R6079 Levothyroxine skin permeation and accumulation

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AIM OF THE WORK

The aim of this work was to determine in vitro the extent of thyroxine (TX) skin permeation and accumulation from different formulations.

The objectives were:

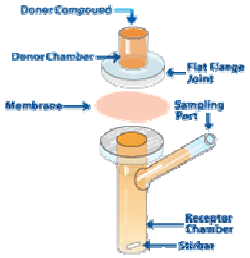
- ✓ To study passive and post-iontophoretic passive TX diffusion (1) from semisolid formulation (i.e. microemulsion and commercial cream).
- ✓ To formulate TX in Patch-non-Patch® films (2).
- ✓ To evaluate the effect of occlusion on TX permeability.

Somatoline® (Manetti & Roberts, Italy) a commercial cream containing thyroxine was used as reference.

METHODOLOGY

Permeation experiments

- Franz diffusion cells
- **Barrier**: rabbit ear skin
- **Receptor solution**: saline
- **Donor**: Microemulsion
  Somatoline®
  Patch-non-Patch®
- **Pre-treatment**:
  cathodal iontophoresis
  (0.5 mA/cm^2) for 1 h



HPLC analysis

- Waters Spherisorb® Cyano (Millipore, USA)
- Mobile phase: H_2O:CH_3CN:H_3PO_4 (70:30:0.1)
- Flow rate: 0.3 ml/min
- UV detection at 225 nm

TX skin extraction

- 0.1 ml 0.01M methanolic NaOH solution
- 0.9 ml HPLC mobile phase
- 40°C for 30 min
- 5000 rpm for 10 min

Patch-non-Patch® composition

	PnP	PnP-ME
PVA 20% (a)	62.00	55.94
PVP 21% (b)	27.00	24.36
Sorbitol (c)	4.00	3.61
Water	6.25	6.32
TX	0.75	0.74
Microemulsion	-	9.02

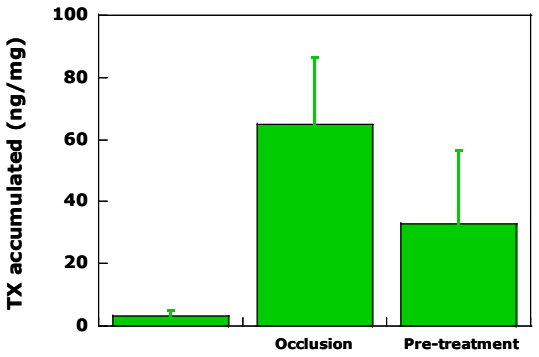
(a) Water solution (p/p)
(b) Water/PEG400 solution (85:15, p/p)
(c) Water solution 70% (p/v)

Microemulsion composition

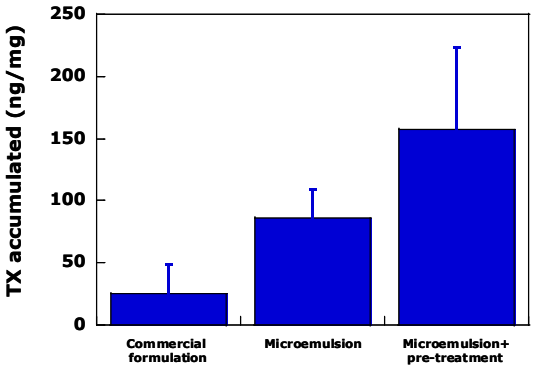
	%
Isopropyl myristate	36.60
Tween 80	20.50
Span 20	20.50
Water	18.20
Isobutanol	4.50
TX	0.75

RESULTS

Commercial formulation (finite dose, 2 µl/cm^2)



Microemulsion (infinite dose)



In the experimental condition adopted, TX was never found in the receptor compartment. All data are reported as mean values ± s.d.

Commercial formulation

- ✓ Occlusion determined significant ($p<0.001$) higher TX skin concentration.
- ✓ The application of electric current did not determine an increase either in skin post-iontophoretic passive flux or skin accumulation.

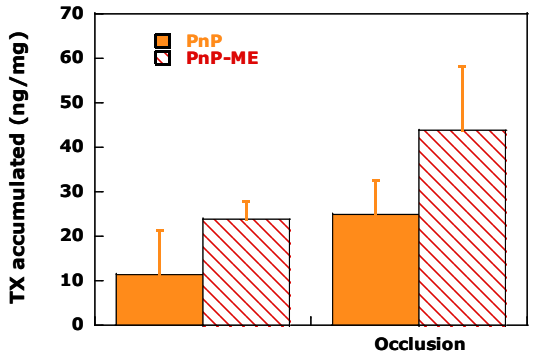
Microemulsion

- ✓ ME determined higher ($p<0.01$) TX skin accumulation compared to commercial formulation.
- ✓ Post-iontophoretic skin flux did not change compared to passive diffusion, but significant differences ($p<0.05$) were observed between the amounts of drug accumulated.

Patch-non-Patch®

- ✓ The presence of an occlusive backing increased TX skin retention, although in a non significant way.
- ✓ Introducing microemulsion in the PnP, the extent of accumulation was not significantly higher but the effect of occlusion was more evident ($p<0.005$).

Patch-non-Patch®



CONCLUSIONS

- The skin serves as an efficient barrier to thyroid hormones permeation: TX is able to accumulate in the skin but not to cross the skin.
- The use of cosmetic formulations containing TX seems not to represent a risk for patients suffering from thyroid disorders.

REFERENCES

1. P. Santi et al., Int. J. Pharm., 266 (2003) 69-75.
2. C. Padula et al., J. Control. Release, 88 (2003) 277-285.