ASSESSMENT OF THE PERCUTANEOUS ABSORPTION OF ABH PLO GEL ACROSS PORCINE EAR SKIN
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PURPOSE
- Pluronic Lecithin Organogels (PLO gels) have exhibited great efficacy in transdermal delivery by enhancing the permeability of certain drugs, especially for hospice patients and patients undergoing palliative care [1].
- Lecithin organogel (Lecithin LipoGel®), haloperidol (Haldol®) (ABH) topical gel is used widely in relieving chemotherapy-induced nausea and vomiting (CINV) for terminally ill hospital patients because of its presumed efficacy and low cost.
- However, one recent study by Smith et al. reported contrary findings that none of the drugs used in the ABH PLO gel exhibited sufficient absorption to be effective in treating nausea and vomiting [2].
- The purpose of this project was to evaluate the percutaneous absorption of lorniprazine, diphenhydramine and haloperidol from the PLO gel across porcine ear and to verify the suitability of topically applied ABH PLO gel for rational use in hospital patients to relieve CINV.

OBJECTIVE(S)
- The main objectives of the project are:
  - To develop and validate an HPLC method for simultaneous analysis of ABH drugs.
  - To study the percutaneous absorption of ABH PLO gel across the porcine skin.
  - To determine the theoretical steady state concentration (Css) of ABH drugs from the flux values.

METHOD(S)
- Methob for the preparation of ABH PLO gel
  - Diphenhydramine (2.2% w/w)
  - Lorniprazine (0.5% w/w)
  - Haloperidol (0.2% w/w)

RESULT(S)
- A high-performance liquid chromatography (HPLC) gradient method was developed and validated for the simultaneous analysis of ABH drugs.
- The mobile phase comprised of acetone (solvent A) and 0.1% formic acid in water (solvent B). Solvent A and solvent B were maintained at 22.7% and 77.3% for 10 minutes.
- Later the composition of solvent A and solvent B was linearly increased to 40% and 60% form 10-13min and the composition was maintained until 20 minutes.
- After completion of the run, the column was re-equilibrated for 5 minutes. The retention times of diphenhydramine, lorniprazine and haloperidol were found to be 5.2, 7.8, and 18.9 minutes, respectively (Fig. 1).

pH, FTIR and Viscosity
- The pH of ABH PLO gel was found to be 5.86 ± 0.13.
- In FTIR spectra of drug loaded PLO gel, there was complete absence of the characteristic drugs peaks, which indicated the absence of uncomplexed ABH drugs in the PLO gel and complete dissolution of functional group of drugs in the formulation.
- The viscosity of PLO gel was evaluated at various shear stresses using a Brookfield viscometer.
- Viscosity of PLO gel represented a non-Newtonian behavior with pseudoplastic flow. The viscosity of the drug-loaded PLO gel at 5 rpm was found to be 31,600 cps.

DSC
- DSC study was done to study the change in the heat absorbed by pure drugs (A, B and H) and ABH PLO gel.
- Diphenhydramine, haloperidol and lorniprazine showed sharp endothermic peaks at 171.7°C, 153.39°C and 187.72°C, respectively (Fig. 2) which corresponds to their melting point.
- Pure drugs peaks were completely absent in the drug-loaded formulation (Fig. 3).

CONCLUSION(S)
- Average flux and cumulative amount permeated values were found to be higher for diphenhydramine followed by lorniprazine and haloperidol.
- Theoretical steady state concentrations (Css) of ABH drugs from the ABH PLO gel were much below the required steady state concentrations.
- None of the drugs were able to permeate in the required therapeutic range.
- Based on the permeability data across the porcine skin, it is concluded that the ABH PLO gel does not provide sufficient permeability of ABH drugs through the porcine skin in order to attain the required therapeutic concentrations [3,4] needed to effectively manage nausea and vomiting in hospital patients.
- The results obtained in this study corroborated with the study done by Smith et al., in a randomized, double-blind, placebo-controlled, cross-over, non-inferiority clinical trial which showed that none of the drugs (diphenhydramine, haloperidol and lorniprazine) exhibited sufficient absorption from the PLO gel.
- The use efficient permeation enhancers is needed to achieve better permeation of drugs across the skin.
- Further studies across the human skin are warranted.

Acknowledgement
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References

Table 1: Line equation and validation parameters for HPLC analysis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Calibration equation</th>
<th>SS (n=5)</th>
<th>LOD</th>
<th>LOQ</th>
<th>RSD</th>
<th>% Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine</td>
<td>y = 6586.4x + 1622.9</td>
<td>8.23E-05</td>
<td>0.70</td>
<td>0.86</td>
<td>0.04</td>
<td>97.68</td>
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<tr>
<td>Haloperidol</td>
<td>y = 95.40x + 12.85</td>
<td>2.65E-05</td>
<td>2.18</td>
<td>1.62</td>
<td>0.01</td>
<td>95.40</td>
</tr>
<tr>
<td>Lorniprazine</td>
<td>y = 1354.9x + 6582.4</td>
<td>3.18E-05</td>
<td>2.65</td>
<td>1.62</td>
<td>0.01</td>
<td>95.40</td>
</tr>
</tbody>
</table>

Table 2: Percent drug content in ABH PLO gel after 30 days

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percent Drug Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine</td>
<td>95.40 ± 1.07</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>95.46 ± 0.49</td>
</tr>
<tr>
<td>Lorniprazine</td>
<td>95.46 ± 0.16</td>
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</tbody>
</table>

Table 3: Theoretical steady state concentrations of ABH drugs in the plasma based on the flux values, lag time and apparent permeability from the in vitro porcine skin permeation study

<table>
<thead>
<tr>
<th>Drug</th>
<th>Theoretical Steady State Plasma Concentration (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine</td>
<td>3.164 ± 0.94</td>
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<tr>
<td>Haloperidol</td>
<td>7.72 ± 0.04</td>
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<tr>
<td>Lorniprazine</td>
<td>3.45E-01 ± 0.05</td>
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