gliwice, Poland.

### 2.2. Synthesis of cationic hydroxypropylcellulose (HPC–APTMAC)

The detailed synthesis of HPC–APTMAC was described elsewhere [19]. Shortly, in a three-necked flask 1.5 g (5 mmol of glucose units) of HPC was dissolved in 15 mL of DMF. The solution was degassed by bubbling with gaseous nitrogen for 30 min, and a solution of the initiator (1.35 g of BPO dissolved in 7.5 mL of degassed DMF) was added. After 5 min a mixture of 16 mL of DMF and 17.72 g of APTMAC, 75 wt.% solution in water was added. The reaction mixture was then heated at 70 °C for 3 h under constant mixing with a magnetic stirrer and simultaneously constantly bubbled with gaseous nitrogen. Then the mixture was cooled down and dialyzed first against DMF for 3 days and after that against a mixture of DMF and water for another 2 days. The fraction of water was gradually increased, and finally the dialysis was performed against pure water. The dialysis was carried out against water for 2 more weeks. The purified product was isolated by freeze-drying.

### 2.3. Synthesis of anionic hydroxypropylcellulose (HPC–SSS)

In a 250-ml three-necked flask 3 g of HPC were dissolved in 100 ml of water. The solution was degassed by bubbling with nitrogen for 30 min. Next, 7.9 mg (0.05 mmol) of $KMnO_4$ dissolved in 1 ml of water was added. After 3 min the solution became colorless and 1.137 g (11 mmol) of $H_2SO_4$ and 4.190 g (30 mmol) of SSS was added. The reaction mixture was then heated and kept at 60 °C for 6 h under constant mixing with a magnetic stirrer and in nitrogen atmosphere. Next, the reaction mixture was cooled down and neutralized with 1 M NaOH solution. The precipitated $MnO_2$ was removed by decantation. The polymeric solution was dialyzed for 2 weeks against distilled water. The obtained product was freeze-dried.

### 2.4. Preparation of HPC–SSS/HPC–APTMAC nanoparticles (HPCNPs)

0.1 wt.% of HPC–APTMAC solution in 1% acetic acid and 0.1wt.% of HPC–SSS solution in water were prepared.