Progesterone loading in lecithin/chitosan nanoparticles for transmucosal delivery

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1 - Introduction and objectives

Polymeric or lipidic nano and microparticles have been proposed as drug carriers to improve bioavailability and modify drug pharmacokinetics. We have previously shown the possibility of obtaining colloidal particles by the interaction of soybean lecithin with chitosan. Nanoparticles with positive surface charge were produced. The aim of this work was to prepare and characterize lecithin/chitosan nanoparticles (LCN) and to evaluate their capability to encapsulate progesterone (PG). PG is nearly insoluble in water and presents bioavailability problems after oral administration. The encapsulation of the drug in nanoparticles could change its absorption profile. Progesterone loaded nanoparticles are suitable for nasal, buccal or oral administration.

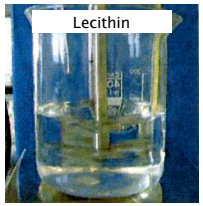
2 – Materials & Methods

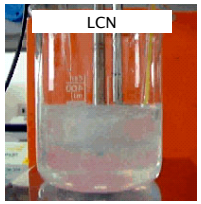
8 ml of ethanolic lecithin solution (25 mg/ml) were injected in 92 ml of chitosan hydrochloric solution (0.01% w/v; pH 2.75) under stirring to obtain a colloidal suspension of particles (LCN). LCN prepared with chitosan batches having different MW, were characterized for size (PCS) and surface charge (PALS). Small angle neutron scattering experiments (SANS) have been performed on D11 instrument at the Institut Laue-Lagevin (Grenoble, France). A preparation obtained using lecithin without the polysaccharide was studied for comparison. Progesterone LCN were produced dissolving PG in the ethanol solution in order to have a drug concentration between 2-20 mg per 100 ml of colloidal suspension. The suspension was centrifuged to separate precipitated PG and PG loaded nanoparticles. The two products were dissolved in ethanol and the PG content assayed by HPLC. The supernatant was also assayed for dissolved PG. The encapsulation efficiency (the ratio between encapsulated PG and total drug) and the PG loading (PG content per dry nanoparticle) were determined.

Results

3.1 - Nanoparticles characterization

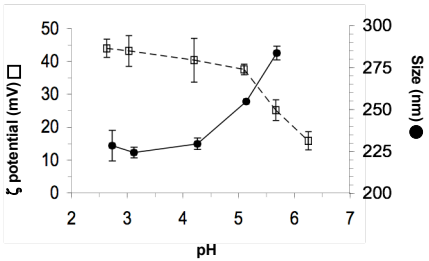
Different colloids have been obtained as a consequence of the presence of chitosan. Lecithin/Chitosan nanoparticles had a size of around 250 nm with a positive surface charge (~ + 40 mV). On the contrary, lecithin colloid particles had smaller size (below 100 nm) and negative surface charge (~ - 50 mV). The encapsulation of progesterone slightly affected the characteristics of the LCN.

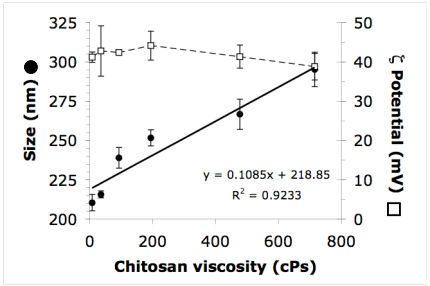




Sample	Size (nm)	ζ potential (mV)
LCN1	239.0 ± 6.6	42.40 ± 0.47
Lecithin	72.6 ± 1.5	- 52.58 ± 0.72
PG loaded LCN (20mg/100ml)	213.9 ± 5.9	45.12 ± 5.54

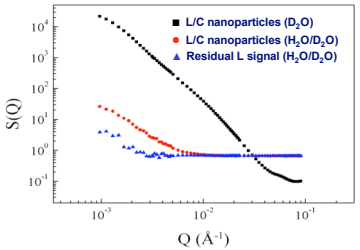
Size and surface charge of LCN were pH-dependent. Increasing the pH value lof the LCN suspensionsed to a decrease of the surface charge along with an increase of particle size. At pH around 6.0, aggregation was noticed, probably due to an insufficient electrostatic repulsion of the particles at this pH value. LCN produced using chitosan with increasing molecular weight showed no significant difference in the surface charge of the colloid, but a linear dependence with the particle size was evidenced.





3.2 – Neutron scattering experiments

SANS experiments on LCN were performed either in D_2O or in a mixture of H_2O/D_2O able to "mask" the contribution of the lipid component, in order to assess the location of the polysaccharide. Experimental data obtained were fitted with a mathematical model describing the scattering, S(Q) of the particle in function of the momentum transfer, Q. Until now, data allow to exclude simple structures as an homogeneous spheres, coated liposomes or alternating layers of polysaccharide and lipids. More complex relationships between the components are involved.



3.3 – Progesterone encapsulation

For progesterone concentrations up to 10 mg/100 ml of suspension, the drug was efficiently encapsulated (~60% encapsulation efficiency) in LCN, with maximum drug loading of 3.3%. For higher concentrations, drug encapsulation efficiency and drug loading were scarcely reproducible, because of the intense precipitation of the drug during nanoparticle production.

PG total amount (mg/100ml)	Encapsulation efficency (%)	Progesterone loading (%)
2	57.2 ± 0.1	0.72 ± 0.1
5	55.1 ± 2.2	1.53 ± 0.2
10	62.4 ± 5.3	3.33 ± 0.5
13	43.2 ± 15.9	2.99 ± 0.2
15	44.9 ± 16.4	3.37 ± 1.4
20	18.2 ± 1.1	2.19 ± 0.2

4 – Conclusions

Nanoparticles composed of lecithin and chitosan have been shown to have physico-chemical properties depending on pH and the chitosan molecular weight, suggesting the presence of the polysaccharide on nanoparticle surface. Neutron scattering experiments helped starting to elucidate the colloid structure, allowing to exclude simple coated liposomes. Progesterone was encapsulated in lecithin/chitosan nanoparticles having positive charge; however for concentration exceeding 10 mg/100 ml the precipitation of the drug decreased its loading.