Permeability and Stability of Dispersion Systems in the Presence of Penetration Enhancers

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ABSTRACT SUMMARY

The aim of this study was to investigate the permeability of unique dispersion systems in the presence of various penetration enhancers prepared by supercritical fluid (SCF) processing, to deliver a maximum amount of bioidentical progesterone (PGN) across mouse skin.

INTRODUCTION

Many of the orally administered drugs undergo extensive degradation due to first pass metabolism, such as progesterone. Therefore, alternative routes of administration are sought for PGN including transdermal delivery. Furthermore, the transdermal route is not without its problems such as permeation through the stratum corneum (SC). In this study, the preparation of PGN loaded dispersion systems with several penetration enhancers using SCF processing was investigated for transdermal delivery.

EXPERIMENTAL METHODS

Particles from a gas-saturated suspension (PGSS) method using supercritical carbon dioxide (SC-CO₂) was used to form dispersion systems of PGN [1]. The semi-solid dispersions were then applied to a Franz cell prepared with mouse skin. In a typical Franz setup, shown in Figure 1, the skin is applied between a donor and receptor chamber and the test formulation added to the skins surface [2]. Full thickness mice skin from fresh nude white CD1 mouse skin (ex-breeders) was collected from the Vermon J Unit (VJU) at the University of Auckland (Auckland, NZ). Any underlying excessive fat on the skin was carefully removed using a scalpel (size 20) and discarded.

Figure 1. Extent of PGN permeation with selected penetration enhancers after 24 hours.

* Represents the control (water) group (147.1 µg·cm⁻²)

RESULTS AND DISCUSSION

The ability of several enhancers to increase the permeation of PGN over 24 hours was conducted to screen for the best penetration enhancer. The penetration enhancer with the largest permeability of PGN was selected to form semi-solid dispersions of PGN made up of d-α-tocopheryl PEG 1000 succinate (TPGS) with or without transcutol P and myritol 318. The SCF dispersions were compared with formulations (1) a current market cream and (2) aqueous suspension. The integrity of the membranes was determined by measurement of the electrical resistance (ER) across the skin. Physical stability testing was completed according to ICH guidelines section Q1A (R2) under accelerated storage conditions at a temperature of 40 ± 2°C and relative humidity of 75 ± 5% RH over 6 months.

Figure 1. Schematic of a Franz cell used to evaluate drug permeation.

Figure 1. Extent of PGN permeation with selected penetration enhancers after 24 hours.

- Represents the control (water) group (147.1 µg·cm⁻²)

* Statistically significant increase of cumulative amount of PGN from the groups in the presence of various penetration enhancers compared to the control (water) group. Results are provided as mean ± SD, n = 3
Table 1. Electrical resistance for mouse skin membranes.

<table>
<thead>
<tr>
<th>Specie</th>
<th>Skin type</th>
<th>ER* (kΩ·cm⁻² ± SD)</th>
<th>ER** (kΩ ± SD)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>mouse</td>
<td>whole</td>
<td>3.98 ± 0.56</td>
<td>6.8 ±0.95</td>
<td>28</td>
</tr>
</tbody>
</table>

* ER cut-off values for mouse skin are equal to or above 5 kΩ.
** Diffusion cells and skin surface area = 1.77 cm²

Results are provided as mean ± SD, n = 28

The extent and flux of PGN permeated from the final TPGS/myrtilol/transcutol P and SCF prepared dispersion system was significantly higher than that of the controls, shown in Figure 3 (p-value < 0.05). The degree of viscosity may have been a factor in the observed profiles. Furthermore, TPGS and Gelucire 44/14 both form micelles on exposure to the aqueous regions of the skin [3]. The water content of stratum corneum is 30 to 50% (w/w) of dry weight in vivo and is varied when occluded by a water impermeable membrane and stored into water. TPGS forms micelles at concentrations ≥ 0.02 g·mL⁻¹ in water and Gelucire 44/14 undergoes micelle formation at approximately 0.1 g·mL⁻¹ [4].

Figure 3. Skin PGN permeation profiles for the TPGS-based dispersion systems (n ≥ 3).

Figure 4 shows the stability results for the PGN dispersion system containing myrtilol 318/transcutol P/TPGS prepared by SCF processing. The findings show that the mean content of PGN reduced to 93% of the original mean amount during the observation period.

CONCLUSION

The preparation of PGN loaded dispersion systems for transdermal delivery was achieved with the presence of Transcutol P and using SCF processing. The permeability of PGN was increased by 2-fold using the PGSS method together with TPGS/myrtilol/ transcutol P. Further investigation must be conducted into optimization of the SCF-based formulation with myrtilol 318 and transcutol P and examine the in vivo permeation of PGN across the human skin.

REFERENCES


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