Application of Skin PAMPA to Differentiate Between Topical Pharmaceutical Formulations of Ibuprofen

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INTRODUCTION

This work studied the ability of a recently introduced skin-mimetic artificial membrane permeability model (Skin PAMPA) to differentiate between different topical pharmaceutical formulations. The Skin PAMPA results were compared with data obtained from in vitro Franz cell permeability measurements.

MATERIALS AND METHODS

Ibuprofen free acid (Figure 1) was purchased from Sigma (St. Louis MO, USA). A novel silicone based anhydrous gel formulation containing 5% ibuprofen (Form A) and a viscous fluid-like test formulation containing silicone and an acrylic co-polymer (Form B) were provided by Dow Corning Corporation (Midland, MI). A commercial benchmark (Form C) ibuprofen formulation (Form C) was also used.

Franz Cell Permeability Measurements

In vitro Franz cell permeability experiments were conducted for 8 h at 32 °C. Heat separated epidermis from human cadaver skin from two donors were used. Receptor fluid was phosphate buffered saline of pH 7.4. About 15 mg of formulation was homogeneously (visually) spread over 0.63 cm² area. The commercial benchmark was evaluated at the same time. Triplicate cells were used for each formulation. The Ibuprofen concentration was measured using Waters’ Acquity™ UPLC.

RESULTS AND DISCUSSION

Skin Permeability Measurements

The amount of ibuprofen (µg/cm²/h) delivered across the skin membrane was determined using an in vitro Franz cell permeability experiment. The experiments were carried out for 8 h through human cadaver epidermis from two donors. The silicone based topical pharmaceutical formulation (Form A) delivered 120-180 µg in 8 hours compared to 22-23 µg by the benchmark (Form C). The benchmark displayed its maximum flux of 8-14 µg/cm²/h at the 1 hour mark while at the same point the flux of the silicone formulation was 24-52 µg/cm²/h. The silicone formulation showed a larger amount of ibuprofen delivered than the benchmark in the first 3 hours. The benchmark’s delivery profile showed significant decline followed by a plateau after about 3 hours whereas the silicone formulations delivered over 6 times more ibuprofen than the benchmark during the 4 to 8 hour period (Figure 5).

A quantitative analysis shown on Figure 7 indicates that the amount of ibuprofen permeated from a novel silicon-based formulation (Form A) is about 3 times larger than the amount permeated from the commercial benchmark at corresponding time points.

The traditional method was modified to study topical formulations (creams, gels, ointments, etc.) Formulations were placed in the top compartment (30 ± 5 µg per well) of the 2-chamber PAMPA sandwich while the bottom compartment was filled with 180 µL pH 7.4 buffer and served as the receiver chamber (Figure 4).

In addition, a slurry (50 mg/mL) of Ibuprofen in DI water was prepared to compare its permeation rate with the formulations.

Stirring in each well of the bottom (receiver) compartment was provided by the Orb Shaker™ device (Pion Inc.).

Figure 6 compares the UV spectra for Ibuprofen in the receiver compartment penetrating through the Skin PAMPA barrier from the different formulations. The spectral influence of the formulations was subtracted by using blank wells with formulations having no API. Even a quick visual comparison indicates that Form A provides the highest response comparing to other formulations or to the slurry.

Figure 7 demonstrates that Skin PAMPA results for rank order of Forms A and Form C agree with the conclusions obtained from Ibuprofen flux measurements through human epidermis presented in Figure 5.

CONCLUSION

The semi-solid topical formulation made using silicone excipients provided by Dow Corning Corp. delivered ibuprofen more efficiently across the skin compared to the commercially available formulation. The Skin PAMPA model can be used with topical formulations to differentiate their ability for transdermal delivery of active pharmaceutical ingredients. Standardization potential and the high-throughput nature of Skin PAMPA can be a valuable cost effective complement to Franz cell permeability experiments for early skin penetration prediction and topical formulation development.

REFERENCES