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# The influence of substituents of cellulose ethers on their interaction with chitosan surfaces

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## ABSTRACT

This study investigated how subtle variations in the number of substituent groups in hydroxypropyl methylcellulose (HPMC) affect its interaction with chitosan surfaces. We used a model system with ultra-thin chitosan films on QCM-D sensors to probe the adsorption of various HPMC grades. The HPMCs had similar molecular weights but differed in their degree of substitution, which was shown to affect their solubility. Hansen solubility parameters and dynamic light scattering (DLS) data revealed that lower solubility and higher aggregation led to stronger adsorption. QCM-D measurements confirmed irreversible adsorption for all HPMC variants, with the least soluble grade exhibiting the highest adsorption. These findings demonstrate that lower solubility enhances HPMC adsorption onto chitosan, providing valuable insights for optimizing polymer interactions in applications such as oral film formulations.

## 1. Introduction

Cellulose derivatives are an important class of semisynthetic polymers that have garnered traction in formulations for pharmaceutical and food applications [1]. This is primarily attributable to their renewable origin and outstanding physicochemical properties. Native cellulose is composed of  $\beta$ -D-anhydroglucose units connected via  $\beta$ -1,4 bonds. The resistance of native cellulose to dissolution in common solvents is typically ascribed to its hierarchical structure and strong inter- and intramolecular interactions [2]. However, an emerging concept of cellulose amphiphilicity is postulated to be the cause of cellulose's non-solvability [3]. The presence of three hydroxyl groups per unit of anhydrous glucose provides excellent opportunities for chemically modifying the cellulose chain and tuning its physicochemical properties, particularly solubility and thermal behavior [4]. Consequently, there are many cellulose derivatives available on the market. The principal determinants of the physicochemical behavior of cellulose derivatives are the type of modification and the degree of substitution. Methylcellulose and ethyl cellulose are outstanding examples of the effect of different substituents on the properties of cellulose derivatives. With the same degree of substitution, the former dissolves in water while the latter does not [5]. Carboxymethyl cellulose is a commercially significant cellulose

derivative whose water solubility varies with the degree of substitution. In general, only degrees of substitution of 0.7 or higher are water-soluble, whereas the others are insoluble [6].

Hydroxypropyl methylcellulose (HPMC), also known as hypromellose, is one of the important cellulose derivatives, and it is mainly used in thermoresponsive gels and pharmaceutical formulations [5]. HPMC has been shown to be an excellent candidate as a release controlling agent for drug delivery from hydrophilic matrix tablets [5,7–9]. Viriden et al., has shown that differences in the degree of substitution and the substitution pattern can significantly affect the release profiles of the HPMC matrix tablets [8,9] also in film formulations, HPMC has been shown to be useful as a film former, and various grades (e.g. degree of substitution, substitution pattern and molecular weight) can be used to tailor the release properties [10]. Recently, Bizmark et al. have explored the thermal behavior of different types of HPMCs, it was observed that the amount of hydroxypropyl groups has a significant effect on the thermal phase transition of HPMCs [11–13]. Apart from aforementioned applications, HPMCs are used as thickening agents, emulsifying agents and film-forming agents, etc. [5]. In many of these applications, HPMC serves a critical role. Cellulose derivatives are often combined with other polysaccharides, such as cellulose and chitosan, for material formulations, e.g. in pharmaceutical preparations [14]. The

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<sup>1</sup> shared first authorship (equal contributions)

**Table 1**

Calculated HSP values for the HPMC grades. Degree of substitution provided by the supplier and the HSP values of water are taken from Hansen [26].

Material	DS <sub>methoxy</sub>	DS <sub>hydroxypropoxy</sub>	$\delta_d$ (Jcm <sup>-3</sup> ) <sup>1/2</sup>	$\delta_p$ (Jcm <sup>-3</sup> ) <sup>1/2</sup>	$\delta_H$ (Jcm <sup>-3</sup> ) <sup>1/2</sup>
HPMC 60 SH 4000	1.9	0.25	13.5	6.8	15.7
HPMC 65SH 4000	1.8	0.15	18.6	7.2	16.5
HPMC 90 SH 4000	1.4	0.20	19.0	7.9	17.7
Water	–	–	15.5	16	42.3

interactions of these cellulose derivatives with other components are of great importance for the performance of the material. One of the main challenges in the development of formulations based on cellulose derivatives is to identify the right polysaccharide derivatives for the target application from the plethora of choices available in the market.

Chitosan is a natural cationic linear polysaccharide, composed of  $\beta$ -(1–4)-linked D-glucosamine and N-acetyl-D-glucosamine. It is obtained from chitin, which can be found in exoskeletons of crabs, shrimps and other crustaceans, as well as in insects and fungi cell walls [15–17]. Deacetylation (> DDA 50 %) of chitin under alkaline treatment results in chitosan [15] where the supramolecular fibrillar structure is lost. Chitosan is widely used in biomedical and pharmaceutical applications due to its desirable properties, such as non-toxicity, biocompatibility, antimicrobial properties and biodegradability [18,19]. Examples of use include wound-healing materials, excipients in various pharmaceutical dosage forms (e.g. films, gels, vaginal preparations, eye drops) and bone tissue engineering scaffolds. Chitosan is only soluble in acidic conditions below its pKa (approx. 6.3), when its amino groups are protonated. Its presence of free hydroxyl and amino groups is advantageous for the formation of hydrogen bonding with other polymers, mucin and various hydrophilic surfaces [18].

The combination of HPMC and chitosan is highly promising for oral film formulations, as they are known to be compatible and can exhibit synergistic properties [20]. This synergy is likely due to the hydrogen bonds between their hydrophilic functional groups [21,22], as well as differences in their solubility at neutral pH (e.g., in the pH in the oral cavity, 5.5–7) [23,24]. Both HPMC and chitosan are also known to be mucoadhesive [23–25], meaning that they interact with mucosal surfaces. This property can be leveraged to prolong the contact time of drug-containing films with the mucosal surface, thereby ensuring confined release of the drug, either for local effect or for absorption through the mucosal membrane [22,25]. In this study, we aim to investigate the influence of the substituent groups of hydroxypropyl methylcellulose on interaction with chitosan. A model system approach has been employed, in which ultra-thin films of chitosan have been used in quartz crystal microbalance with dissipation (QCM-D) to probe the interaction of HPMCs with the chitosan surface. We evaluated applicability of Hansen solubility parameters (HSP) to predict the interaction of HPMCs with different degree of substitution with chitosan surfaces. We anticipate that our results can help to make informed choices in material formulations, for instance in development of oral films formulations.

## 2. Materials and methods

### 2.1. Materials

Hydroxypropyl methylcelluloses with trade names 60SH 4000, 65SH 4000 and 90SH 4000 were obtained from Shin-Etsu Chemical Co. Ltd., Japan, and used as received. Specific details regarding the substituent are provided in Table 1. Chitosan with the tradename Chitopharm™ CM

(degree of deacetylation: 98 %) was received from Chitinor, Norway. Acetic acid and sodium hydroxide (NaOH) were obtained from Sigma Aldrich.

### 2.2. Dynamic light scattering (DLS)

The hydrodynamic size of HPMCs in different concentrations was determined using DLS (Litesizer 500, Anton Paar, Austria). HPMC solutions with a concentration ranging from 0.005 wt% to 1 wt% were prepared by dissolving HPMC in Milli-Q water and stirring overnight to ensure complete dissolution. Prior to characterization, all solutions were filtered through 0.45  $\mu$ m hydrophilic PTFE syringe filters. Dynamic Light Scattering (DLS) measurements were conducted at 25 °C using disposable plastic cuvettes. Each sample was measured in triplicate, with each measurement consisting of 25 individual runs. For the determination of the hydrodynamic diameter, a refractive index of 1.55 was used for HPMC. Additionally, the analysis accounted for concentration-dependent changes in solution viscosity to ensure accurate particle size calculations.

### 2.3. Viscosity of the HPMC solutions

The viscosities of HPMC solutions at concentrations of 0.005, 0.01, 0.05, and 0.1 wt% were measured using a Brookfield DV2T viscometer (Middleboro, MA, USA) equipped with a 40Z spindle. Measurements were performed at 25 °C with a sample volume of 500  $\mu$ l, an endpoint of 2 min, and a rotation speed of 30 rpm. Each sample was measured in triplicate.

### 2.4. Preparation of chitosan ultra-thin films

Ultrathin films of chitosan were prepared according to the method reported by Katan et al. with a slight modification [27]. Briefly, chitosan powder was dissolved in 1 % (v/v) acetic acid solution to obtain 1 % chitosan solution. The solutions were stirred overnight to ensure complete dissolution and filtered through 0.2  $\mu$ m syringe filter to remove undissolved chitosan. The 150  $\mu$ l of chitosan solution was then spin-coated on a cleaned SiO<sub>2</sub> coated QCM-D sensor (5000 rpm, acceleration 2500 rpm/min, for 60 s). The spin-coated sensors were then immersed in 0.5 M NaOH solution for 10 min to neutralize the films and thereby obtain stability. The films were then cleaned with water, dried with nitrogen and stored in a desiccator until use.

### 2.5. Atomic force microscopy

The film morphology and uniformity were analyzed using atomic force microscopy (INTEGRA Prima setup NT-MDT Spectrum Instruments, Moscow, Russia). The height profiles of three random spots on the film were recorded in semi-contact mode, and the root-mean-square roughness was calculated using Gwyddion software to assess the quality of the film.

### 2.6. Stability studies of chitosan thin films

The stability of chitosan films was studied using QCM-D (Biolin scientific, Gothenburg, Sweden). The chitosan-coated surfaces were placed in QCM-D flow cell, and solutions of different pH (7–3) were injected into the flow cell. The frequency and dissipation responses were monitored to check the film stability.

### 2.7. Adsorption studies using Quartz crystal microbalance

The interactions of HPMCs with chitosan surfaces were studied using QCM-D at 25 °C. The HPMC solutions (0.1 % w/w) for adsorption experiments were prepared by dissolving HPMC in MilliQ water and stirred overnight to ensure complete dissolution. The spin-coated chitosan

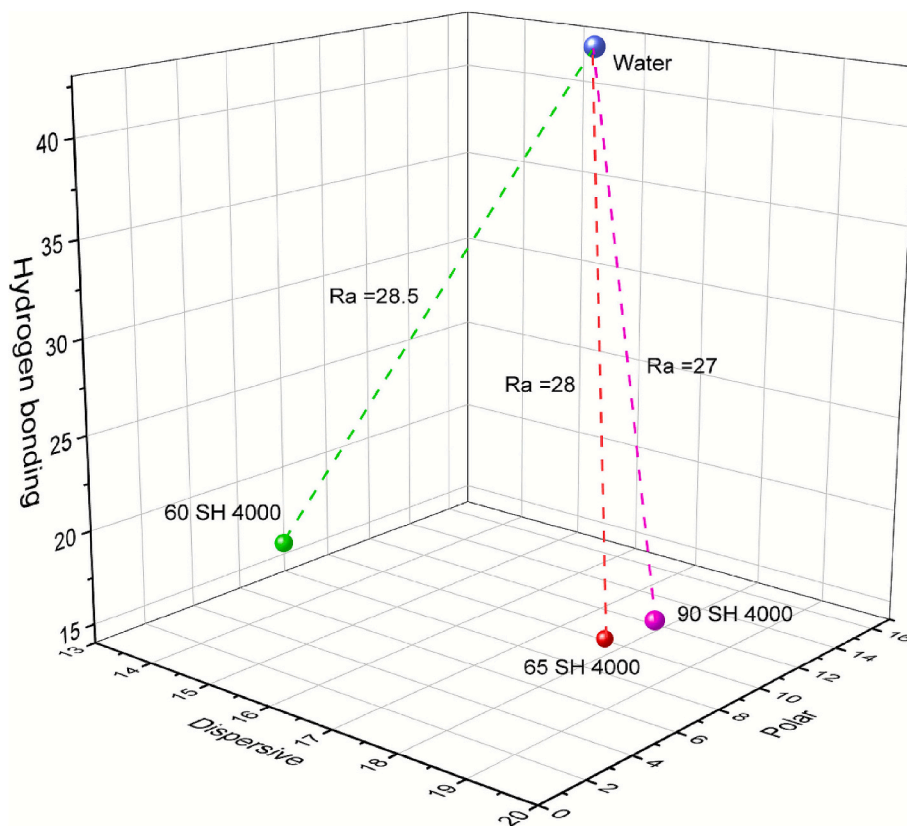


Fig. 1. The distance between different HPMCs and water in Hansen's solubility space.  $R_a$  is the HSP distance between water and different HPMCs.

films were then placed in the flow cell and equilibrated in water for 30 min to obtain a stable baseline. 0.1 % HPMC solutions were then injected into the flow cell, and frequency shift and dissipation response were monitored. After reaching the equilibrium, water was reintroduced to the flow cell to remove the loosely bound HPMC chain from the chitosan surface. The frequency response at this point would correspond to the irreversibly attached HPMC on the surface. The adsorbed mass of HPMC on chitosan thin films was computed using Johannsmann's model [28].

## 2.8. Hansen solubility parameters

Hansen solubility parameter (HSP) is an effective tool in the prediction of the miscibility of components. It is an extended version of Hildebrand's solubility parameters. Hansen solubility parameter considers three different types of molecular interactions, namely non-polar interactions due to dispersive forces, polar interactions due to permanent dipoles in molecular structure and hydrogen bonding [29]. The total squared HSP is defined as the ratio of the total cohesive energy ( $E_{tot}$ ) to the molar volume ( $V_{molar}$ ), and it can be expressed as the sum of squares of aforementioned interaction-components, as follows.

$$\delta_{TOT}^2 = \frac{E_{tot}}{V_{TOT}} = \frac{E_D + E_P + E_H}{V_{TOT}} = \delta_D^2 + \delta_P^2 + \delta_H^2 \quad (1)$$

The individual solubility parameters for HPMCs were computed by using the method suggested by Hoftyzer and van Krevelen (VKH) [30]. The VKH equations for the different solubility parameters are given by following equations

$$\delta_d = \frac{\sum n_i F_{di}}{\sum n_i V_i} \quad (2)$$

$$\delta_p = \frac{\sqrt{\sum n_i F_{pi}^2}}{\sum n_i V_i} \quad (3)$$

$$\delta_h = \frac{\sqrt{\sum n_i E_{hi}}}{\sum n_i V_i} \quad (4)$$

where the contribution from each molecular structural component to dispersive forces, polar interactions and hydrogen bonding are weighted against an average degree of substitution ( $n_i$ ) of each group in a monomer unit. The dispersion components ( $F_d$ ), polar components ( $F_p$ ), hydrogen bond energy components ( $E_h$ ) and Fedor's molar volumes ( $V_f$ ) of different groups in hydroxypropyl methylcellulose were taken from literature [30].

The Hansen solubility parameters can be represented in a 3-dimensional space, The distance between two compounds ( $R_a$ ) in the Hansen solubility space can provide information on their miscibility.

$$(R_a)^2 = 4(\delta_{d2} - \delta_{d1})^2 + (\delta_{p2} - \delta_{p1})^2 + (\delta_{h2} - \delta_{h1})^2 \quad (6)$$

## 3. Results and discussions

### 3.1.1. Hansen solubility parameters and solution properties of hydroxypropyl methylcellulose

Hydroxypropyl methylcelluloses (HPMCs) with similar molecular weights but varying degrees of substitution were selected to evaluate the influence of substituents on solubility. First, the Hansen solubility parameters (HSPs) of the different HPMCs were calculated using the group contribution method (Table 1). The solubility radii ( $R_a$ ) between water and each HPMC were then determined and are presented in Fig. 1.

According to HSP calculations, HPMC 90SH 4000 exhibited the strongest interaction with water, as evidenced by its smallest solubility radius in Hansen space (Fig. 1). In contrast, HPMC 60SH 4000 displayed

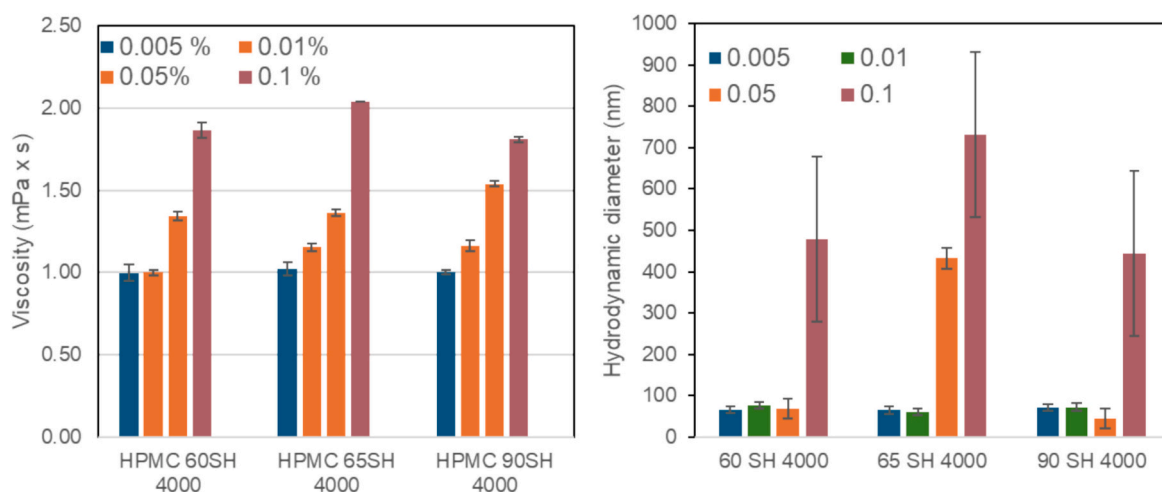


Fig. 2. The viscosity (left) and hydrodynamic diameter measured by dynamic light scattering (right) of HPMCs in different concentrations.

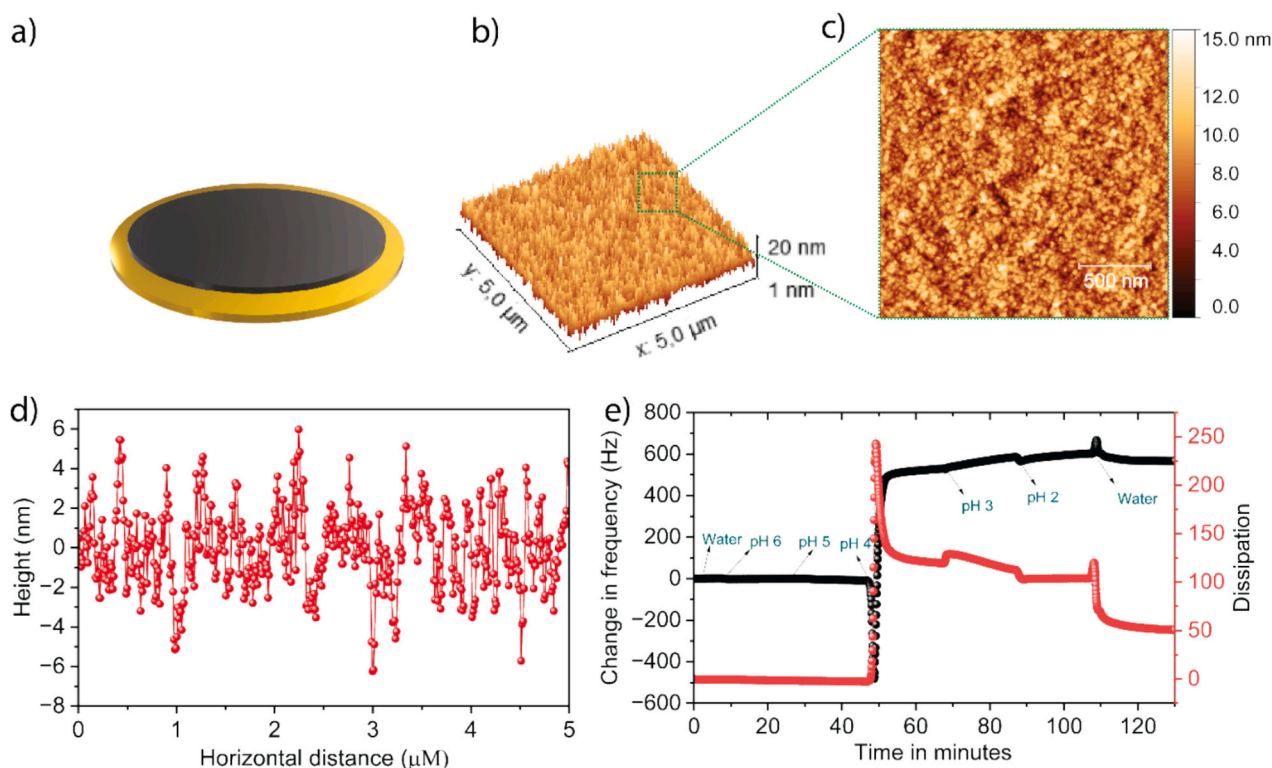


Fig. 3. a) Illustration of chitosan-coated QCM-D sensor, b, c) AFM micrograph of chitosan thin film on QCM-D sensor, d) High profile of chitosan thin films, e) Frequency and dissipation response of chitosan thin films in different pH conditions (between pH = 6 to pH = 2).

a comparatively weaker interaction, reflected in its larger solubility radius.

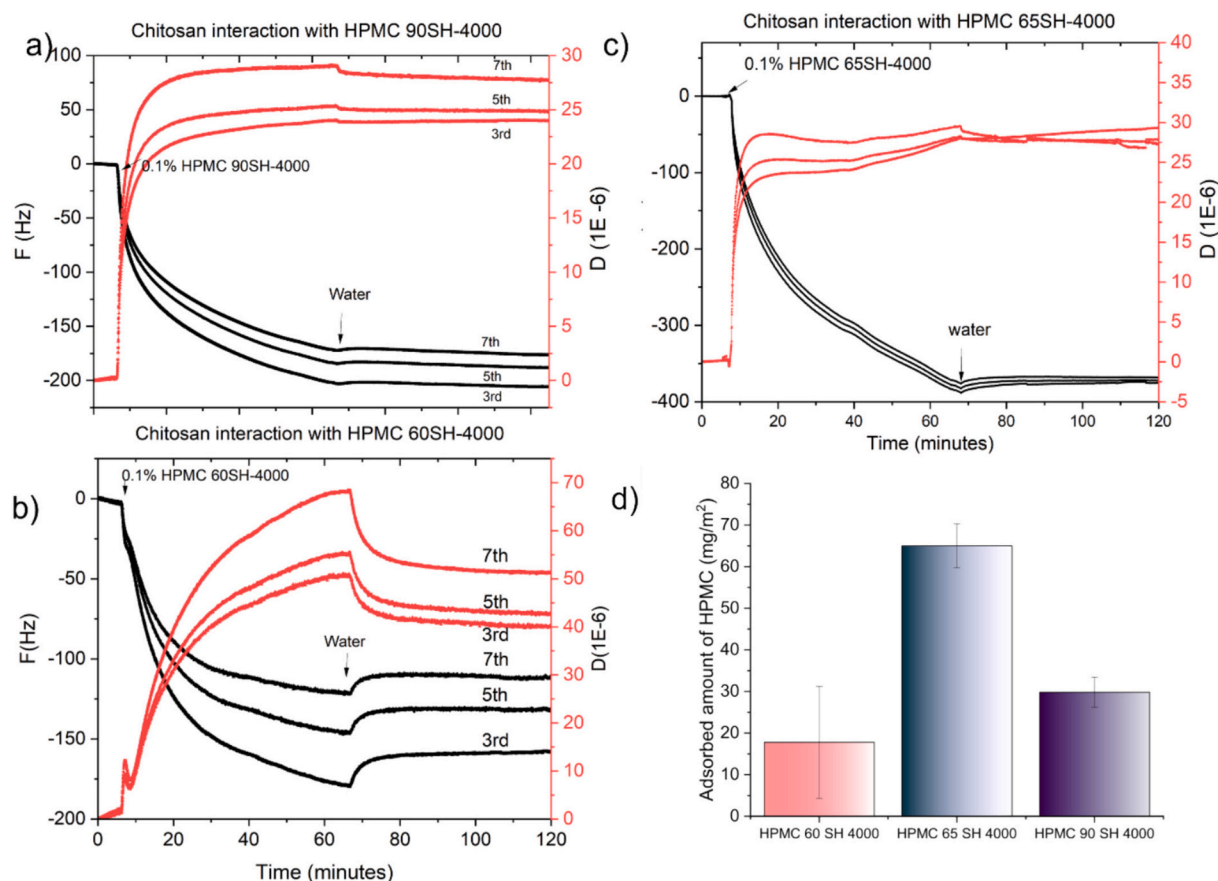
To further assess the solution behavior of these polymers, viscosity and DLS measurements were conducted at various polymer concentrations (see Fig. 2). The viscosity increases as expected with increasing HPMC concentration. All samples, except HPMC 65SH, showed similar hydrodynamic diameters. Notably, the hydrodynamic diameter of HPMC 65SH increased markedly from about 60 nm to 730 nm, indicating substantial aggregation or association of polymer chains in solutions. Although Hansen solubility parameters (HSPs) predicted HPMC 60SH to be the least soluble, experimental data indicated that HPMC 65SH exhibited greater association in aqueous solution. This suggests HPMC 65SH has a lower effective interaction with water than

anticipated. This discrepancy between predicted and observed behavior likely arises because HSP calculations do not account for the relative positioning of functional groups, which plays a decisive role in determining solution properties and polymer association, as noted by Viriden et al. [26].

### 3.1.2. Interaction of different hydroxypropyl methylcellulose with chitosan studied using quartz crystal microbalance with dissipation (QCM-D)

The uniformity and stability of chitosan thin films on the SiO<sub>2</sub>-coated QCM-D sensors are crucial to extract in order to get reliable information from the interaction studies. Therefore, the spin coated chitosan films were evaluated for uniformity and stability using atomic force microscopy and pH dependent frequency response in QCM-D. Fig. 3a) shows a

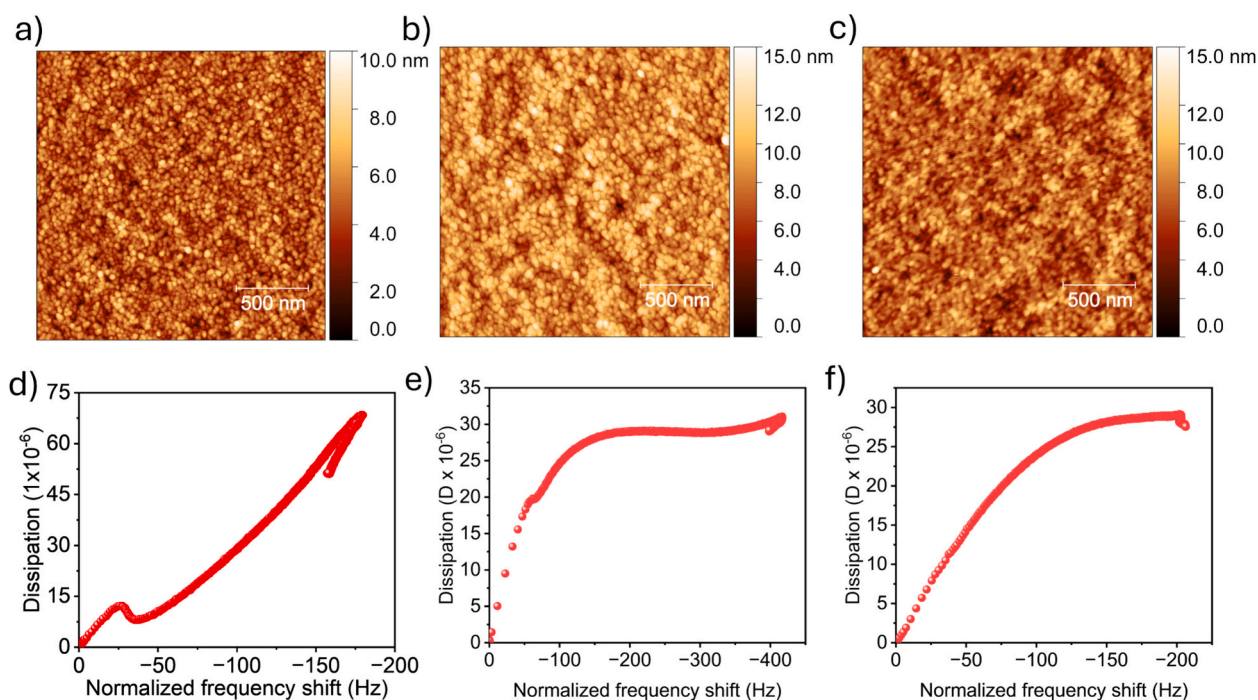




**Fig. 4.** Representative QCM-D response curves for adsorption of a) HPMC 90SH-4000, b) HPMC 60SH-4000, c) HPMC 65SH-4000, d) amount of HPMC adsorbed on the chitosan surface. The standard deviation is based on at least three independent measurements.

representative AFM micrograph of spin coated chitosan thin films on QCM-D sensor. The spin coated chitosan films exhibited a uniform

smooth morphology with an average root mean square roughness of 0.67 nm (Fig. 3b-d), which is lower compared to the value reported by



**Fig. 5.** Representative AFM micrographs of QCM-D sensors after the adsorption a) HPMC 60SH-4000, b) HPMC 65SH-4000, c) HPMC 90SH-4000, and corresponding Dissipation-Frequency plots (d-f).

Katan et al., probably due to the differences in the chitosan grade used for spin coating [27]). However, the morphological features were comparable.

The frequency and dissipation response of chitosan films in different pH conditions is shown in Fig. 3e). From the figure, the frequency doesn't change appreciably when switching from water to pH 6 and pH 5. However, the introduction of a solution with pH 4 resulted in a sudden decrease in frequency, corresponding to swelling, followed by an immediate increase up to 600 Hz, indicating detachment of the chitosan film from the surface. At acidic conditions, the amino groups in chitosan become protonated, which increases the solubility of chitosan in water. The dissipation response was also in agreement with the instability of films under acidic conditions. All the HPMC solutions used in the interaction studies had a neutral pH; therefore, the films were stable in the measurement conditions.

Figs. 4a-c show representative QCM-D response curves for adsorption of different HPMC grades on cellulose surfaces. In all cases, the injection of HPMC solutions led to an immediate decrease in frequency, indicating the adsorption of HPMC at the interface. Rinsing with water did not result in any increase in frequency for any of the HPMC grades examined, suggesting that HPMC adsorbs irreversibly onto the chitosan surface. The relatively high dissipation values further confirm that the adsorbed layers are viscoelastic, as expected. The amount of HPMC adsorbed on the chitosan surface was calculated using Johannsmann's model and is presented in Fig. 4d. Among the tested variants, HPMC 65SH 4000 exhibited significantly higher adsorption compared to HPMC 60SH 4000 and HPMC 90SH 4000. These results clearly demonstrate that the degree and type of substituent groups influence the interaction of HPMC with the chitosan surface.

To investigate morphological changes, the QCM-D sensors were characterized using AFM following the adsorption process (Fig. 5a-c). Interestingly, the surface morphology remained largely unchanged post-adsorption, despite the DLS data indicating HPMC aggregation in the bulk solution. Analysis of the D-F plots (dissipation vs. frequency) provided further insight into the interfacial dynamics (Fig. 5d-f). In all cases, the initial adsorption phase exhibited a linear relationship, followed by a distinct change in slope except in the case of HPMC 90SH where the frequency-dissipation relationship was almost linear.

The change in slope of D-F plots in the case of 60SH 4000 and 65SH 4000 suggests significant conformational reorganization of the polymer chains at the interface. These combined results imply that while the polymers exist as aggregates in solution, they undergo structural reorganization upon contact with the chitosan surface to form a more uniform distribution.

The observed differences in the adsorption can be rationalized using the framework proposed by Scheutjens and Fleer, who describe polyelectrolyte adsorption in terms of four key parameters:  $\chi$  (polymer-solvent interaction),  $\chi_s$  (polymer segment-surface interaction),  $q_m$  (surface charge), and  $\sigma_0$  (polymer segmental charge) [31]. While HPMCs are non-ionic, rendering  $q_m$  and  $\sigma_0$  irrelevant, and adsorption is solely governed by  $\chi$  and  $\chi_s$ . In this context, lower solubility (higher  $\chi$ ) typically enhances adsorption, as the polymer favors interaction with the surface over remaining solvated in bulk. This trend aligns well with our observations: HPMC 65SH, which exhibited lower solubility as indicated by dynamic light scattering, showed the highest level of adsorption, whereas the more soluble HPMC 60SH displayed the lowest adsorption onto the chitosan surface [32].

Hydroxypropyl (HP) substituents in HPMC can, due to their chemistry, react with each other and form short HP chains. Previous studies using enzymatic degradation and MALDI analysis have shown that this tendency is more pronounced in hydroxypropyl cellulose (HPC) than in HPMC; for HPMC, mainly mono-HP or short oligomers with two HP groups were detected [33]. To the best of our knowledge, no systematic studies have yet addressed the effect of HP chaining or substitution heterogeneity on HPMC adsorption mechanisms.

## 4. Conclusions

This study provides a comprehensive investigation into how the degree of substitution in HPMC influences its solubility and interactions with chitosan surfaces. The dynamic light scattering revealed that subtle variations in methoxy and hydroxypropoxy substitution significantly affect the aqueous behavior of HPMC, particularly in terms of aggregation and effective solubility. This behavior was not captured in Hansen solubility parameters, since the HSP calculations do not consider the relative positions of functional groups. The QCM-D measurements demonstrated that all HPMC variants adsorb onto chitosan films, with HPMC 65SH 4000 exhibiting the highest adsorption. This behavior was rationalized using the Scheutjens-Fleer framework, where lower solubility (higher  $\chi$ ) enhances surface affinity due to reduced polymer-solvent interactions. The findings underscore the importance of substitutional chemistry in tailoring polymer-polymer interactions and provide valuable insights for the rational design of cellulose-based formulations, particularly in applications such as oral films, hydrogels, and controlled-release systems.

## CRediT authorship contribution statement

**Vishnu Arumughan:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Karin Korelc:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Ingunn Tho:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Anette Larsson:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

## Declaration of competing interest

Authors declare no financial interest or personal relationships that could have appeared to influence the work reported in this paper.

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## Data availability

Data will be made available on request.

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