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On the Importance of Mucin Corona to prevent Nanocapsules Aggregation for Oral Delivery

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Extended Abstract

Bacterial biofilms, that are multispecies colonies, provide bacteria with protection against adverse environmental conditions and lead to the appearance of multi-drug resistant strains. Inhibition of virulence by disrupting *quorum sensing* (*QS*), which is a cell-cell communication strategy, has been recognised for the fight against multidrug resistant bacteria. *N,N'*-(Di-m-methylphenyl)urea (DMTU) can be used to fight against oral biofilms, given its *QS* inhibition capacity that blocks the expression of virulence factors in *Streptococcus mutans* [1].

Chitosan(CS)-coated oil-in-water nanocapsules (CS-coated o/w NC), prepared by solvent displacement, entrap lipophilic molecules and enhance their bioavailability in physiological conditions [2-4]. Besides, the CS coating provides a net positive charge to o/w NC which facilitates its interaction with negatively charged surface of bacteria, mammalian cells and mucins [5-7] Mucins are the main component of mucus layer that cover all the mucosal surfaces and of saliva that covers all the surfaces in the oral cavity, such as teeth, tongue or gums. Given the fact that CS-coated o/w NC will interact with saliva prior its interaction with biofilms in oral cavity, the study of their interaction with mucin glycoproteins is of sum interest as the aggregation of CS-coated o/w NC would result in the loss of their goodness as nanometric drug delivery system.

In this work, the interaction between the soluble and purified fraction of mucin type III (Sigma-Aldrich), used as a model, and CS-coated DMTU-loaded o/w NC was carried out. The mucin suspension was prepared at 5 mg/mL and then serially diluted by half up to 0.16 mg/mL. This mucin concentration range included the mucin concentration in saliva, 0.37, mg/mL [8]. The interaction analyses at mucin: CS-coated DMTU-loaded o/w NC ratios equal to 2.68, 1.34, 0.67, 0.34, 0.17 and 0.08 w:w has been investigated by dynamic light scattering (DLS) and ζ-potential [5]. The hydrodynamic diameter and ζ-potential of the structures formed upon the interaction of both counterparts was measured immediately after being mixed, considered as time 0, and after 24 h of incubation at 37 ºC.

The results show that the initial size and ζ-potential of CS-coated DMTU-loaded o/w NC were 287 ± 6 nm and +54 mV, respectively. Interestingly, at mucin: CS-coated DMTU-loaded o/w NC ratio equal to 0.17 w:w, which corresponds to the physiological concentration of mucin, the presence of mucin in the system was not enough to coat the nanocarriers completely. At time 0 the ζ potential of the nanostructures formed decreased into the instability region (lower than +20 mV) and after 24 h, massive structures with size larger than 2000 nm and ζ-potential nearly 0 mV were recorded. Indicating that CS-coated DMTU-loaded o/w NC had aggregated. Increasing the mucin content, at mucin: CS-coated DMTU-loaded o/w NC ratio equal to 0.34 w:w, the o/w NC were coated with a mucin corona which reverts their net charge and protects them from aggregation as their size after 24 h was lower than ~500 nm. Further increase in mucin content, at mucin: CS-coated DMTU-loaded o/w NC ratio equal to 0.67 w:w, mucin coated completely CS-coated DMTU-loaded o/w NC as seen by the highly negative charge recorded immediately after their interaction (< -20 mV). After 24 h, the structures showed an hydrodynamic diameter of ~250 nm, which agrees with previously reported results that relate the decrease in the size with an increase in polymers flexibility [9]. Future studies will evaluate the stability of the mucin: CS-coated DMTU-loaded o/w NC in simulated saliva fluid. The results of this work offer new insights into the modification of the surface identity and stability of chitosan-coated nanocapsules which full potential in buccal delivery is yet to be realised.

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