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Development of an In Vitro Release Method for Mechlorethamine Hydrochloride Topical Gel

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PURPOSE

In vitro release testing (IVRT) is a critical performance test for semi-solid dosage forms as described in the United States Pharmacopeia (USP) General Chapter <1724>. IVRT result is also used as a supportive evidence to demonstrate bioequivalence of semi-solid dosage forms such as gels. Development of an IVRT method for drug products such as Valchlor® (mechlorethamine hydrochloride) gel, eq 0.016% base is challenging, because the drug substance, mechlorethamine hydrochloride, is a highly reactive compound and unstable in various media such as water.

The purpose of the current study is to develop a sensitive and discriminatory IVRT method for mechlorethamine hydrochloride topical gel.

METHOD(S)

Screening studies were performed to identify suitable receptor solutions that may be used in an IVRT study by assessing the solubility of mechlorethamine hydrochloride in propylene glycol, diethylene glycol monoethyl ether (Transcutol®), isopropyl alcohol, glycerin and mixtures containing varying amounts of each solvent. Based on the data from the solubility studies, stability of mechlorethamine was then studied at 32°C in the selected receptor solutions. Specifically, solutions of mechlorethamine were prepared in two solvent systems: solvent system A (propylene glycol: water 50:50 v/v with 0.5% w/v ascorbic acid) and solvent system B (diethylene glycol monoethyl ether: water 50:50 v/v with 0.5% w/v ascorbic acid). At each sampling time (0 hr and 4 hrs) samples were withdrawn from each vial and analyzed. The two receptor solutions and two different types of membrane, nylon (SteriTech®) and a polytetrafluoroethylene (PTFE, Millipore Fluoropore®), were evaluated in the method development studies. Pilot IVRT studies were conducted using a vertical diffusion cell apparatus with a permeation area of 0.636 cm^2 and receptor volume of 14 mL. 300 mg/cm^2 of mechlorethamine hydrochloride topical gel was dosed onto the membrane after it was equilibrated at 32 ± 1 °C (measured at the surface of the membrane) with the receptor solution. At specific time points (0.5, 1, 2, 3, and 4 hours), 500 µL samples were withdrawn from the receptor solution. Mechlorethamine content in all the samples were quantified using a liquid chromatography–mass spectrometry method (LC-MS). N = 3 cells per membrane were evaluated for each solvent system in this method development work.

RESULT(S)

❑ Drug solubility in receptor solutions

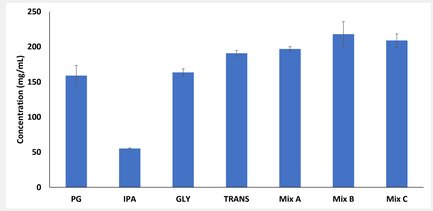

Figure 1: Mechlorethamine solubility in various solvents (PG: propylene glycol, IPA: isopropyl alcohol, GLY: glycerin, TRANS: diethylene glycol monoethyl ether, Mix A: TRANS:PG:IPA:GLY (3:1:1:1, v/v/v/v) with 0.01% v/v butylated hydroxytoluene, Mix B: TRANS:PG:IPA:GLY (1:1:1:1, v/v/v/v) with 0.01% v/v butylated hydroxytoluene, Mix C: TRANS:PG (1:1, v/v) with 0.01% v/v butylated hydroxytoluene. Data are presented as Mean ± SD, n = 3)

❑ Drug stability in receptor solutions

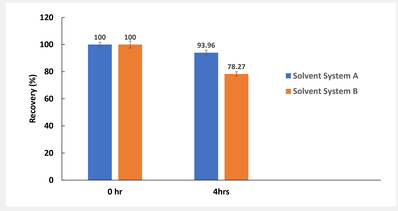

Figure 2: Mechlorethamine stability in solvent system A and B (Data are presented as Mean ± SD, n = 3)

- Mechlorethamine was more soluble in the solvent mixtures compared to the individual solvents (Figure 1).
- The stability data indicated that mechlorethamine was more stable in solvent system A after 4 hours of incubation at 32 °C (Figure 2).

❑ Membrane compatibility study

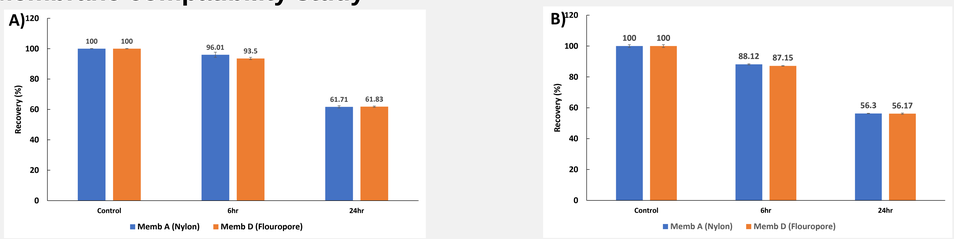

Figure 3: Mechlorethamine membrane compatibility study in A) solvent system A and B) solvent system B (Data are presented as Mean ± SD, n = 3)

❑ Mechlorethamine release study in different receptor solutions and membranes

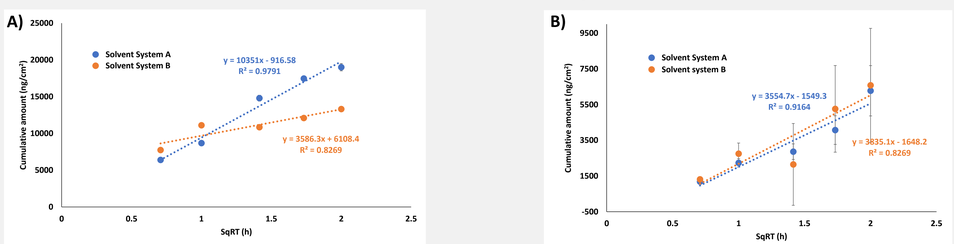

Figure 4: Mechlorethamine in vitro release study with A) Nylon membrane and B) PTFE membrane (Data are presented as Mean ± SD, n = 3)

- The observed release profile did not meet the currently recommended threshold for linearity for solvent system A with the PTFE membrane (Figure 4), or solvent system B with either membrane.

RESULT(S)

❑ IVRT pilot study

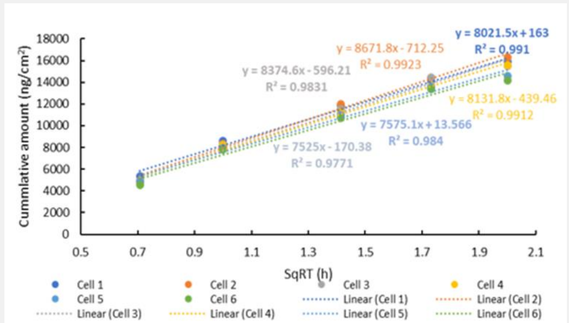

Figure 5: IVRT release profile of mechlorethamine in solvent systems A using the nylon membrane (Data are presented as Mean, n = 3)

- Pilot IVRT data (Figure 5) suggested that the release of mechlorethamine was linear ($r^2 > 0.97$) over the 4-hour IVRT study duration when nylon membrane was utilized with solvent system A.

CONCLUSION(S)

The current work demonstrates that:

- ➢ It may be feasible to develop an IVRT method for mechlorethamine hydrochloride topical gel using a vertical diffusion cell.
- ➢ Mechlorethamine hydrochloride is stable and soluble in solvent system A and compatible with the nylon membrane evaluated in this study.
- ➢ Additional work is needed to assess the discriminatory capability of the method to be able to use such a method as a component of characterization-based approaches for evaluating bioequivalence.

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