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**Light Scattering Experiments on Aqueous Solutions of Selected Cellulose Ether:
Contribution to the Study of Polymer-Mineral Interactions in a New Injectable
Biomaterial.**

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Abstract

Hydroxypropylmethylcellulose (HPMC) is used as a ligand for a bioactive calcium phosphate ceramic (the filler) in a ready-to-use injectable sterilized biomaterial for bone and dental surgery. Light scattering experiments were usually used to study high water-soluble polymers and to determine the basic macromolecular parameters. In order to gain a deeper understanding of polymer/mineral interactions in this type of material, we have investigated the effect of divalent and trivalent ions (Ca^{2+} , PO_4^{3-}) and steam sterilization on dilute solutions of HPMC and HEC. The sterilization process may cause some degradation of HEC taking into account its high molecular weight and some rigidity of the polymer chain. Moreover, in the case of HPMC, the changes in the conformations rather than degradation process are supposed. These effects of degradation and flocculation are strengthened in alkaline medium. Experimental data suggested the formation of chelate complexes between Ca^{2+} and HPMC which improve its affinity to the mineral blend and consolidate the injectable biomaterial even in the case of its hydration by biological fluid.

Keywords : Light scattering, injectable biomaterial, calcium phosphate, cellulose ether

Introduction

Cellulose is a fundamental constituent of vegetables and a major component of various industrial products. It is a linear and polydisperse polysaccharide consisting of anhydroglucose units linked by 1,4- β -glycosidic bond. Wood and cotton are the most important raw material for cellulose production. Water-soluble polysaccharides can be obtained by etherification of cellulose. They are very interesting for industrial applications because of their solubility, gelification properties and availability in a large range of molecular weights¹. Moreover, cellulose ether and polysaccharides exhibit appropriate biological properties which make them suitable for biomedical applications². For example hydroxypropylmethylcellulose (HPMC) is biocompatible³, and can be used⁴ in pharmaceuticals (tablet binder, ophthalmic preparations), cosmetics (shampoos and toothpaste) and wound care devices.

Recently, these polysaccharides have been used in an injectable bone graft biomaterials⁵ for non invasive surgery and bone repair⁶. Such biomaterials usually constitute of 40 % of an aqueous solution of hydroxypropylmethylcellulose (2 % w/wt) and 60 % of biphasic calcium phosphate (BCP) which has all the suitable physicochemical and biological properties for bone tissue reconstruction^{7, 8}. The polymer used in such injectable paste must be blend to a mineral charge and sterilized. It is rather difficult to study polymer-mineral interactions in HPMC-BCP blends due to low polymer contents and high spectroscopic response of the mineral components. FT-IR⁹ and XPS¹⁰ investigations carried out on the pure and blended polymer did not reveal any significant chemical changes occurring upon the formation of the blend. However significant change in the viscosity of the injectable mixture are observed under

sterilization or calcium salt contact¹¹. These modifications in the inherent viscosity values can be considered as a phenomenological manifestation of the polymer molecular weight changes.

Light scattering measurements are the most suitable method for studying high water-soluble polymers¹² because they permit the determination of the most fundamental parameters characterizing a macromolecule. The weight average molecular weight M_w and other macro-molecular parameters of significance like the radius of gyration R_g and the second virial coefficient A_2 ¹³ can be extracted from such studies. This method is absolute, rapid, requires less sample and allows an accurate measure over a whole range of molecular weight (commonly 10^3 - 10^7 g/mol).

The purpose of this study is to investigate cellulose derivatives in solution containing divalent (Ca^{2+}) or trivalent (PO_4^{3-}) ions with different pH, and/or exposed to steam sterilization using light scattering method. This constituted an approach to understand possible polymer calcium phosphate interactions. Only few studies on light scattering in aqueous solutions of HPMC^{1,14} and HEC¹⁵ have been reported. Similarly thermogelification of cellulose ethers have been investigated in detail¹⁶⁻²⁰. To our knowledge this is the first work dealing with analysis of the evolution of basic molecular parameters of cellulose ethers caused by the presence of minerals ions of biological interest.

Experimental

Materials

Commercially available cellulose derivatives used in this research, i.e. hydroxypropylmethylcellulose (HPMC), Benecel MP 824 and MP 651, and hydroxyethyl-cellulose (HEC), Natrosol HHX-pharm were purchased from Aqualon (France). For the clarity of the paper we used MP 824, MP 651 and HEC for polymer used. Glasshouse and sample tubes were made dust-free by soaking in concentrated Deconex (Borer Chemie, Switzerland) solution and then rinsing with filtered distilled water. In all operations and in the preparation of the solutions, ultrapure deionized distilled-water was used. The light scattering studies were carried out in the following solutions NaOH (pH = 13), $\text{Ca}(\text{OH})_2$ (pH = 11.5), HCl (pH = 3) and H_3PO_4 (pH = 2.5). These solutions were prefiltered using 0.22 μm filters (Millipore Sterivex-GV, France) before polymer was added. In order to study the effect of the ionic components on the macromolecular parameters of cellulose ether, identical set of scattering experiments were carried out in the solution of polymers in pure water.

Preparation of polymer solutions

Polymer solutions were obtained by dissolving of the appropriate cellulose derivative in a powder form in 200 ml of the above mentioned aqueous solutions at 25 °C. The concentrations of the polymer were varied by dilution of the stock solution with distilled water. They were in the range of 0.9-5 mg/mL for MP 651 and 0.3-2 mg/mL for MP 824 and HEC. In order to remove traces of dust viscous polymer solutions were directly filtered under a laminar flow area into glass scintillation-vials used as scattering cells, through 0.45 μm filters (Millipore Millex-HV,

France). By measuring the dry weight of the polymer we have verified that no loss in polymer concentration take place during the filtration.

A portion of each solution was sterilized in an water-vapor autoclave (120°C, 20 min) in 50 ml bottles. The whole sterilization cycle took about 60 min ; heating up 20 minutes, exposure at 120°C 20 minutes and cooling down 20 minutes. After removing from the autoclave, the bottles were stored together with those containing non-sterilized solutions for 12 hours at 25°C prior to light scattering analysis.

Light scattering experiments

Static light scattering equipment is the same as the one used by one of us to study amylose²¹. Experiments were performed at $25 \pm 0.1^\circ\text{C}$ over the angular range 30-150°. A 3-W Argon Ion Spectra Physic laser operated at 514.5 nm and 100 mW was used as a light source. The incident radiation was vertically polarized. Optical alignment was checked over the angular range 10-150° using filtered benzene. Incident radiation was focused on the sample cell which was held in a thermostated vessel filled with refractive index matching decaline. Outer surface of the cells were rinsed with filtered acetone and carefully wiped up prior to light scattering analysis. Data were analyzed using a Zimm extrapolation method¹³ and values of dn/dc for HPMC and HEC in water equal to 0.146 and 0.139 were taken from the literature^{13,15}. These values were also used for the other solvents. This extrapolation is supported by a recent work²²

Results and Discussion

Aqueous polymer solutions without ionic components

Figure 1 show typical Zimm plot obtained at 25°C for HPMC in water, whereas in table 1 principal molecular parameters deduced for four different non-sterilized (US) and sterilized (S) solutions are collected. The precision of the molecular weight determination is of the order of 15%. In the case of HPMC we sometimes registered at low angles of observation (30°, 45°) variation in the total scattered intensity which may contribute to molecular weight determination error. This could be associated to the presence of minute amount of dust or with the occurrence of a weak microgel. Nevertheless, data for unsterile HPMC solutions are in accordance with those found in the work of Neely¹⁴ on cellulose ethers with a similar substituent content. For HPMC similar to MP 824, he found $M_w = 690\,000$ g/mole. and those similar to MP 651 he found $M_w = 298\,000$ g/mole.

A_2 values reflect the interactions between an individual polymer molecule and the solvent²³ and the high virial coefficient for HEC (see table 1) confirms that this polymer has a great affinity with water owing to a high content of the hydroxyl groups. HPMC has a weaker affinity to water, particularly the MP 651 polymer. Since the presence of few hydroxypropyl groups can inhibit association of methylcellulose (MC) chains¹⁸ the difference between A_2 values of the two types of HPMC studies can probably be rationalized on the basis of a higher percentage²⁴ of hydrophobic methoxy substituents in MP 651 (29% O-CH₃) as compared to MP 824 (21% O-CH₃). On the contrary a higher content of hydroxypropyl groups makes the hydrophilous behavior of the polymer more pronounced and prevents from hydrophobic interactions¹⁴. If

hydration is not sufficient in different parts of the polymer chain, the hydrophobic interactions become to dominate which in turn, leads to minimalisation of contact with the solvent. This tendency is reflected by lower A_2 values. These observations are coherent with the aggregated ‘bundles’ or ‘fringe micelle’ models proposed respectively by Haque¹⁸ and Burchard²⁵.

Effect of ionic components

All modifications induced by the presence of ionic components were referred to molecular parameters obtained for unsterilised water solutions of cellulose ethers. For the clarity of the paper it is convenient to discuss the influence of the acid and basic media separately.

For MP 824 minimal changes in the M_w values are observed in phosphoric acid and hydrochloric acid solutions. However a decrease of M_w values in the same solutions are registered for MP 651 and HEC (table 2). In addition an increase in the A_2 value observed for HEC indicates that the affinity towards the solvent is greater than in the case of the distilled water. In general in acidic media only minor changes in the M_w and R_g values were observed : molecular weight is either the same as measured for distilled water system or slightly decreases. This means that the degradation phenomena and/or chemical interactions of the polymer and the ionic component are of minor importance.

Similar behavior as describe above is registered for NaOH solution. However note that for HEC the decrease in the M_w value is of the order of 20% together with an increase in A_2 value. Same changes in the values of the principal molecular parameters were reported by Brown *and al.*²⁶ for HEC of low molecular weight in NaOH. To the contrary the molecular parameters changes are made more pronounced in the case of $Ca(OH)_2$ solutions. In fact at very high pH (12.4) the mixture studied become

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heterogeneous as manifested by a white precipitate. In addition upon filtration important loss of the polymer occurred. Since for similar pH in NaOH solutions no such phenomena were observed we attribute this behavior to the interactions with calcium anions. However at pH = 11.5 clear solutions were obtained with no loss in the polymer content upon filtration. As it has been already stated for all three types of the polymers studied a large decrease in the M_w and R_g values were registered. In addition the negative value of A_2 illustrated by the zimm plot in figure 2 indicate that the solute-solute interactions become predominant. It is probable that small cations like Ca^{2+} may form chelate-type complexes with the polymer using the oxygen lone pair of electrons. Such complexes between polyether type of compounds and salt small cations have been reported in the literature²⁷. These formation of complexes with intra and inter molecular bonds will lead to polymer dehydration and in some case to its precipitation. The complex formation is also manifested by extreme difficulty to extract calcium from the polymer-BCP blend⁹. This type of interactions significantly limit the reliability of the analysis by light scattering.

Steam sterilization

We have experienced significant difficulties in the determination of the M_w of the MP 824 in water after its sterilization. These difficulties arise from the fact that the sterilization induced inhomogeneity of the solution. At the conditions of the sterilization the HPMC aqueous solutions undergo some gelification followed by the flocculation and formation of aggregates²⁸. After the heat treatment a white precipitate could be observed in the sterilized vessel which progressively redissolved at room temperature to give clear solutions. This sequence of phase transitions results in the dehydration of the polymer which then partially redissolve on cooling²⁰. Similar behavior has been

reported by Chemtob *and al.*²⁹. We can therefore suppose that irreversible aggregates persist even in clear filtered solutions. This irreversibility could be explain by considering that rehydration is less favored than dehydration. The formation of irreversible aggregates is consistent with the observed decrease in viscosity of MC and HPMC solutions^{29, 30}. In such case the data extrapolation by Zimm method is rather difficult. However the obtained data allow for a rough estimation of the changes in the molecular parameters occurring upon the heat treatment. For both types of HPMC a decrease of A_2 value is observed indicated lower affinity for water. Such behavior were already observed in the thermal treatment of MC solutions and explained by the concept of microblock structure of polymer chains³¹. Hence, in view of the above discussed observations a change in polymer conformation is expected rather than its degradation. The HEC solutions behave differently. No precipitate was observed, in this case, during the steam sterilization and the A_2 value remained essentially constant. Nevertheless a large decrease in M_w and R_g values seems to indicate some kind of degradation process. Under thermal agitation some chain scission may occur in extended and rather inflexible molecules of HEC²⁶. However oxidative-type degradation must also be taken into account³².

The above discussed phenomena are even more pronounced after the addition of the ionic components to the solution being sterilized. In acidic media significant decrease in M_w and R_g values are observed in the cases of MP 824 and HEC. The decrease is especially significant in phosphoric acid solutions. The second virial coefficient A_2 , remains stable for HEC acidic solutions and it decreases for MP 824. In the later case it adopts a negative value in the phosphoric acid. Thermal treatment results in dehydration of the polymer manifested in the destruction of the water layers.

Since the layer preventing from polymer-polymer interchain interactions is no longer existing the glucosidic linkage is exposed to hydrolytic splitting.

In basic media, steam sterilization catalyzes strong associations leading to a white precipitate which does not redissolved at room temperature. Moreover significant losses of the polymer occurring during the filtration make the analysis of such solution difficult. With the exception of HEC in $\text{Ca}(\text{OH})_2$ solution the molecular parameters could not be determined with acceptable precision when data were treated by Zimm method. In this case M_w increase (table 2), and A_2 decreased in a manner characteristic of the aggregate formation. A possible flocculation in presence of Ca^{2+} ions is reinforced by dehydration caused by the salt and heat treatments.

CONCLUSION

Light scattering experiments allowed us to distinguish significant differences in polymer water affinity depending on the substituent content and their type. In spite of its good affinity to water and a good salt tolerance, HEC appears to be sensitive to sterilization. In alkaline media a decrease in its molecular weight is registered. The reliability of light scattering data (Zimm plot method) have to be taken with caution taking in account the some modifications of the polymer solubility for salts aqueous solutions.

The water affinity of HPMC MP 824 is rather good and the results seem to favor chain conformation changes during steam sterilization rather than a degradation processes. For $\text{Ca}(\text{OH})_2$ basic media, the formation of chelate-type complex between Ca^{2+} and the polymer is proposed. The values of R_g and A_2 obtained in dilute solution are not closely related to the properties of the polymers in more concentrated solution but possible

conformational changes can explain the observed variations of viscosity in calcium phosphates mineral fillers blended with the polymer solutions after sterilization. This study raise the question of the stability of this type of biomaterials during sterilization and storage and consequently the part of degradation and/or conformational changes of the polymer chain in the blend have to be elucidated. Good affinity to water observed for HPMC MP 824 together with the supposed ionic association favor its use as a ligand for an injectable biomaterial. In fact good dispersion of this composite in biological fluid and a partial affinity with calcium phosphate (i.e. the filler of the blend) facilitates its storage in surgical site.

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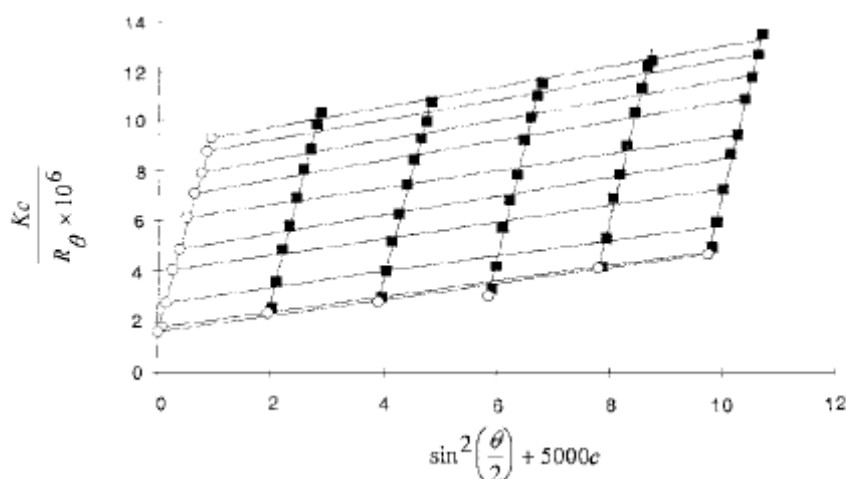


Figure 1 Typical Zimm plot of HPMC MP 824 in water at 25 °C.

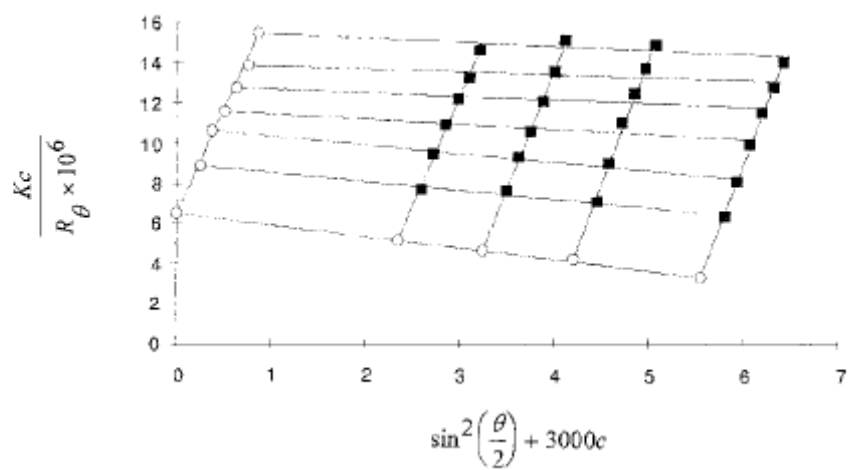


Figure 2 Zimm plot at 25 _C of HPMC MP 824 in a Ca(OH)₂ aqueous solution (pH.11.5).

Table. I. Mean molecular parameters obtain by static light scattering for HPMC MP 824, MP 651 and HEC HHX-Pharm in distilled water at 25°C.

Sample	M_w ($\times 10^5$ g/mol)		R_g (nm)		A_2 ($\times 10^{-4}$ mol.cm ³ /g ²).	
	US*	S**	US	S	US	S
HPMC MP 824	7 ± 1.2	13 ± 7	130 ± 12	140 ± 27	10 ± 3	3 ± 1.5
HPMC MP 651	1.8 ± 0.3	2.4 ± 0.5	89 ± 9	97 ± 17	0.6 ± 0.3	0.4 ± 0.6
HEC HHX pharm	17 ± 2.4	7.7 ± 0.7	170 ± 21	115 ± 7	17 ± 1	17 ± 2

Values reported are the mean of 4 measurements.

* US : Unsterilized samples

** S : Sterilized samples

Table. II. Mean molecular parameters obtain at 25°C by static light scattering for HPMC and HEC in various aqueous solutions

Sample	Solvent	Mp (X10 ⁵ g/mol)	R _g (nm)	A ₂ (X10 ⁻⁴ mol cm ³ /g ²)			
		US*	S**	US	S	US	S
MP 824	HCl	6.9	6	130	120	7	4
	H ₃ PO ₄	6.35	4.15	125	85	11	-9
	NaOH	7.3	nd	130	nd	17	nd
	Ca(OH) ₂	1.6	nd	61	nd	-8	nd
MP 651	HCl	1.4	-	75	-	0.9	-
	H ₃ PO ₄	1.05	-	61	-	-2	-
	NaOH	1.8	nd	85	nd	-2	nd
	Ca(OH) ₂	0.76	nd	50	nd	-10	nd
HEC HHX-Pharm	HCl	10.2	11	145	160	19	17
	H ₃ PO ₄	15	13	170	165	21	18.5
	NaOH	11.8	nd	155	nd	24	nd
	Ca(OH) ₂	6.65	13	105	79	10	-0.7

* US : Unsterilized samples

** S : Sterilized samples

n.d., not determined.

Running headline : Light scattering study of polymers for biomaterials