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Physicochemical attributes and dissolution testing of ophthalmic ointments

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ABSTRACT

The investigation of semisolid ophthalmic ointments is challenging due to their complex physicochemical properties and the unique anatomy of the human eye. Using Lotemax® as a model ophthalmic ointment, three different manufacturing processes and two excipient sources (Fisher® (OWP) and Fougera® (NWP)) were used to prepare loteprednol etabonate ointments that were qualitatively and quantitatively the same across the manufactured formulations. Physicochemical properties including drug content and uniformity, particle size and distribution, as well as rheological parameters (onset point, crossover modulus, storage modulus and Power law consistency index) were investigated. In addition, USP apparatus 2 with enhancer cells was utilized to study the *in vitro* drug release characteristics of the ophthalmic ointments. Both manufacturing processes and excipient sources had a significant influence on the physicochemical attributes and the *in vitro* drug release profiles of the prepared ointments. Ointments prepared *via* the hot melt processes exhibited higher rheological parameters and lower drug release rates compared to ointments prepared without hot melting. Ointments prepared with OWP demonstrated higher rheological parameters and lower *in vitro* drug release rates compared to ointments prepared with NWP. A strong correlation between the rheological parameters and *in vitro* drug release rate was shown using logarithmic linear regression. This correlation may be useful in predicting *in vitro* drug release from measured physicochemical properties, and identifying the critical quality attributes during the development of ointment formulations.

1. Introduction

The unique anatomy of the human eye makes ocular drug delivery complicated. In addition, ophthalmic dosage forms suffer from poor bioavailability as a result of precorneal factors: non-productive absorption, the relative impermeability of the corneal epithelial membrane, tear dynamics and the brief residence time in the conjunctival cul-de-sac of the eye (Pal Kaur and Kanwar, 2002; Saettone, 2002; Araujo et al., 2009; Gaudana et al., 2010; Kompella et al., 2010). This results in low drug absorption (≤1%) of the administered dose. In recent years, the development of ocular drug delivery systems has undergone a paradigm shift to ameliorate their poor drug bioavailability and absorption (Davies, 2000; Patel et al., 2013; Boddu et al., 2014). Research has been carried out to develop an array of ophthalmic dosage forms: solutions, drops, suspensions, ointments, injections, emulsions, microspheres, liposomes, nanoparticles, implants, niosomes, pharmacosomes, inserts, minidiscs and contact lenses for the treatment of a wide range of ophthalmic disorders (Baranowski et al., 2014; Thakur Singh et al., 2016). Fig. 1 shows the anatomy of the human eye and the different routes of administration through which the above dosage forms are administered (Aldricha et al., 2013).

For treatment of diseases of the anterior segment of the eye (*e.g.* cornea, conjunctiva and sclera) such as infection and inflammation, topical drug delivery (such as eye drops, ointments, suspensions, gels and emulsions, *etc.*) is most convenient and allows for adequate patient compliance since it is simple and non-invasive. While several reviews have summarized the advances in

Abbreviations: OWP, white petrolatum from Fisher®; NWP, white petrolatum from Fougera®; SRT, simple mixing at room temperature; HMIC, hot melt and immediate cooling at −20 °C; HMRT, hot melt and cooling at room temperature; OP, onset point; CM, crossover modulus; SM, storage modulus.

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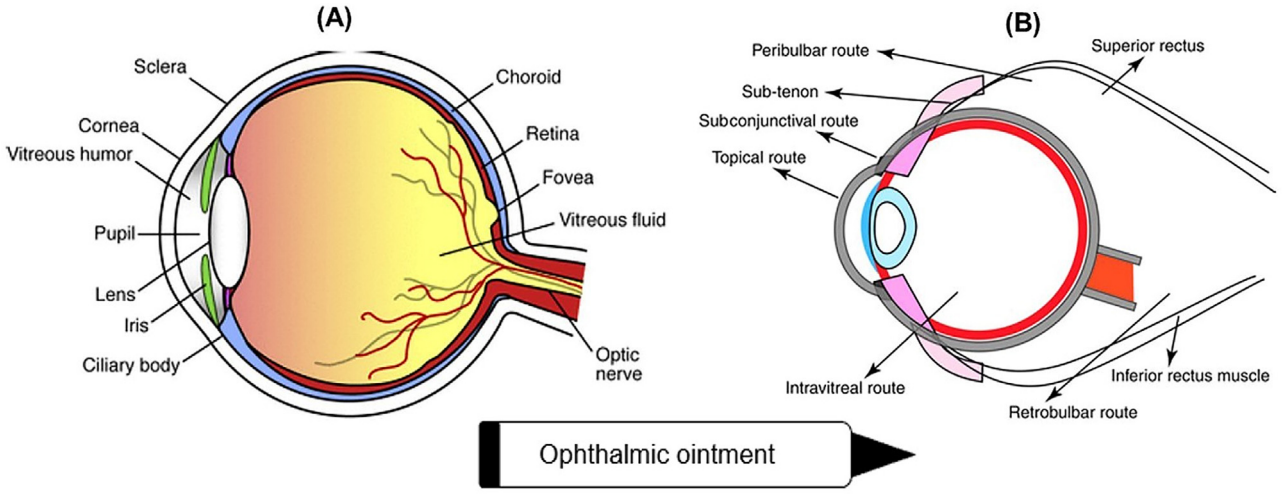

Fig. 1. (A) Anatomy of human eye; (B) routes of administration into the eye (reproduced with permission from Aldricha et al. (2013)).

ocular drug delivery in detail (Edelhauser et al., 2010; Chen, 2015; Yellepeddi and Palakurthi, 2016), few papers focus directly on ophthalmic ointments (Xu et al., 2015). This may be due to formulation and performance challenges associated with this dosage form, such as: (1) poor content uniformity and resultant poor reproducibility of *in vitro* drug release; (2) lack of complete characterization methods; and (3) difficulties in developing good discriminatory dissolution testing methods. Different ointment bases, such as white petrolatum, mineral oil, lanolin alcohol, liquid paraffin, and glycols (propylene glycol and different molecular weight polyethylene glycols), have been screened for use as excipients in pharmaceutically acceptable ophthalmic ointments (Gaudana et al., 2010; Patel et al., 2013; Robin and Ellis, 1978). Ideally, ophthalmic ointment formulations should display shear thinning rheological properties and should not cause discomfort or blurred vision following application. In addition, drug release and *in vivo* bioavailability of an ideal ointment formulation should be significantly improved compared to its solution formulation. FDA approved ophthalmic ointment formulations are listed in Table 1 along with their ointment bases. The most commonly used ointment bases are oleaginous (water-free) and are composed of white petrolatum and may include liquid petrolatum (*i.e.* mineral oil). White petrolatum is a semisolid mixture of hydrocarbons and is suitable for ophthalmic ointment preparation due to the following properties: (1) its melting point ranges from 36 to 60 °C, and therefore the ointment viscosity will decrease following application to the eye; (2) it does not cause irritation of the human eye; and (3) the white petrolatum-mineral oil based ointments can prolong the residence time of drugs on the eye surface compared to aqueous ophthalmic vehicles (Greaves et al., 1993).

Loteprednol etabonate (molecular weight: 486.96 g/mol) is a topical corticosteroid (analog of prednisolone) used to treat eye inflammation. It is an ester of loteprednol with ethyl carbonate and has a melting range of 220.5–223.5 °C. The aqueous solubility of loteprednol etabonate is 8 μg/l; it has two pK_a values (12.01 and −2.9); and its log $K_{acetonitrile/water}$ is 3.04 (FDA, 2016; FDA-CDER, 1997). Lotemax® ophthalmic ointment, 0.5%, an oleaginous based ophthalmic ointment formulation of loteprednol etabonate manufactured by Bausch and Lomb, was approved by the FDA in 2011 for the treatment of post-operative eye inflammation (Daily Med, 2016).

In the development of generic products, formulations that are composed of the same inactive ingredients (qualitatively the same (Q1)) and in the same concentration (quantitatively the same (Q2)) as the reference listed drug (RLD) may demonstrate significant differences in their physicochemical properties and *in vitro* release characteristics as a result of different manufacturing processes (Shen et al., 2015). To date, there have been no literature reports investigating the effect of manufacturing differences on Q1/Q2 ophthalmic ointment formulations. In the present research, ointment formulations were manufactured with Q1/Q2 sameness, using loteprednol etabonate as the active pharmaceutical ingredient (API), and their physicochemical properties (drug content and uniformity, particle size and distribution, rheology and *in vitro* drug release) were investigated. Lotemax® ointment was chosen as a model ophthalmic ointment to investigate the effect of processing parameters on critical physicochemical attributes of ophthalmic ointments. Ointments were prepared using three different manufacturing processes: (1) stirring at room temperature; (2) hot-melt mixing and quenching to room temperature; and (3) hot-melt mixing and quenching to −20 °C. Two different sources of white petrolatum were also screened. USP apparatus 2 with enhancer cells was used for *in vitro* drug release testing. In addition, a correlation was investigated between the rheological parameters and the *in vitro* drug release rate using log–log linear regression.

2. Material and methods

2.1. Materials

Loteprednol etabonate with a particle size of 19 μm was purchased from Pure Chemistry Scientific Inc. Two different sources of white petrolatum (OWP (laboratory grade) and NWP (USP grade)) were purchased from Fisher® and Fougera Pharmaceutical Inc., respectively. Mineral oil USP, sodium chloride, calcium chloride, and sodium dodecyl sulfate (SDS) were purchased from Sigma–Aldrich. Sodium bicarbonate was purchased from Fisher®. Unless otherwise specified, all materials were of analytical grade.

2.2. Preparation of loteprednol etabonate ointments

To prepare semisolid ophthalmic ointments of loteprednol etabonate that are qualitatively and quantitatively close to Lotemax®, a model was developed to determine the ratio of components (white petrolatum and mineral oil) in the commercial product. In brief, a serial of different ratios of white petrolatum and