

## Chitosan-coated mucoadhesive fucoidan/poly-lysine nanogels for the prevention of inhaled corticosteroids-related oral candidiasis

Inhaled corticosteroids (ICS) are widely used for treating chronic respiratory diseases. However, prolonged high-dose ICS therapy, especially via dry powder inhalers, can cause excessive drug deposition in the oral cavity. This may disrupt the oral microbiome and promote the growth of *Candida albicans*, leading to oral thrush (candidiasis). This study aims to develop mucoadhesive, antifungal nanogels (NGs) composed of fucoidan (FD) and poly-L-lysine (Poly-L), coated with low molecular weight chitosan hydrochloride (Cs), intended for oral spray administration to prevent ICS-associated infections.

FD and Poly-L solutions (0.25–2% and 0.025–0.2% w/v, respectively) were prepared in MilliQ water. Poly-L was extruded into FD through a 25G needle at volume ratios of 1:1, 2:1, and 3:1, forming colloidal dispersions. These were characterized for hydrodynamic diameter (HD) and particle concentration (particles/mL) using Nanoparticle Tracking Analysis (NTA). Polydispersity index (PDI) and zeta potential ( $\zeta$ -potential) were evaluated by Dynamic Light Scattering (DLS) and Electrophoretic Light Scattering (ELS), while morphology was examined by Scanning Electron Microscopy (SEM). The most promising NGs were coated with Cs to produce positively charged CsNGs. Cs solutions (0.25–1% w/v) were prepared in MilliQ water and adjusted to pH  $\sim$ 6 using phosphate-buffered saline (PBS). CsNGs were characterized as previously described. Mucoadhesion was assessed by turbidimetric and  $\zeta$ -potential methods. Cytocompatibility was tested on Normal Human Dermal Fibroblasts (NDFH), and short-term stability study was conducted.

Optimized formulations yielded highly concentrated and homogeneous dispersions with  $\sim$ 200 nm HD and  $-20$  mV  $\zeta$ -potential. Cs coating increased both NG size and  $\zeta$ -potential, confirming successful surface coating and enhanced mucoadhesive potential. CsNGs did not show adverse effects on NDFH.

Mucoadhesive Cs-coated FD/Poly-L NGs with small size and low PDI have been successfully developed. Future perspectives include the assessment of antifungal efficacy against *Candida albicans* and the evaluation of CsNG spreadability and sprayability through measurements of surface tension, viscosity, contact angle on mucin films, and spray pattern analysis.