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Influence of the Ester Group Structure of Modified Alginates on the Preparation of Microparticles by Transacylation with Serum Albumin

Imane HADEF^(a,b), e-mail: imane.hadef@univ-reims.fr; Mehdi OMRI^(a,b), e-mail: mehdi.omri@etudiant.univ-reims.fr; Christophe BLIARD^(b), e-mail: christophe.bliard@univ-reims.fr; Barbara ROGE^(b), e-mail: barbara.roge@univ-reims.fr; Florence EDWARDS-LEVY^(a), e-mail: florence.edwards@univ-reims.fr

Institut de Chimie Moléculaire de Reims, CNRS UMR 7312;

^(a) U.F.R. Pharmacie, 51, rue Cognacq-Jay, 51096 Reims.

^(b) U.F.R. sciences exactes et naturelles, Campus du Moulin de la Housse 51687 Reims.

INTRODUCTION

Microencapsulation using the transacylation reaction in a W/O emulsion¹ is based on the creation of amide bonds between free amine functions of a protein and polysaccharide ester groups in the aqueous phase after alkalization. Several proteins have been implicated in this process (animal/plant proteins or enzymes), whereas commercial propylene glycol alginate (PGA) has been the only modified polysaccharide used up to now². The intrinsic properties of PGA such as viscosity, molecular mass, ester type and substitution degree limit its use in microparticle preparation hence the need to study other potential polysaccharide esters.

The purpose of this work is to study the effect of the alginate polysaccharide ester structure and properties on the transacylation reaction and on microparticle characteristics. Various alginate esters were synthesized and tested for transacylation with human serum albumin (HSA) chosen as reference protein. The physicochemical properties of the new alginate derivatives were subsequently studied to explain their behavior during transacylation (esterification degree, viscosity...). Furthermore, the difference in their reactivity during transacylation was followed by the determination of critical aggregation concentrations based on Coomassie blue³ spectral change. The influence of polysaccharide esterification degree, ester chain length as well as the role and position of hydroxyl groups on the ester chain were investigated.

EXPERIMENTAL METHODS

Synthesis of alginate derivatives

The synthesis was derived from the procedure described by Della Valle and Romeo (1990)⁴. The new alginate derivatives were obtained by an esterification reaction in homogeneous medium (dimethylsulfoxide, DMSO) of an alkyl bromide or hydroxyalkyl bromide (with two or three carbon atoms), with the carboxylic groups of the alginic acid, in the form of their tetrabutylammonium (TBA) salts. After 24h reaction, the remaining TBA cations were

exchanged in a concentrated NaCl solution and the final product was purified by dialyses against distilled water.

New alginate derivatives characterization

Esterification degree

The degree of esterification (DE) of alginate derivatives was determined by ¹H-NMR analysis and by titrimetry.

Viscosity measurement

The viscosities of 2% (w/w) alginate ester solutions were measured by means of Rheomat RM300 reometer (Lamy rheology).

Determination of critical aggregation concentrations

The absorbance of Coomassie blue (at 618 nm) was measured in the presence of increasing concentrations of alginate derivatives. Their critical aggregation concentration was obtained from the plot of relative optical density (OD_{blend} / OD_{standard blue solution}) vs alginate concentration.

Microparticle preparation

The aqueous solution was prepared by dissolving 2% (w/w) of new alginate ester with 10% HSA (w/w) (LFB biomédicaments) in water. The aqueous solution was emulsified in isopropyl myristate containing sorbitan trioleate. After five minutes stirring, the transacylation reaction was triggered by adding NaOH /EtOH solution to the emulsion and the reaction was stopped afterwards by adding a pH 7 buffer. Microparticles, if existing, were washed successively with polysorbate aqueous solution and with distilled water. A reference batch was also prepared from 10% HSA-2% commercial PGA (DE 84%, FMC BioPolymer) mixture.

Microparticle characterization

Microparticles were sized by a laser diffraction technique (Mastersizer 2000 analyzer Malvern).

The structure of the inner network was observed on cross-sections (cryotome Leica CM1850, Leica Microsystems) by means of a light microscope (BX51, Olympus) after coloration with methylene blue.

RESULTS AND DISCUSSION

Microparticle preparation from novel alginate derivatives

Some of the novel modified alginates were successfully used in microparticle preparation using the standard procedure (Table 1).

Microparticles prepared from the new alginate esters were smaller in size compared to the commercial PGA ones. This difference could be attributed to the lower molecular weight of alginic acid used for ester preparation which resulted in less viscous aqueous solutions and in turn smaller particles.

It was found that hydroxyalkyl alginates (hydroxyethyl and 3-hydroxypropyl) were suitable candidates for the transacylation reaction. On the other side, alkyl esters (C2 or C3) did not lead to microparticles with HSA.

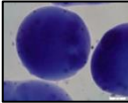
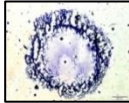
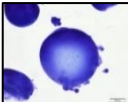
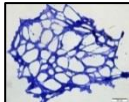
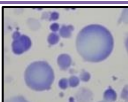
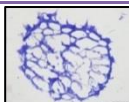
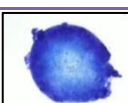
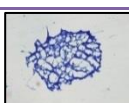
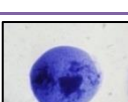
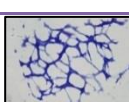
Alginate ester	RBr equivalent (DE %)	Micro-particles	Cross-sections	Size μm
PGA	Commercial (84%)			908
R= Hydroxyethyl	0,5 (58%)			279
	1 (81%)			319
R=3 - Hydroxypropyl	0,5 (48%)			243
	1 (76 %)			364

Table 1. 10% HSA-2% alginate ester (w/w) microparticles prepared by transacylation.

No microparticle could be prepared from synthetic PGAs (2-hydroxy propyl alginate) in the chosen conditions because of their low esterification degree (30%) which was recurrently obtained even after using a large excess of bromide reagent (Results not shown).

Critical aggregation concentrations

It was found that hydrophobic microdomains were formed due to the association of alkyl chains at lower polymer concentrations compared to hydroxyalkyl esters (Figure 1).

Moreover, increasing the esterification degree or the length of the ester chain led to the formation of hydrophobic microdomains at lower polymer concentrations too, except for propylene glycol alginates for which increasing the esterification degree reduced significantly their hydrophobicity (data not shown).

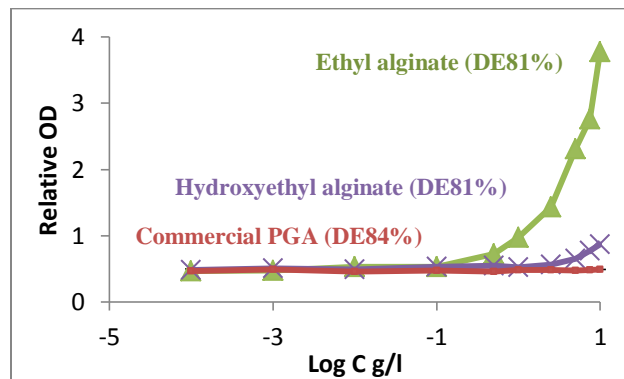


Figure 1. Absorbance change of Coomassie blue as a function of alginate ester type and concentration.

CONCLUSION

This study demonstrated that it was possible to replace commercial PGA by a variety of synthetic alginate derivatives in the process of microparticle formation with the transacylation procedure. The best candidates for the reaction with HSA were alginate esters with the highest critical aggregation concentrations. The use of low molecular weight alginates could decrease the aqueous solution viscosity as well as the size of resulting microparticles.

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