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ASSESSMENT OF THE PERCUTANEOUS ABSORPTION OF ABH PLO GEL ACROSS PORCINE EAR SKIN

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PURPOSE

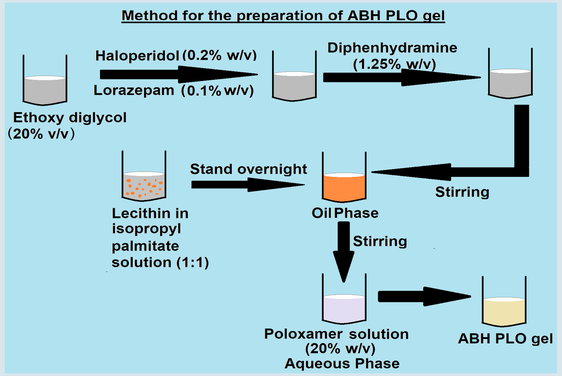
- Pluronic Lecithin Organogels (PLO gels) have exhibited great efficacy in transdermal delivery by enhancing the permeability of certain drugs, especially for hospice patients and patients undergoing palliative care [1].
- Lorazepam (Ativan®), diphenhydramine (Benadryl®), haloperidol (Haldol®) (ABH) topical gel is used widely in relieving chemotherapy-induced nausea and vomiting (CINV) for terminally ill hospice patient because of its presumed efficacy and its 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 lorazepam, 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 hospice 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 ear skin.
- To determine the theoretical steady state concentration (C_{ss}) of ABH drugs from the flux values.

METHOD(S)



Permeability study

- Permeability studies were performed using porcine skin membrane using Franz cells.
- A sample of 0.5g of ABH PLO gel was added onto the outer surface of the skin specimen inside the donor chamber of Franz cells.
- An aliquot (500µl) was withdrawn at regular time points of 0, 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 32 and 48h, and replaced with an equal amount of fresh receptor solution.
- Receptor solution and skin layers samples were analyzed by using the HPLC method.
- The mass balance recovery was in the range of 100±20%.

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 acetonitrile (solvent A) and 0.1% formic acid in water (solvent B). Solvent A and solvent B was maintained at 22.7% and 77.5% for 10minuties.
- Later the composition of solvent A and solvent B was linearly increased to 40% and 60% from 10-13mins 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, haloperidol and lorazepam were found to be 5.2, 7.8, and 18.9 minutes, respectively (Fig. 1).

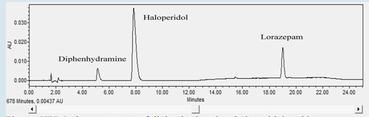


Fig. 1: HPLC chromatogram of diphenhydramine, haloperidol and lorazepam

Table 1: Line equation and validation parameters for HPLC analysis

Drugs	Calibration equation	LOD	LOQ	RSD	% recovery
Diphenhydramine	y = 958.66x - 1622.9	1.050ng	3.18ng	0.13-1.95%	99.87-101.02%
Haloperidol	y = 1154.9x - 6582.4	0.51ng	1.55ng	0.04-1.41%	100.07-100.57%
Lorazepam	y = 5960.9x - 3180.5	0.28ng	0.86ng	0.70-0.80%	100.15-102.25%

pH, FTIR and Viscosity

- The pH of ABH PLO gel was found to be 5.66 ± 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 gels 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 lorazepam showed sharp endothermic peaks at 171.77ºC, 153.99ºC and 187.72ºC, respectively (Fig. 2) which corresponds to their melting point.
- Pure drugs peaks were completely absent in the drug-loaded formulation (Fig. 3).

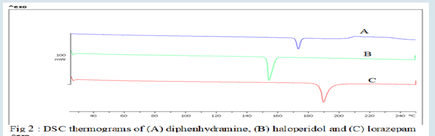


Fig 2 : DSC thermograms of (A) diphenhydramine, (B) haloperidol and (C) lorazepam

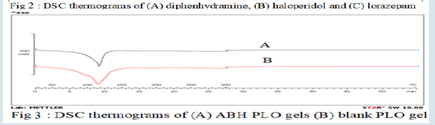


Fig 3 : DSC thermograms of (A) ABH PLO gels (B) blank PLO gel

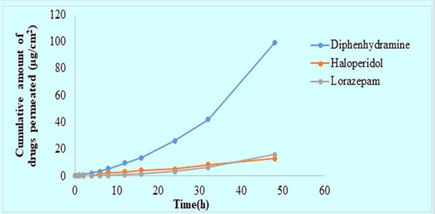


Figure 4: Permeation profile of diphenhydramine, haloperidol and lorazepam across excised porcine skin from PLO gel. Values are expressed as mean ± SD (n=5).

Stability study

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

Temperature	Diphenhydramine	Haloperidol	Lorazepam
25ºC	95.40±1.07	97.17±8.23	97.68±1.73
35ºC	95.43±1.66	95.44±8.24	96.19±1.39
45ºC	95.29±4.50	96.43±1.25	95.38±1.07

All the values are expressed in mean ± SD (n=3), SD: Standard Deviation

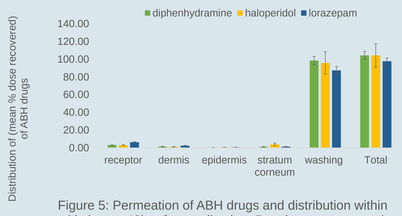


Figure 5: Permeation of ABH drugs and distribution within skin layers 48hr after application. Results are expressed in mean±SD(n=5)

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

Drugs	Flux (µg/cm²/h)	Lag time (h)	Apparent permeability (cm/h)	Clearance (L/h)	Theoretical Steady State Plasma Concentration, C_{SS} (ng/ml)	Required therapeutic Concentration C_{SS} (ng/ml)
Diphenhydramine	2.18±0.043	7.72±1.04	3.45E-04±1.2E-05	33.6	1.62	30-100 or 25-112
Haloperidol	0.26±0.004	1.08±0.84	2.65E-04±6.49E-06	50.4	0.13	6-245
Lorazepam	0.42±0.01	12.96±0.96	8.31E-04±2.9E-05	4.62	2.50	20-250

All the values are expressed in mean ± SD (n=5). SD: Standard Deviation

- All three drugs were found to be stable in the formulation at 25ºC, 35ºC and 45ºC for 30 days(Table 2).
- Flux values were found to be greater for diphenhydramine, followed by lorazepam and haloperidol(Table 3).
- Cumulative amount of drug permeated per unit area for diphenhydramine, haloperidol and lorazepam were 99.14±2.74, 12.49±0.20 and 16±0.35 respectively(Fig. 4).

CONCLUSION(S)

- Average flux and cumulative amount permeated values were found to be higher for diphenhydramine followed by lorazepam and haloperidol.
- Theoretical steady state concentrations (C_{ss}) 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 [2,3] needed to effectively manage nausea and vomiting in hospice patients.
- The results obtained in this study corroborated with the study done by Smith et al., in a randomized, double-blind, placebo controlled, crossover, non-inferiority clinical trial which showed that none of the drugs (diphenhydramine, haloperidol and lorazepam) 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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