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School of Pharmacy and Pharmaceutical Sciences
Isfahan University of Medical Sciences

Preparation and multi-objective optimization of surface-treated methotrexate-loaded nanogels to brain delivery

A. Azadi[1,*], M. Hamidi[2], M. Khoshayand[3], M. Amini[4], M. Rouini[1]

[1]Biopharmaceutics and Pharmacokinetic Division, Department of Pharmaceutics, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Pharmaceutics, School of Pharmacy, Zanjan University of Medical Sciences, Zanjan, Iran
[3]Department of Drug and Food Control, Tehran University of Medical Sciences, Tehran, Iran
[4]Department of Medicinal Chemistry and Drug Design and Development Research Centre, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

Background and Aims: Several studies have attempted to overcome the Blood-Brain-Barrier (BBB) to facilitate central nervous system (CNS) entry of therapeutic agents. Among these, polymeric nanoparticles are promising candidates because some of these carriers have great potential to pass through the tight junctions of the BBB. The ultimate aim of this study was to present a novel and comprehensive approach via multi-objective optimizing the chitosan-based nanogel preparation intended for brain delivery.
Methods: Nanogels loaded with methotrexate (MTX) were prepared by an ionic gelation process using chitosan and sodium tripolyphosphate. The preparation process was optimized by a systematic multi-objective-optimization approach in terms of the size, poly-dispersity index (PDI), loading-efficiency (LE) and loading-capacity (LC) of the resulting nanocarriers. As the ultimate goal, the surfaces of the MTX-loaded nanogels were modified by polysorbate-80 for the purpose of brain targeting. Finally, a series of in-vitro characterization tests were carried out on the prepared functionalized nanogels to evaluate their potential for entry prior to our prospective final step of in-vivo investigations.
Results: The final particle size, PDI, LE and LC corresponding to the optimal conditions were 118.56±15.93 nm, 0.34±0.05, 61.82±6.83% and 53.68±3.09%, respectively. This condition corresponds to the maximum desirability function within the range of experimental values (D=0.815). The surface modification of nanogels by the surfactant was confirmed by Fourier transform infrared spectroscopy (FT-IR) and atomic force microscopy (AFM). The size analysis of samples by transmission electron microscopy (TEM), while confirming the size profiles obtained by particle size analysis, showed highly spherical shapes. Finally, the cumulative in-vitro release profiles of surfactant-modified and unmodified nanogels were almost identical and showed acceptable performance.
Conclusions: Considering these findings and other general excellent bio-properties of nanogels, it seems that these optimized surface-modified MTX-loaded nanogels may be a good candidate for the delivery of this anticancer agent to the CNS.

Keywords: Nanogel; Methotrexate; Multi-objective Optimization; Brain delivery