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DRUG DELIVERY SYSTEM BASED ON pH-RESPONSIVE NANOFIBERS FOR THE PREVENTION OF SEXUALLY TRANSMITTED INFECTIONS

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The present work aims to develop electrospun nanofibers, coated with a pH-responsive polymeric film, to be used as vaginal drug delivery systems for the prevention of sexually transmitted infections. More specifically, the film coating should remain intact at vaginal pH, protecting the inner nanofibers loaded with the drug; the increase in the environmental pH due to the presence of the seminal fluid should cause film solubilization, resulting in nanofiber exposure, and their subsequent hydration and adhesion to the vaginal mucosa.

For the fiber preparation, polyvinyl alcohol (PVA; Sigma-Aldrich, I) and carrageenans (κ-CAR and ι-CAR; Sigma-Aldrich, I) were dissolved in MilliQ water (2h at 85°C); different concentrations of PVA (10-20 % w/v) and CARs (1-2% w/v) were considered. PVA and CARs solutions were mixed at 9:1 weight ratio at 95°C for 1 h[1]. Mixture viscosity at 30°C (MCR 102, Anton Paar, I), surface tension (DY-300 Dynamaster, K) and conductivity (Mettler Toledo, O) were investigated. PVA/CAR solutions were electrospun (STIKIT-40; Linari Engineering, I) at controlled temperature (25-30°C) and relative humidity values (30%-40%). The fibers obtained were characterized for morphology (SEM; PhenomTM Pure Desktop, Thermoscientific, I) and mucoadhesive properties (TA.XT plus Texture Analyzer; Stable Micro Systems, UK), using a commercial mucin suspension in simulated vaginal fluid[2] (SVF) as biological substrate.

Afterwards, polymeric films were prepared by casting 8% w/v Eudragit L100 (EL100, Evonik, I) solutions prepared in absolute ethanol and added with 12% w/v glycerol (Gly, Sigma-Aldrich, UK) or 5.6 % w/v polyethylene glycol (PEG, Sigma-Aldrich, I)[3]. 5 ml of such solutions were placed in silicone mold and let evaporated in heater at 50°C for 24 h. Film mucoadhesive and mechanical properties were investigated by means of Texture Analyzer. Since vaginal pH is influenced by women age, phase of the menstrual cycle and pregnancy, films were subjected to *in vitro* dissolution assays in SVF at different pH (3.8, 4.2 and 5)[4] over a period of 7 days at 37°C, and to a dissolution test in SVF/SSF for 24 h at 37°C.

Finally, PVA/CAR fibers were coated with the polymeric film. The final system was tested for mucoadhesive properties after hydration at different times in SVF+SSF and in terms of mechanical properties.

PVA/CARs solutions, containing the highest PVA and CARs concentrations, characterized by high values of viscosity (10-5 Pa*s) and conductivity (> 1000 μS/cm), lead to the production of bead-free homogeneous PVA/CAR nanofibers with a mean diameter of about 500 nm. In addition, such nanofibers demonstrated good mucoadhesive properties. Both EL100/Gly and EL100/PEG films showed i) mechanical and mucoadhesive properties suitable to allow their administration avoiding ruptures and to promote intimate contact with the vaginal mucosa, ii) a proper stability in SVF at all the pH tested, and iii) a quick dissolution in SFF to permit the exposure of PVA/CAR nanofibers after the contact with a potentially infected seminal fluid. Finally, the presence of nanofibers did not alter the mechanical properties of the final system and the mucoadhesive properties are maintained at each analyzed time after immersion in SVF+SSF, resulting thus able to provide an intimate interaction with the vaginal mucosa after the contact with seminal fluid.

In conclusion, promising nanofibers coated with pH-responsive films, characterized by suitable mechanical, mucoadhesive and dissolution properties at the different pH tested, were successfully developed. Ongoing studies are focused on nanofiber loading with mucus-penetrating micelles; such approach should guarantee that the drug loaded into the nanosystems reaches the vaginal epithelium underlying the mucus.

References

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