Naringenin-Cyclodextrin Complex Imprinted Contact Lenses; Sustained Drug Release and Enhanced Ocular Penetration to Treat Posterior Eye Diseases

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Background: Naringenin (NAR), a flavonoid having anti-inflammatory and antioxidant properties, has been investigated for the treatment of age-related macular degeneration (AMD) and other posterior eye diseases. Our goal is to develop a novel drug delivery system that can replace intravitreal injections for posterior eye disease treatments. To accomplish this, NAR and sulfobutylether-ß-cyclodextrin (SBE-ß-CD) complex: (NAR:CD), imprinted contact lenses (CLs) were fabricated to facilitate the controlled release and enhanced ocular permeation of NAR into the eye.

Methods: Initially, NAR:CD was made using 1:3 molar ratio (1 mg NAR and 24.71 mg SBE-ß-CD). Based on NAR daily therapeutic concentration (0.08 to 66 µg/day) and ocular pharmacokinetics of 1% NAR eye drops in rabbits, briefly, 1 mg and 5 mg of NAR:CD were separately mixed with the pre-polymerization mix (i.e., NVP, HEMA, TBA, PG, AMA, EDGMA and AIBN in 0.67, 0.013, 0.034, 0.11, 0.0034, 0.0025 and 0.00054 mols, respectively), which was thermally cured to form two types of NAR:CD imprinted CLs i.e., MiC_1 and MiC_2, respectively. Additionally, the non-imprinted lens (NiL) was also prepared excluding NAR:CD from the pre-polymerization mix. Thermal curing was followed by release, hydration, sterilization and template removal from these lenses, which were then re-immersed in NAR:CD solutions (i.e., 10 mg/3 mL) of release media (PBS + 0.1% Tween 80, pH 7.4) for reloading experiments. Physicochemical characterizations, *in vitro* drug release and *ex vivo* permeation experiments were executed to assess various CL properties.

Results: A total of 36.9 µg NAR was quantified in 1 mg of NAR:CD complex. NAR reloaded into MiC_1, MiC_2 and NiL was 21 ± 3.6 µg, 15 ± 1.7 µg and 80 ± 8.4 µg, respectively. The developed lenses showed commercial standard physicochemical attributes having average equilibrium water content (%EWC) of 72.5 ± 2.1%, light transmittance (%T): > 95%, refractive index (RI): 1.373 ± 0.001 and contact angle (θ): 44.5° ± 3.1, with no significant difference when compared to NiL ($p>0.05$). Both MiC and NiL demonstrated diffusion- and swelling-controlled NAR release following Higuchi (R^2 = 0.996 ± 0.15) and Korsmeyer Peppas (R^2 = 0.937 ± 0.08) models for 120 h. Similarly, MiC_1 and MiC_2 showed NAR accumulation of 7.3 ± 1.8 and 8.7 ± 1.1 µg/cm^2 in cornea, while 8.2 ± 2.6 and 10.3 ± 3.9 µg/cm^2 in sclera, respectively.

Conclusions: Our findings demonstrated that MiC lenses released NAR in a controlled manner. These commercial standard NAR:CD imprinted CLs with diffusion-controlled release of NAR could prove to be revolutionary non-invasive drug delivery devices that could also lead to improved ocular penetration of therapeutics with enhanced patient compliance.