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Effect of poloxamers on acyclovir penetration and skin accumulation during transdermal iontophoresis

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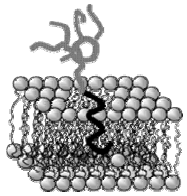
AIM OF THE WORK



Pluronic® are low toxicity nonionic surfactants that could be used as chemical penetration enhancer. The association of chemical enhancers with iontophoresis, a physical penetration enhancement method, could produce a synergic effect on the transport of low permeating drugs, such as acyclovir (ACV), in order to achieve therapeutic local doses.

Objectives

We intended to study the effect of poloxamers on acyclovir penetration and skin retention after anodal iontophoresis application. Pluronic® F127 and F68 were used. Pluronic® solutions were characterized by Dynamic Light Scattering (DLS).
A saturated solution of ACV buffered at pH 5.8 was used as control.

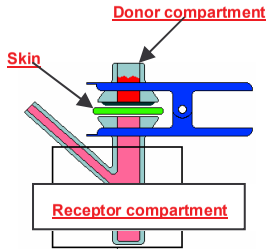
METHODOLOGY

Pluronic solution characterization

- ✓DLS (Zeta Plus, Brookhaven Instrument Corp., USA)
- ✓Pluronic® solution in 25 mM Hepes buffer pH 5.8, 133 mM NaCl
- ✓Evaluation of the formation of micelles
- ✓Micelles size determination

Donor solution composition

Donor solutions	Pluronic type and conc.	ACV conc (mg/ml)
Control	-	1.0
F68	Pluronic® F68 5%	1.1
F127	Pluronic ® F127 5%	1.6



Permeation experiments:

- ✓ Vertical Franz type diffusion cells (area 0.6 cm²)
- ✓ Frozen skin of rabbit ear
- ✓ DONOR: 1 ml of ACV solutions (pH 5.8)
- ✓ RECEPTOR: PBS pH 7.4 (4 ml)
- ✓ Experimental conditions: 5 or 24 hs, 37°C
- ✓ Anodal iontophoresis
  - ✓ Current density: 0.50 mA/cm²
  - ✓ Time of application: 5 hours

Skin extraction

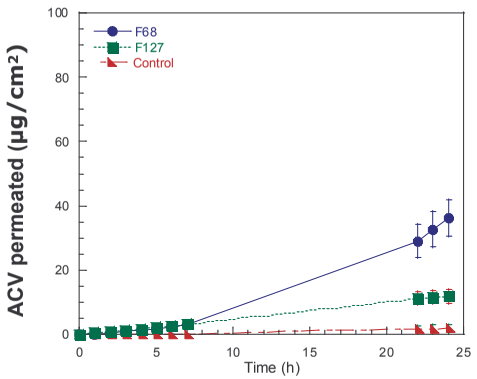
- ✓Heat skin separation (epidermis/dermis)
- ✓0.5 ml of H_2O @ 60°C, 30'
- ✓0.5 ml of $HClO_4$, protein precipitation

HPLC analysis

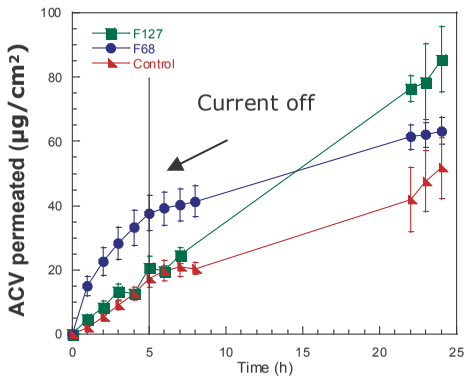
- ✓Column: C18 Jupiter (5µm, 250x4.6 mm, Phenomenex, USA)
- ✓Mobile phase: distilled and Millipore filtered water.
- ✓Flow: 1.2 ml/min
- ✓UV detection: 254 nm

RESULTS

ACV passive diffusion



ACV permeation after iontophoresis



Pluronic solution characterization

Only Pluronic® F127 was able to form detectable micelles in our experimental conditions:

Pluronic® solution	ACV conc. (mg/ml)	Micelle size (nm)	Polidispersity
F127 5%	-	25.2±0.3	0.208±0.007
F127 5%	1.6	25.4±0.3	0.215±0.007

ACV retained in epidermis and dermis after 5 or 24 h permeation experiments (mean±sd)

Treatment	ACV recovered (µg/mg of tissue)			
	Epidermis		Dermis	
	5 h	24 h	5 h	24 h
Control	0.18±0.05	0.47±0.08	0.00±0.00	0.03±0.00
Control + ionto	0.42±0.08	0.35±0.18	0.04±0.01	0.07±0.05
F68	0.09±0.05	0.22±0.14	0.00±0.00	0.06±0.03
F68 + ionto	0.19±0.02	0.14±0.04	0.03±0.01	0.02±0.01
F127	0.13±0.06	0.23±0.09	0.02±0.02	0.02±0.02
F127 + ionto	0.18±0.05	0.44±0.02	0.02±0.00	0.04±0.01

CONCLUSIONS

- ✓ Pluronic® F127 was able to self assemble in nanometric micelles: micelles size was not influenced by ACV presence.
- ✓ Pluronics® increased the passive transport of ACV across the skin, F68 being more effective than F127, but, on the contrary decreased ACV skin retention.
- ✓ Pluronic® F68 showed synergic effect during 5 hours current application, while F127 produced a reservoir in skin, ensuring a constant ACV post-iotophoretic release.
- ✓ In passive conditions, the time of contact increased the amount of ACV retained in the skin layers.
- ✓ ACV recovered in the skin after 5 hours of iontophoresis was similar to the amount retained after 24 hours of passive diffusion, but higher than after a post-iontophoretic transport (24 h), for control and F68 solutions.
- ✓ Pluronic® F127 gave the higher accumulation of ACV in epidermis, after post-iontophoretic diffusion, confirming a reservoir effect, probably due to micelles formation.

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