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In vitro release testing method development for ophthalmic ointments

Quanying Bao[a], Jie Shen[a,1], Rajan Jog[a], Carmen Zhang[a], Bryan Newman[b], Yan Wang[b], Stephanie Choi[b], Diane J. Burgess[a,*]

[a] University of Connecticut, School of Pharmacy, Storrs, CT 06269, United States
[b] FDA/CDER, Office of Generic Drugs, Office of Research and Standards, Division of Therapeutic Performance, Silver Spring, MD 20993, United States

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ABSTRACT

It is essential as well as challenging to develop a reliable *in vitro* release testing method for determining whether differences in release profiles exist between qualitatively and quantitatively equivalent ophthalmic ointment formulations. There is a lack of regulatory guidance on *in vitro* release testing methods for ophthalmic formulations. Three different *in vitro* release testing methods 1) USP apparatus 4 with semisolid adapters; 2) USP apparatus 2 with enhancer cells; and 3) Franz diffusion cells were investigated. Qualitatively and quantitatively equivalent ointments were prepared *via* hot melting and simple mixing methods using four different sources of excipients (*i.e.* white petrolatum). The ointment formulations were characterized for content uniformity, particle size, and rheological parameters. All the formulations showed adequate content uniformity and similar particle size. The ointments prepared *via* the hot melting processes showed higher rheological parameters, as did the ointments prepared using 'white' petrolatum that exhibited a yellowish color. The three *in vitro* release testing methods were compared and evaluated for reproducibility, discriminatory capability, and correlation with the rheological parameters. Compared with the compendial methods, the non-compendial method (Franz diffusion cells) showed poorer reproducibility. All three methods possessed the ability to discriminate between the ophthalmic ointments with manufacturing differences. However, the USP apparatus 4 method displayed the largest margin of discrimination between the release profiles of the different ophthalmic ointments. In addition, the *in vitro* release rate obtained using the USP apparatus 4 method showed the strongest logarithmic linear correlation with the rheological parameters (Power law consistency index (K value) and crossover modulus) compared to the other two methods.

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1. Introduction

One of the major challenges for topical ocular drug delivery is the limited precorneal retention time of active pharmaceutical ingredients (APIs), which results in low bioavailability. The impermeability of human corneas as well as the biological barriers of the other parts of the human eye limits drug absorption. In conventional topical ocular drug delivery, aqueous solutions (i.e. eye drops) are the most convenient and patient compliant dosage form. However, ophthalmic solutions have particularly poor bioavailability due to their transient retention time on the eye surface. A plethora of strategies including ointments (Greaves et al., 1993), gels (Kushwaha et al., 2012; Patel et al., 2013), liposomes (Monem et al., 2000; Agarwal et al., 2016), nanoparticles (Diebold et al., 2007; Calvo et al., 1996; Gupta et al., 2010; Seyfoddin et al., 2016), and mucoadhesive formulations (Snejdrova et al., 2016) have been utilized to increase drug retention time at the corneal surface. Compared to eye drops, ophthalmic ointments possess higher viscosity and therefore can prolong drug-ocular contact time and reduce systemic toxicity (Greaves et al., 1993; Robin and Ellis, 1978). There are four types of ointment bases listed in the USP 36 ⟨711⟩: hydrocarbon, absorption, water-removable

Abbreviations: Q1/Q2 equivalent, qualitative and quantitative sameness; OWP, white petrolatum from Fisher®; NWP, white petrolatum from Fougera®; VWP, white petrolatum from Vaseline®; PWP, white petrolatum from Penreco; RLD, reference listed drug, Lotemax®; 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; K value, Power law consistency index; CV, coefficient of variance.

* Corresponding author at: Department of Pharmaceutical Sciences, School of Pharmacy, University of Connecticut, Storrs, CT 06269 USA.
E-mail address: d.burgess@uconn.edu (D.J. Burgess).
[1] Current address: Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, Kingston, RI 02881, United States.

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and water-soluble. To date, most of the ophthalmic ointment formulations available on the market (Bao et al., 2017) are hydrocarbon based. Even though ophthalmic ointments are a conventional dosage form, there is a paucity of literature reports regarding formulation development and characterization (such as physicochemical properties, *in vitro* drug release testing, and *ex vivo* and *in vivo* performance).

In vitro release testing is a fundamental tool to ensure consistent performance and quality of generic products. Release testing of ophthalmic ointments is an effective approach to monitor post-approval changes, scale-up, lot-to-lot changes and stability studies in the pharmaceutical industry (Shah et al., 1999). In generic product development, formulations that possess qualitative (Q1) and quantitative (Q2) sameness may present different physicochemical properties and *in vitro* and *in vivo* performance due to different manufacturing processes. Therefore, a discriminating release testing method is pivotal to identify all the possible changes to product performance generated from manufacturing to the final formulations. There is no standard *in vitro* release testing method suggested in the US pharmacopeia regarding semisolid ophthalmic ointments. Although the FDA's guidance for scale-up and post approval changes for non-sterile semisolids (SUPAC-SS) that are Q1/Q2 equivalent recommends the Franz diffusion cell method for *in vitro* release testing (FDA, 1997), this method may or may not be appropriate for ophthalmic semisolid ointments. In the past several decades, the Franz diffusion cell method and modifications thereof have been commonly utilized for *in vitro* release testing of most topical formulations (Shah and Elkins, 1995; Valenta et al., 2000; El Gendy et al., 2002; Yoshida et al., 2004; Özsoy et al., 2004; Ishii et al., 2009). There have also been a few literature reports of using USP apparatus 2 with different sample loading cells to perform *in vitro* release testing of topical formulations (Chattaraj et al., 1998; Ahmed et al., 2011; Xu et al., 2015). In addition, there has been one report of using USP apparatus 4 with an 'insertion cell' for *in vitro* release testing of semisolid formulations (Chattaraj and Kanfer, 1996). However, this method with the 'insertion cell' showed poor reproducibility. To date, there have been no reports published regarding the evaluation of the reproducibility and discriminatory capability of different *in vitro* release testing methods for semisolid ophthalmic ointments.

Three different *in vitro* release testing methods (Franz diffusion cells, USP apparatus 2 with enhancer cells, and USP apparatus 4 with semisolid adapters) were utilized and evaluated for their reproducibility and ability to discriminate among Q1/Q2 ophthalmic ointment formulations with manufacturing differences. Loteprednol etabonate, a corticosteroid for treatment of ophthalmic inflammatory conditions (Howes, 2000), was used as a model drug molecule and the commercial product Lotemax® was used as the reference listed drug (RLD). Three different manufacturing processes and four different sources of white petrolatum were utilized to prepare the Q1/Q2 equivalent loteprednol etabonate ointments. These formulations were characterized for drug content uniformity, particle size and rheological parameters. Correlation between the critical rheological parameters (crossover modulus and K value) and the *in vitro* drug release profiles was evaluated based on a previously reported relationship (Bao et al., 2017).

2. Material and methods

2.1. Materials

Loteprednol etabonate (particle size: 19 μm) was purchased from Pure Chemistry Scientific Inc. Four different sources of white petrolatum (OWP (laboratory grade), NWP (USP grade), VWP (USP grade) and PWP (USP grade)) were purchased from Fisher®, Fougera Pharmaceutical Inc., Vaseline®, and Penreco, respectively. Mineral oil USP, sodium chloride, calcium chloride, sodium dodecyl sulfate (SDS), was 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

Loteprednol etabonate ointments that have Q1/Q2 sameness to the commercial product Lotemax® ointment were prepared as previously reported (Bao et al., 2017). In brief, a mixture (batch size: 50 g) of white petrolatum, API and mineral oil was added in a plastic jar (Unguator®). The mixture was processed with three different manufacturing methods including: 1) simple mixing at room temperature (SRT); 2) hot melting at 65 °C and mixing with cooling at room temperature (HMRT); and 3) hot melting at 65 °C and mixing with immediate cooling in a −20 °C freezer (HMIC). The stirring speed of mixing (Unguator® e/s mixer, GAKO® International GmbH) was 1450 rpm and the mixing time for the simple mixing and hot melting methods were 6 and 5 min, respectively. Four different sources of white petrolatum (Fisher® (OWP), Fougera® (NWP), Vaseline® (VWP) and Penreco (PWP)) and a mean particle size of 19 μm of the API were used to prepare the loteprednol etabonate ophthalmic ointment formulations.

2.3. HPLC analysis of loteprednol etabonate

The concentration of loteprednol etabonate was determined using a PerkinElmer Flexar HPLC system with a UV detector set at 244 nm. The mobile phase was a mixture of acetonitrile, water, and acetic acid (65/34.5/0.5, v/v/v). Zorbax® Eclipse XDB-Phenyl C18 (250 × 4.6 mm, 5 μm; Agilent Technologies, USA) column was used with a flow rate of 1 ml/min and the column temperature was set at 30 °C. Fifty microliters of the samples were injected into the HPLC. The chromatographs were analyzed using the Chromera software kit V3.0. Adequate linearity was shown in the concentration ranges of 0.02 to 1.00 μg/ml (r^2 = 0.99) and 0.10 to 5.00 μg/ml (r^2 = 0.99). Both concentration ranges showed adequate inter- and intra-day precision (RSD (%) <2.0).

2.4. Drug loading and content uniformity

The drug was extracted from the ointment using melting and the addition of acetonitrile. 100 mg of the ointments (3 replicates from different regions of the jar containing the formulations) were weighed and 1.0 ml of acetonitrile was added into a vial and tightly sealed. The vials were put into a water bath at 65 °C for 1 min and then vortexed immediately for 2 min. This heating-vortex cycle was repeated three times to ensure complete drug extraction. The extracted solution was diluted with mobile phase and centrifuged at 14,000g for 5 min. The samples were filtered (Millex® HV, PVDF 0.45 μm syringe filter) and further diluted with the mobile phase. The loteprednol etabonate concentration in the solution was determined *via* HPLC.

2.5. Particle size analysis

The particle size and distribution of loteprednol etabonate in the ointments were analyzed using an Olympus BX51 polarized light microscopy (PLM) (Olympus America Inc. New York). Aliquots of ointments were spread on a glass slide and dispersed with one drop of mineral oil. Cover slips were placed on top of the dispersed ointment samples. At least three microscopy images were acquired at 20× magnification while maintaining constant camera parameters (*e.g.* image capture time, contrast and tone) for each sample.

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