

TACROLIMUS-LOADED CHITOSAN NANOPARTICLES BY A MODIFIED IONIC GELATION TECHNIQUE FOR THE MANAGEMENT OF PLAQUE PSORIASIS

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Background: Polymeric nanoparticles, especially charged ones, were proven to be superior compared to lipidic ones in dermal deposition and skin retention, particularly in inflamed skin(1). Chitosan is a polymer of natural origin and hydrophilic cationic biocompatible nature. Tacrolimus is a natural macrolide that exhibits an anti-proliferative action by T-lymphocytic cells inhibition (2). Hence, it was tested as a potential topical treatment to improve and control psoriatic plaques. Risk of associated systemic side effects embraces the need for efficient topical drug delivery systems to enhance local disposition with minimal systemic absorption. In our study, we successfully incorporated for the first time the lipophilic Tacrolimus into the hydrophilic chitosan nanoparticles in order to achieve the desired therapeutic response and minimize systemic absorption by means of dermal retention of the synthesized nanoparticles using a modified ionic gelation technique that suits the hydrophobic nature of the drug without using any hazardous organic solvents.

Methods: Chitosan nanoparticles were prepared by an initial solubilization of the drug in a water-miscible organic solvent, propylene glycol at 60 C. Then, mixing the solution with tripolyphosphate aqueous solution. Afterwards, the aqueous solution was injected in chitosan solution under vigorous stirring at rpm, 1100. The synthesized colloidal suspension was tested in terms of particle size, zeta potential, entrapment efficiency, rheological behavior, FT-IR, XRD, in vitro drug release, ex-vivo skin permeation and deposition using rat skin on franz diffusion cells. Therapeutic efficacy was tested on imiquimod (IMQ) mouse model and compared to the standard marketed product (Tacrolimus® ointment).

Results: The hydrophobic drug, Tacrolimus, was successfully encapsulated into the synthesized round-shaped positively-charged particles with particle size ($140.84\text{ nm} \pm 50$), Zeta potential ($22.2\text{ mv} \pm 4.06$) and EE of ($65.45\% \pm 1.3$). The drug release profile followed the Higuchi diffusion model. Local skin deposition of the drug was significantly enhanced with $82\% \pm 0.6$ of the drug retained in the skin compared to $34\% \pm 0.9$ From the marketed product. This was confirmed with the lower flux rate from the nanoparticles formula ($0.932\text{ Ug/cm}^2/\text{hr}$) compared to ($4.32\text{ Ug/cm}^2/\text{hr}$) from the market product. The determined FT-IR spectrum denoted successful drug encapsulation. XRD confirmed the formation of nanoparticles due to the appearance of an amorphous-like chart with no sharp distinctive peaks. The formulation showed superior therapeutic response in vivo compared to the marketed product, in terms of PASI (psoriasis area severity index) score, total drug deposition in skin, spleen to body weight ratio and histopathological examination of skin samples. All results were statistically significant ($p < 0.05$).

Conclusions: The modified ionic gelation technique is successful in formulation of chitosan nanoparticles loaded with hydrophobic drugs by a fast and non-tedious method without using any hazardous organic solvents. Tacrolimus-loaded chitosan nanoparticles are a promising drug delivery system in the management of chronic plaque psoriasis. Further experimentation on human volunteers is suggested as a future perspective.

References: 1. Abdel-Mottaleb et al., Eur. J.Pharm.Biopharm.. 2011;79(1):36–42.
2. Dheer et al., Eur. J. Pharm. Sci. 2018;114:217–27.