

Polymeric Nanoparticles Encapsulating NSAIDs for Ocular Delivery: Corneal Penetration and Polymorphonuclear Leukocyte Migration Studies*

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INTRODUCTION: As the ocular efficacy of drugs is greatly influenced by the corneal contact time, the most common method of improving the ocular availability of drugs is to increase precorneal residence time by using adequate drug delivery systems [1-2]. This paper describes the efficacy of mucoadhesive copolymeric micelle nanoparticles made of N-isopropylacrylamide (NIPAAM), N-vinylpyrrolidone (VP) and acrylic acid (AA) having cross-linkage with N, N' Methylene bis acrylamide (MBA) and containing non-steroidal anti-inflammatory drugs (NSAIDs) into the polymeric network as ocular drug carriers for enhanced bioavailability.

METHODS: NSAIDs loaded copolymeric nanoparticles of NIPAAM, VP and AA were synthesized as reported in our recent patent [3]. The drug loaded nanoparticles were characterized by various physicochemical methods like DLS, TEM, SEM, FT-IR, ¹H-NMR, XRD, UV/visible and fluorescence spectroscopic studies. The Drug release studies from the nanoparticles were done in different pH buffers at 25 and 37°C.

In this study, an attempt was made to examine the performance of these drug loaded nanoparticle formulations by in vitro corneal permeability through goat cornea as well as in vivo anti-inflammatory activity in rabbit eyes by determining the polymorphonuclear (PMN) leukocyte migration in tears.

RESULTS AND DISCUSSION: Copolymer formed by random copolymerisation of NIPAAM and VP with AA, when dissolved in water shows amphiphilic character and forms micelle with a hydrophobic inner core and hydrophilic outer shell. Water insoluble NSAIDs like indomethacin or nimesulide was dissolved into the polymeric micelles. The size of the drug-loaded particles as measured by dynamic light scattering was found to be around 35-nm diameter at 25°C and temperature dependent. TEM picture showed that the particles are spherical and highly monodispersed. The release of the drug from the nanoparticles was found to be temperature and pH dependent.

In vitro corneal permeation studies (fig-1) with nanoparticulated drug indicated much higher

increase in ocular availability with no corneal damage compared to an aqueous suspension containing same amount of drug as in nanoparticles. The formulations showed that the percent inhibition of PMN migration with nanoparticle formulations was much higher and longer lasting than aqueous suspension of drug of equivalent concentration (Fig.2).

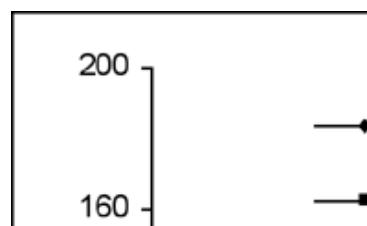


Fig.-1: Comparison of permeation of indomethacin (solid line) and nimesulide (broken lines) from nanoparticle formulation with aqueous suspension of drug of same concentration (2.0 mg/ml) through goat cornea.

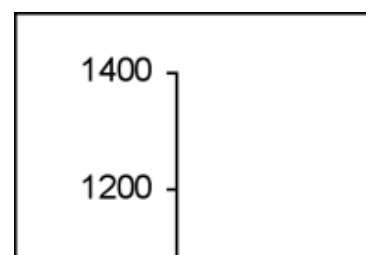


Figure2: Comparison of effect of indomethacin (solid line) and nimesulide (broken lines) loaded micelle formulation with aqueous suspension of drug of same concentration (0.05%) on PMN migration in tears of rabbit eye.

CONCLUSIONS: The above studies indicate that these formulations can be effectively used as ocular drug carriers in ocular delivery for higher therapeutic efficacy at much lower concentrations of drugs.

REFERENCES: [1] Bourlais, C.L. et al; *Prog. Retinal Eye Res.* (1998) 17 1, 33-58
[2] Gupta, A.K. et al; (2000) *Int. J. Pharm.* 209, 1-14
[3] A. Maitra, A. K Gupta, D. Majumdar, S Madan; **US Patent No.:** 6,579,519 Dated 17-06-2003.

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