Evaluation of the Physical and Chemical Compatibility of Tacrolimus Ointment, 0.1% (Fujisawa) and Desoximetasone Ointment, 0.25% (Taro)

By Jacob Levitt, M.D.*, Terry Feldman, Ph.D.**, Ildiko Riss, M.Sc.**, and On-Tai Leung, Ph.D., Chem.**

**Abstract**
Desoximetasone ointment, 0.25% and tacrolimus ointment, 0.1% are widely used in the treatment of atopic dermatitis. To determine if these drugs are physically and chemically compatible when mixed, a one-to-one mixture of desoximetasone ointment, 0.25% (Taro) and Protopic® ointment, 0.1% (Fujisawa) was prepared and stored under three different temperature/humidity conditions. Unmixed ointments served as controls. Mixed and unmixed samples were stored at 25ºC, 60% relative humidity, 30ºC, 60% relative humidity, and 40ºC, 75% relative humidity. Samples were evaluated at Days 1, 2, 7, 14, and 28 for color, degree of physical separation, and chemical stability via reverse-phase high performance liquid chromatography. Quantitation was based on authentic drug substance standard for desoximetasone and was based on Protopic Injection® (5mg/1mL) for tacrolimus. Mixtures remained white for all time periods except at Day 28, at which time both the desoximetasone control and the mixtures at all storage conditions were pale yellow. No more than slight separation was observed at any time period under any of the three storage conditions. For all time periods and storage conditions, potency recovery ranges for the active drug substances were as follows: Tacrolimus: Mixture 70.9-79.2%, Tacrolimus, Control: 70.8-79.3%, Desoximetasone, Mixture: 95.2-100.2%, and Desoximetasone, Control: 93.9-103.5%. The range of % relative recovery for all storage conditions (% Mixture/% Control x 100, are: Tacrolimus: 89.6 - 109.3% and Desoximetasone: 95.3 - 109.7% respectively. No significant difference in either physical appearance or chromatographic profile between the mixture and individual ointments was observed. Conclusion: Desoximetasone ointment, 0.25% (Taro) and Protopic® ointment, 0.1% (Fujisawa) are compatible both physically and chemically up to four weeks when mixed at a ratio of 1:1 (w/w).

**Objective**
To determine the physical and chemical compatibility both qualitatively and quantitatively of the combination of tacrolimus 0.1% ointment (Protopic®) and desoximetasone 0.25% ointment (generic of Topicort®) in the treatment of atopic dermatitis, psoriasis, and seborrheic dermatitis.

**Significance**
Doctors prescribe Protopic® and steroids in atopic dermatitis, psoriasis, and seborrheic dermatitis.
Desoximetasone 0.25% ointment is a Group II steroid
- Side effects: atrophy, telangiectasia, hypopigmentation
- Protopic® 0.1% ointment is a non-steroid topical immunomodulator
- Side effects: itching, burning, stinging
- Physical compatibility allows confident SIMULTANEOUS application, theoretically decreasing tacrolimus side effects and enabling further steroid sparing
- Some compounds are not stable when mixed, due to:
  - Compound/compound incompatibility
  - Vehicle/compound incompatibility
  - Vehicle/vehicle incompatibility

**Examples of Incompatibility**
- Dovone® 0.005% ointment and:
  - Salicylic acid 6% ointment
  - Ammonium lactate 12% lotion
  - Hydrocortisone-17-valerate 0.2% ointment
- Tazoratene 0.05% gel and:
  - Betamethasone dipropionate 0.05% gel (vs. compatible with ointment, cream, or lotion)
  - Hydrocortisone 0.1% ointment (vs. compatible with ointment)

**Chemical Structures**

**Desoximetasone**

**Tacrolimus**

**Results - Qualitative**
- No more than slight separation was observed over any time period under any of the three storage conditions
- Mixtures remained white, except for pale yellow appearance at Day 28 under all storage conditions of the mixture and desoximetasone control

**Results - Quantitative**
For all time and storage conditions, ranges of recovered materials were:
- Tacrolimus, Mixture: 70.9-82.3%
- Tacrolimus, Control: 67.9-81.3%
- Desoximetasone, Mixture: 95.3-109.7%
- Desoximetasone, Control: 93.9-103.5%

**Results - Quantitative**
- Range of % Relative Recovery (% Mixture/% Control) x 100 for All Storage Conditions and All Time Periods:
  - Tacrolimus: 89.6 - 109.7%
  - Desoximetasone: 90.0 - 103.4%

**Graphically**

**Methods**
- 80g desoximetasone ointment 0.25% (Taro) and 80g Protopic® ointment 0.1% (Fujisawa) were mixed at room temperature and stored in glass vials (1:1 w/w)
- Stability of 10g of mixture and control (non-mixed) samples were measured at Day 1, 2, 7, 14, and 28 under three different temperature/humidity conditions:
  - 25ºC, 60% relative humidity
  - 30ºC, 60% relative humidity
  - 40ºC, 75% relative humidity
- Potency recovery ranges for all storage conditions (% Mixture/% Control x 100, are: Tacrolimus: 89.6 - 109.3% and Desoximetasone: 95.3 - 109.7% respectively
- No significant difference in either physical appearance or chromatographic profile between the mixture and individual ointments.
- Protopic ointment, 0.1% (Fujisawa) and desoximetasone ointment, 0.25% (Taro) are compatible both physically and chemically up to 4 weeks when mixed at a ratio of 1:1 (w/w).

**Conclusion**
- There is no significant difference in either physical appearance or chromatographic profile between the mixture and individual ointments.
- Protopic ointment, 0.1% (Fujisawa) and desoximetasone ointment, 0.25% (Taro) are compatible both physically and chemically up to 4 weeks when mixed at a ratio of 1:1 (w/w).

**References**

*Department of Dermatology, Mount Sinai Medical Center, New York, NY 10029
**Taro Pharmaceuticals Inc., 130 East Drive, Brampton, Ontario L6T 1C1