Topical delivery of hexamidine dihydrochloride: Targeting the skin through chemical permeation enhancers (CPEs)

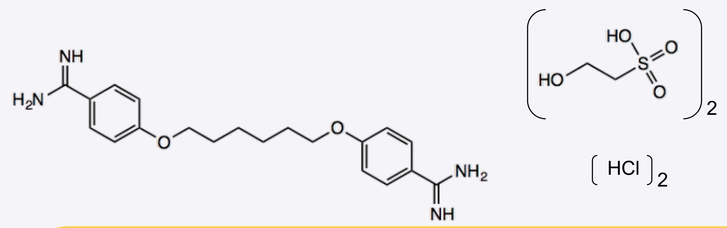
Paz-Alvarez Miguel [a], Parisi Nicola [a], Lane Majella E [a]

[a] UCL School of Pharmacy, 29-39 Brunswick Square, London, WC1N 1AX, UK

I. Introduction & Objectives

Hexamidine dihydrochloride – what is it?

It is the result of the **in-house purification of hexamidine diisethionate (HEX D),** a commercially available ingredient present in personal care formulations



HEX H

HEX D

Traditionally used as a **biocide** in topical preparations since 1950

Recent evidence of effects in skin homeostasis

- Inhibitory effect on inflammatory proteases → **Role in skin ageing**
- In vivo studies **showed improvement in skin barrier function** (with other ingredients)

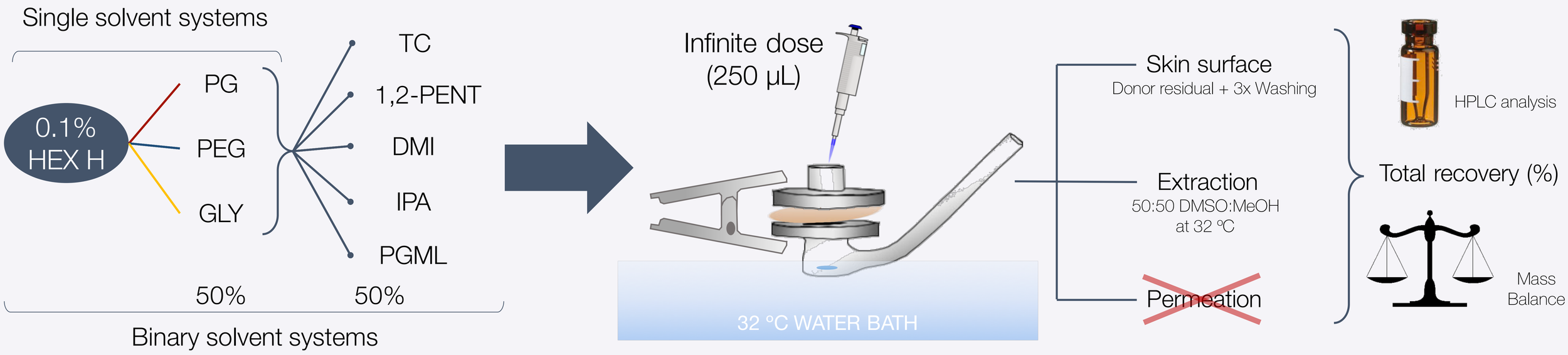
BUT

Topical delivery profile has not been studied

Interaction with different CPEs remains unexplored

Which salt is more appropriate for skin delivery?

II. Methods



III. Results

1 In vitro permeation and mass balance studies with single solvents

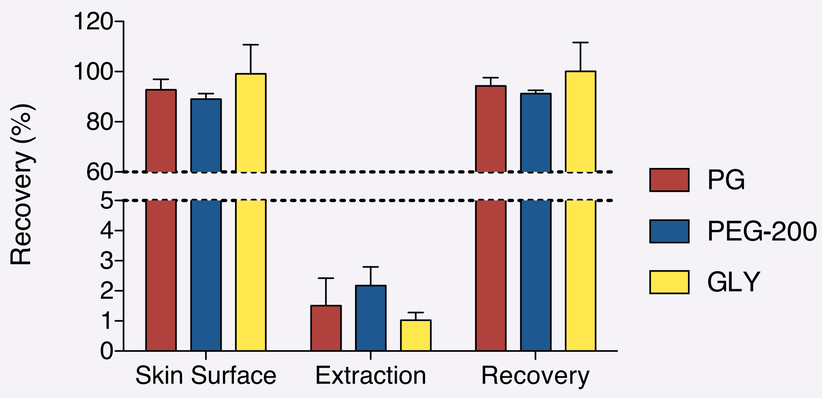


Fig. 1. Mass balance of 0.1% HEX H after 48 h permeation for single solvent systems, expressed in % recovery. 4<n<5

No permeation was observed for the solutions of HEX H, and more than **85% of the applied dose was recovered** from the skin.

Skin total recovery was not statistically different from skin surface recovery. There was **no statistical difference either among the three solvents** for the skin extraction of the active (individual samples t-test, $p > 0.05$)

2 In vitro permeation and mass balance studies with binary solvents

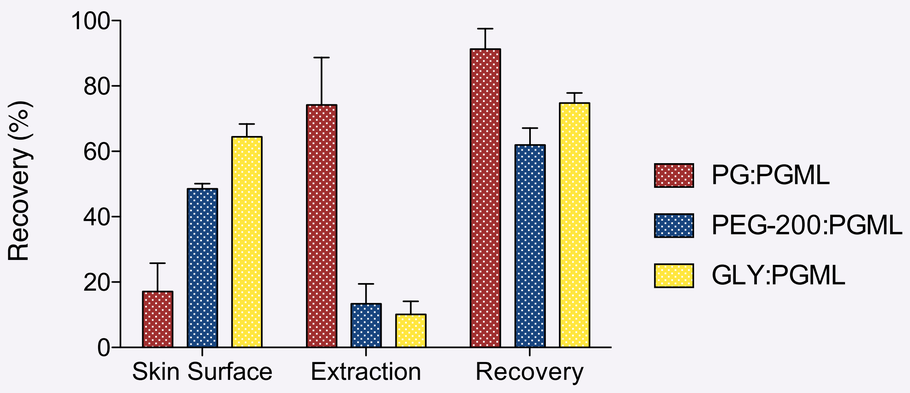


Fig. 2. Mas balance of 0.1% HEX H after 48 h permeation for binary solvent systems 50:50 (PG:PGML, PEG-200:PGML, GLY:PGML), expressed in % recovery. 4<n<5

PGML enhanced skin extraction to **up to 70% of the applied dose**!

PROPYLENEGLYCOL MONOLAURATE (PGML)

- Significantly **higher skin extraction** (up to 75% of the applied HEX H)
- Specific **skin targeting** (no permeation was observed)

PGML is currently used in topical formulations as an emulsion stabiliser, ingredient solubiliser and has shown synergistic enhancing effects with other vehicles such as PG.

Unsuccessful CPEs in binary systems

TRANSCUTOL P (TC)

- **Single solvent systems delivered a higher amount of active** than binary systems with TC.
- Widely used CPE with reported excellent solubilising properties and safety records. It was expected to promote topical delivery

ISOPROPYL ALCOHOL (IPA)

- Present in many formulations for topical and transdermal delivery
- Low boiling point → **capable of increasing the thermodynamic activity** of the compounds.
- IPA did not improve HEX H skin extraction.

1,2-PENTANEDIOL (1,2-PENT)

- Enhancement of delivery for a model hydrophilic compound and dependent to the enhancer´s concentration
- In this case 1,2-PENT **did not improve the topical delivery of HEX H**

DIMETHYL ISOSORBIDE (DMI)

- Did not provide any topical delivery enhancement of HEX H
- Less than 0.9% of the applied dose was recovered from the skin

IV. Conclusions

HEX H did not permeate through the skin.

Only **1 out of 5 sets of binary systems significantly improved** the skin extraction compared to the single solvent system, setting PGML as the best option for HEX H skin targeting.

HEX H can be delivered topically more effectively than HEX D using PGML as chemical permeation enhancer

It is key to elucidate the **permeation enhancer's mechanism of action** for rational formulation development in the future.

References

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Acknowledgements

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