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Effect of surfactant chain length on drug release kinetics from microemulsion-laden contact lenses

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ABSTRACT

The effect of surfactant chain lengths [sodium caprylate (C_8), Tween 20 (C_{12}), Tween 80 (C_{18})] and the molecular weight of block copolymers [Pluronic F68 and Pluronic F 127] were studied to determine the stability of the microemulsion and its effect on release kinetics from cyclosporine-loaded microemulsion-laden hydrogel contact lenses in this work. Globule size and dilution tests (transmittance) suggested that the stability of the microemulsion increases with increase in the carbon chain lengths of surfactants and the molecular weight of pluronics. The optical transmittance of direct drug-laden contact lenses [DL-100] was low due to the precipitation of hydrophobic drugs in the lenses, while in microemulsion-laden lenses, the transmittance was improved when stability of the microemulsion was achieved. The results of *in vitro* release kinetics revealed that drug release was sustained to a greater extent as the stability of microemulsion was improved as well. This was evident in batch PF127-T80, which showed sustained release for 15 days in comparison to batch DL-100, which showed release up to 7 days. An *in vivo* drug release study in rabbit tear fluid showed significant increase in mean residence time (MRT) and area under curve (AUC) with PF-127-T80 lenses (stable microemulsion) in comparison to PF-68-SC lenses (unstable microemulsion) and DL-100 lenses. This study revealed the correlation between the stability of microemulsion and the release kinetics of drugs from contact lenses. Thus, it was inferred that the stable microemulsion batches sustained the release of hydrophobic drugs, such as cyclosporine from contact lenses for an extended period of time without altering critical lens properties.

1. Introduction

In more than 95% of cases, ophthalmic drugs are delivered through eye drops. However, the inefficiency of eye drops as a delivery dosage form for ophthalmic drugs is well-recognized (Lang, 1995). Scientists have explored therapeutic contact lenses to address the limitations of direct instillation of drug solutions to eyes (eye drop therapy) (Caló and Khutoryanskiy, 2015). Several animal studies have proven that when therapeutic contact lenses are placed on the cornea, the drug diffuses through the hydrogel matrix and releases in pre- and postlens tear film. It has been also reported that the drug molecules have a much longer residence time and improved bioavailability through contact lenses compared to eye drop therapy (Peterson et al., 2006; Wolffsohn et al., 2010; Hsu et al., 2014). However, the drug-laden contact lenses prepared by conventional soaking method showed the weak interactions between the drug and aqueous channels of the lens matrix which in turn resulted into low drug loading and failure of sustaining the drug release (Soluri et al., 2012; Guzman-Aranguez et al., 2013). The different methodologies adopted till now for prolonging the drug release duration from the contact lenses are like molecular imprinting (White et al., 2011; Zhang et al., 2014), use of vitamin E (Paradiso et al., 2016; Hsu et al., 2015), drug loaded nanoparticle (Maulvi et al., 2016a; Jung et al., 2013), *etc.* for prolonging the drug release duration from contact lenses. The drug loaded microemulsion-laden contact lenses had shown promising results owing to their thermodynamic stability, simple preparation method, high drug-loading capacity and increased wettability of biomaterials (Maulvi et al., 2016c; Maulvi et al., 2016b).

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Chung and co-workers developed timolol-loaded microemulsion-laden contact lenses using ethyl butyrate and Pluronic F127. These lenses showed controlled drug release up to 20 days (Li et al., 2007). Lokendra et al. used 10% ionic surfactants to load dexamethasone 21-disodium phosphate in ACUVUE® contact lenses, which showed 50 h of sustained release with improvement in the wettability of biomaterials (Bengani and Chauhan, 2013). Changhai et al. developed dexamethasone acetate loaded silica shell micelles cross-linked methoxy(polyethylene glycol)-block-polycaprolactone hydrogel contact lenses for controlled drug delivery up to 30 days without altering the transmittance of biomaterial for contact lens application (Lu et al., 2013). Chauhan et al. developed drug-loaded Brij micelles-laden contact lenses for improving the bioavailability of ophthalmic drugs. The system showed controlled drug delivery only for cyclosporine; however, the drugs (dexamethasone and dexamethasone 21 acetate) with low partition toward micelles were not effective (Kapoor et al., 2009). Cho et al. fabricated a novel tri-branched polyethylene glycol (PEG)-substituted hydrazide biomaterial, which showed a reduction in protein adsorption (Cho and Jee, 2015).

The aim of the present research work was to fabricate cyclosporine-loaded microemulsion-laden soft contact lenses to achieve *in vivo* controlled drug release, so that the *in vivo* concentration of tear fluid is within the therapeutic range. A novel aspect of this study was to investigate the effect of surfactant chain lengths [sodium caprylate (C_8), Tween 20 (C_{12}), Tween 80 (C_{18})] and molecular weights of block copolymer [Pluronic F68 and Pluronic F 127] on the stability of microemulsion and on the release rate profile from contact lenses. It was hypothesized that stable microemulsion would prevent the precipitation of the drug in the contact lenses (after hydration) due to the solubilization of the drug, which facilitates the release of the drug from contact lenses. Thus, by tailoring the size of the microemulsion droplets, the release pattern of drugs from hydrogel matrix can be modified. To accomplish this objective, we entrapped cyclosporine in oil-in-water (o/w) microemulsions (using surfactants with different chain lengths), followed by its incorporation in contact lenses. The contact lenses were fabricated by cast molding method using Darocur® as photo initiator. It was also hypothesized that developed therapeutic contact lenses would slowly diffuse the drug from the hydrogel matrix of the lens and enter the postlens and prelens tear film. Using drug-loaded microemulsion-laden contact lenses, drug molecules would have a much longer residence time in the tear film. The *in vivo* release study in rabbit tear fluid was also conducted to establish *in vitro in vivo* correlation (IVIVC).

2. Materials and methods

2.1. Materials

Hydroxylethylmethacrylate (HEMA), ethylene glycol dimethacrylate (EGDMA), methacrylic acid (MAA), and Darocur® (2, 4, 6-trimethyl benzoyl-biphenyl-phosphinoxide) were purchased from Sigma-Aldrich Chemicals (St. Louis, MO, USA). Cyclosporine was purchased from Swapnroop Drugs and Pharmaceuticals (Maharashtra, India). Ultrapure water (18.2 MΩ-cm) was obtained from synergy U.V. Millipore water purification system. All other reagents were purchased from Sigma-Aldrich Chemicals (MO, USA).

2.2. Dynamic surface tension

Dynamic surface tension of surfactants was measured using a bubble tensiometer (Biolin, model BPA 800P) at 25 ± 0.5 °C. The selected surfactants were prepared using ultra-pure deionized water at concentrations of 1 mg/ml. The dynamic surface tension measurements were taken using 18 gauge needle with a gas flow rate of 5 cm^3/min (which corresponds to 3–10 bubbles/s). Compressed air was used as the bubbling gas while the capillary was connected to the pressure transducer to determine the bubble frequency and the dynamic surface tension values. Critical micelle concentrations (CMCs) of sodium caprylate, Tween 20, Tween 80, Pluronic F 68, and Pluronic F 127 are 300 mM, 0.06 mM, 0.015 mM, 0.04 mM, and 0.0028 mM, respectively (Stanley et al., 2009; Haque et al., 1999; Attwood et al., 1985; Dutra et al., 2015).

2.3. Formulation of microemulsion

Six different batches of microemulsions were prepared as shown in Table 1 by using Pluronic F 68 and Pluronic 127 and varying the carbon chain lengths of co-surfactants Sodium Caprylate (C_8), Tween 20 (C_{12}) and Tween 80 (C_{18}). The different batches of microemulsion were formulated as follows: In the ME-P68-SC batch, 75.75 mg of cyclosporine was dissolved in 150 μl of isopropyl myristate (IPM, oil phase). A solution of Pluronic F 68 (1 gm) and sodium caprylate (4 gm) in a 1:4 ratio was prepared separately in deionized water (10 ml). The drug-oil solution was added drop-wise to the surfactant solution with continuous stirring until it became clear. The other batches were prepared in similar fashion.

2.4. Characterization of drug-loaded microemulsion

2.4.1. Globule size, zeta potential, and transmission electron microscopy (TEM)

The change in globule size at regular time intervals (1 h, 4 h, 24 h, and 48 h after preparation of microemulsions) was measured using photon correlation spectroscopy with an in-built Zetasizer (Malvern Nano-ZS, UK) at 633 nm. All the measurements were acquired at a scattering angle of 90° and a temperature of 25 °C. The droplet size was calculated using the Stokes-Einstein relationship. Electrophoretic mobility (mm/s) was measured using small-volume disposable zeta cell and converted to zeta potential by in-built software using the Helmholtz–Smoluchowski equation. TEM (Philips Tecnai 20 G2, FEI) was performed to carry out

Table 1
Composition of microemulsion batches.

Batches	IPM (ml)	Pluronic F68 (gm)	Pluronic F127 (gm)	Sodium caprylate (gm)	Tween 20 (gm)	Tween 80 (gm)	Water (ml)
ME-P68-SC	0.15	1	–	4	–	–	10
ME-P68-T20	0.15	1	–	–	4	–	10
ME-P68-T80	0.15	1	–	–	–	4	10
ME-P127-SC	0.15	–	1	4	–	–	10
ME-P127-T20	0.15	–	1	–	4	–	10
ME-P127-T80	0.15	–	1	–	–	4	10

IPM = Isopropyl Myristate.