Formulation optimization of a new bioadhesive film for dermal/transdermal drug delivery

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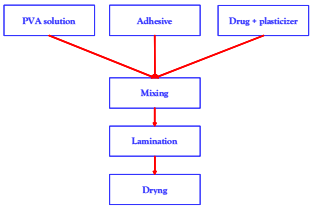
PURPOSE

The aim of this work was to optimize the formulation of the transdermal bioadhesive film named Patch-non-Patch® **(1,2)**. This system is a polymeric film, flexible, water permeable, electrically conductive, not self-adhesive but only when applied on wet skin, obtained from a solution/suspension of a film forming agent, an adhesive and a plasticizer. In particular we investigated the mechanical properties, the in vitro transdermal penetration and the in vivo skin accumulation of a model drug (lidocaine) as a function of the composition of the film.



METHODS

Mechanical properties

Tensile strength (T.S.) and elongation at break (E.B.) **(3)**

- ★Dynamometer (Acquati, Milan, I)
- ★5 kg load cell
- ★Film strip: 20x100 mm
- ★Rate: 30 mm/min

$$T.S. = \frac{\text{Breaking Force}}{\text{Cross Sectional Area}}$$

$$E.B. = \frac{\text{Increase in Length at Breaking Point}}{\text{Original Length}} \times 100$$

Permeation studies

- ★ Franz type diffusion cells (0.6 cm^2)
- ★ Rabbit ear skin
- ★ Receptor: saline solution
- ★ Donor: Patch-non-Patch

Stratum corneum distribution

- ★ 4 volunteers (age range 24-30)
- ★ Patch-non-Patch, Luan gel
- ★ Application time: 30 min
- ★ Tape stripping (15 times)
- ★ Lidocaine extraction (1 ml CH_3CN: pH4 phosphate buffer (20:80, v/v), 45°C, 30 min)

RESULTS

Mechanical properties (placebo)

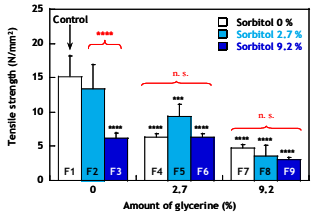
Films composition (factorial design)

Formulation	Factor A	Factor B
F1	-	0
F2	-	+
F3	-	-
F4	0	-
F5	0	0
F6	0	+
F7	+	-
F8	+	0
F9	+	+

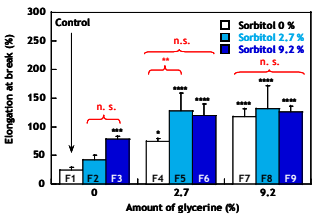
(A) = glycerin
(B) = sorbitol
(-) = absence
(0) = 2.7%
(+) = 9.2%

	F1	F2	F3	F4	F5	F6	F7	F8	F9
PVA 49K	56.36	56.36	56.36	56.36	56.36	56.36	56.36	56.36	56.36
Plastoid® E 35 H	24.55	24.55	24.55	24.55	24.55	24.55	24.55	24.55	24.55
Mannitol	0.91	0.91	0.91	0.91	0.91	0.91	0.91	0.91	0.91
Glycerin	-	-	-	2.73	2.73	2.73	9.19	9.19	9.19
Sorbitol	-	2.73	9.19	-	2.73	9.19	-	2.73	9.19
Water	18.18	15.45	9.19	15.45	12.72	6.26	9.19	6.26	-

Tensile Strength



Elongation at break



In vivo adhesion

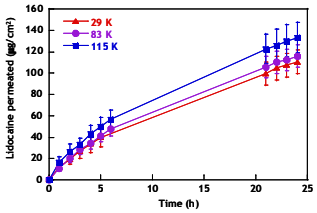
	Detachment Force (N)	Work of adhesion (mJ)
F1	3.19± 0.88	85.73±21.23
F2	1.66±0.68[(a)]	42.35±23.52
F3	2.47±1.11	71.32±45.56
F4	2.41±0.82	55.71±29.79
F5	0.96±0.40[(c)]	23.66±8.56[(b)]
F6	1.10±0.35[(c)]	23.95±7.94[(b)]
F7	1.92±0.59	38.39±13.58
F8	1.92±0.70	54.73±30.58
F9	1.31±0.38[(b)]	29.31±13.56[(a)]
Diclofenac	0.3	10.3

(a) p<0.05; (b) p<0.01; (c) p<0.001 with respect to control

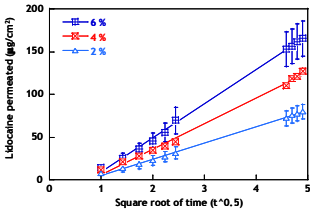
ANOVA analysis: * p<0.05 ** p<0.01 *** p<0.001 **** p<0.0001

Permeation studies

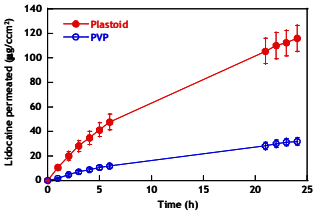
Effect of PVA molecular weight



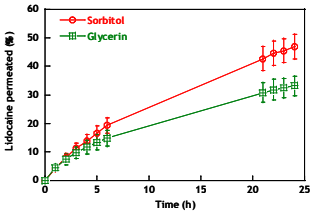
Effect of drug loading



Effect of adhesive

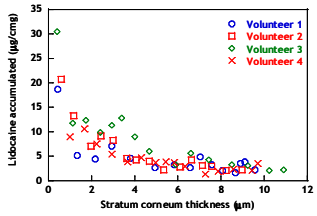


Effect of plasticizer

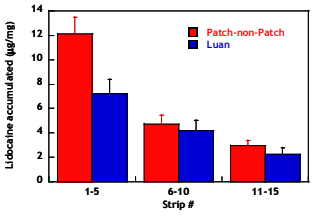


In vivo studies

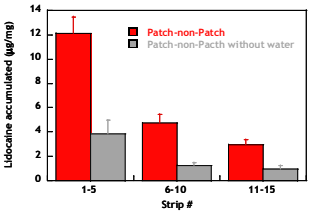
Stratum corneum concentration profile



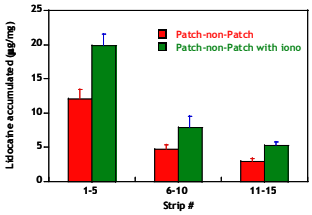
Comparison with commercial gel



Effect of water



Effect of iontophoresis



CONCLUSIONS

The addition of a plasticizer to the formulation is essential to improve the mechanical characteristics of the film.
Lidocaine permeation across rabbit ear skin from dermal patches follows Higuchi's kinetics. The choice of the adhesive seems to be an important variable governing drug transport from transdermal film.
Patch-non-Patch® is more effective than commercial formulation in accumulating lidocaine in the stratum corneum.
Iontophoresis increases in a significant way the amount of lidocaine accumulated in the stratum corneum.

REFERENCES

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2. C. Padula, G. Colombo, S. Nicoli, P.L. Catellani, G. Massimo, P. Santi, Bioadhesive film for the transdermal delivery of lidocaine: in vitro and in vivo behavior, J. Control. Release, 88 (2), 277-285, 2003.
3. T. A. Khan, K. K. Peh, and H. S. Ch'ng. Mechanical, bioadhesive strength and biological evaluations of chitosan films for wound dressing. J. Pharm. Pharmaceutic. Sci. 3: 303-311 (2000).