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DEVELOPMENT OF A THERMO-RESPOSIVE AND MUCOADHESIVE INTRANASAL SPRAY FOR THE PREVENTION OF INFECTIOUS PULMONARY DISEASES

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The respiratory system is continuously exposed to pathogens and particles that can cause diseases for which effective prevention strategies and specific pharmaceutical treatments are required [1].
The present work aims to develop a thermo-gelling and mucoadhesive intranasal spray intended to be administrated for the prevention of viral infectious diseases. The systems have been prepared by the addition of different types of cyclodextrins (CDs) known in the literature for their antiviral activity [2], such as hydroxypropyl-β-CD (HPβ-CD; Sigma-Aldrich, I) and randomly methylated-β-CD (rβ-CD; CycloLab, HU), to an aqueous solution containing a hydrophobically-modified hydroxypropyl-methyl cellulose (Sangelose, SG; DAIDO, JA). At room temperature, SG/CDs aqueous solutions are characterized by a low viscosity due to SG/CDs complexation. As the temperature increases to physiological values, SG/CDs complex dissociates: SG hydrophobic chains interact with each other, causing the system sol-gel transition, and with nasal mucosa, exerting a mucoadhesive effect [3].
SG/CD solutions, based on 0.5% w/w SG and different HPβ-CD or rβ-CD concentrations (0.1-0.5% w/v and 0.025-0.2% w/v respectively), were characterized in terms of rheological behavior by a rotational rheometer and gelation temperature (T_{gel}) and time (t_{gel}) were determined. The mucoadhesive potential was tested by means of a Texture Analyzer using 8% w/v mucin suspension in simulated nasal fluid as biological substrate. Sprayability and spreadability were investigated for the most promising SG/CD solutions by the measurement of the spray coverage area and the determination of tension surface and contact angle on gelatin-mucin or gelatin substrates. Spray droplets size was investigated by means of SprayTech, while spray deposition and coverage pattern were evaluated through a silicon nasal cast model. *In vitro* experiments were performed to assess system cytocompatibility on different cell lines (HeLa, MRC-5, A549, and HEp-2 cells). *In vitro* tests were also conducted on nasal epithelium to test the cytocompatibility of SG/CD solutions at 24, 48 and 72 hours after treatment.
The addition of both HPβ-CD and rβ-CD to SG solution was responsible for a sol-gel transition within a physiological temperature range (29-34°C) in about 1 minute. SG/CD systems were characterized by viscoelastic properties at 37°C and an optimal mucoadhesive potential. Sprayability and spreadability resulted to be suitable for nasal administration. Deposition test showed that SG/rβ-CD systems with a low viscosity deposit in the anterior nasal regions and have a major deposition area. All the sprays were characterized by droplets with size > 100 μm, functional to avoid droplets exhalation or lung deposition. Finally, *in vitro* test demonstrated that the systems do not alter the viability of any of the cell lines used and no damage of nasal epithelium was produced by any SG/CD solutions within the 72 hours after treatment.
The thermo-gelling and mucoadhesive systems obtained are proved to be easily sprayed through an appropriate device into the nasal cavity and to form a gel at physiological conditions that should act as a physical barrier to the entry of pathogens into the respiratory tract.

[1] Williamson S, et al.; BMJ Open (2022); 12.
[2] Braga SS, et al.; Pharmaceutics (2021); 13: 409.
[3] Iohara D, et al, Mol. Pharmaceutics (2017); 14: 2740-2748

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