63° SIMPOSIO AFI
RIMINI 5·6·7
GIUGNO2024

Associazione Farmaceutici Industria
Società Scientifica

TITOLO (maiuscolo)

Autore (i)

Ente di appartenenza

Riassunto

Carattere: ARIAL
Corpo: 10
Interlinea: 1

DEVELOPMENT OF INJECTABLE *IN-SITU* THERMOGELLING SYSTEMS FOR VITREOUS REPLACEMENT

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Diseases affecting the visual system can modify the characteristics of the vitreous body compromising the patient's quality of vision. *In-situ* thermogelling systems, based on biopolymers, are known to be ideal vitreous substitutes because of a sol-gel transition that provides ease of administration (sol, 25°C) and proper viscoelastic properties (gel, 37°C) to protect the eye from external shocks and to keep the retina in place (1).

Different systems, based on hydrophobically-modified hydroxypropylmethylcellulose (Sangelose, SG) and cyclodextrins (CDs), were obtained by mixing SG and CD aqueous solutions under magnetic stirring, for 2 h, in an ice bath (2); different concentrations and types of SG (60L and 90L; KISCO, DE) and CDs (β-CD and hydroxypropyl β-CD (HPβ-CD); Sigma Aldrich, I) were considered. A Design of Experiments (DoE, Chemometric Agile Tool software) approach was performed to evaluate, on a statistical basis, the contribution of different factors (SG and CD types and concentrations) on SG/CD system thermogelling behaviour. Viscosity measurements (MCR102, Anton Paar, I) at 25 and 37°C were performed on each SG/CD systems to calculate the normalized rheological parameter, $\Delta\eta/\eta$, at 10 s^{-1}. Viscoelastic properties of SG/CD samples were also investigated at 25°C and 37°C (MCR102, Anton Paar, I) and compared with those of a simulated vitreous fluid (SVF), prepared following (3). The best prototypes were further investigated in terms of gelation temperature (TG) and time (tg). Briefly, viscoelastic measurements at 0.05 Pa stress and 1 Hz frequency were performed in the range 20-40°C; the gelation point and time were determined when G'=G''. Density, pH (Mettler Toledo, O), refractive index (Litesizer 500, Anton Paar, A), surface tension (DY-300 Dynamaster, K) measurements were also realized on such SG/CD systems. Transmittance (T%) was obtained from spectrophotometric measurements at 400-700 nm (Perkin Elmer Instruments, S) to evaluate system transparency. Syringeability was also investigated using a texture analyser (TA.XT plus, Stable Micro Systems, UK) by measuring the maximum force of extrusion (F_{MAX}) from 30G needle. Preliminary sterilization (T=121°C; t=15 min) studies were also performed. Lastly, cytotoxicity and proliferation assays on normal human dermal fibroblasts (NHDF) were performed on SG/CD systems.

SG/CD systems were characterized by $\Delta\eta/\eta$ values higher than those of SG 60 and SG 90 solutions, indicating that the presence of CD affects SG behavior on increasing temperature. DoE approach was successfully used to investigate the influence of SG type and SG and CD concentrations on SG/CD system thermogelling behavior, finding the best SG/CD quali-quantitative composition. The viscosity and the viscoelastic properties of the best *in-situ* gelling systems resulted to be similar to those obtained for SVF; such results suggest that SG/CDs systems were suitable for performing the protective function of the vitreous. They exhibit TG and tg values which ensure a complete fast gelation at 37°C. *In-situ* gelling systems, characterized by physico-chemical properties similar to those of the vitreous, able to be extruded easily from a 30G needle and to be sterilized without losing the thermogelling property, were obtained. *In vitro* studies confirmed the systems biocompatibility and their potentiality to enhance NHDF cells proliferation .

Promising *in-situ* thermogelling systems consisting of SG and CDs were successfully developed for vitreous replacement and to enhance its regeneration.

(1) Indu Y, et al. J. Biomed. Mater. Res. 8: 1156-1176 (2021);
(2) Iohara D, et al. Mol. Pharmaceutics 14:(8), 2740–2748 (2017);
(3) Sapino S, et al. Nanomater 9: 1461-1487 (2019).

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