The Effect of Adhesive Compliance on Flux in Transdermal Acrylate Adhesives

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Introduction

To examine the effect of adhesive creep compliance on in vitro penetration of testosterone across hairless mouse skin (HMS) in the presence of penetration enhancers. In addition to their intended effect, penetration enhancers typically plasticize and soften an adhesive. This study was done to see whether the softening of the adhesive formulation leads to increased penetration rates independently of changes in penetration enhancers.

Methods

Inherent viscosity (I.V.) - This was measured using a Cannon-Fenske viscometer at 25°C with ethyl acetate as the solvent. The inherent viscosity can be correlated to the molecular weight (M.W.) of the polymer, with increasing I.V. correlating to increasing M.W.

Shear Creep Compliance - This is a measure of the ability of the adhesive to flow. Thin sheets of adhesive sandwiched between PET films are placed on either side of a slip-plate in a shear creep compliance rheometer. The adhesive layers are held in place by pressure applied to stationary plates above and below the slip plate. The slip-plate is then caused to move by application of a force. The compliance, J(t) is determined from the displacement vs. time curve using the equation J(t)=2Ax/hf, where A is the area of the adhesive sample, x is the displacement at time t, h is thickness of the adhesive sample and f is the applied stress. The compliance is typically reported in cm^2/dyne, and values presented here are for a time of 3 minutes.

In-vitro penetration - This was performed using 2.0 cm^2 Franz diffusion cells. Hairless mouse skin was used as a membrane. The receptor fluid was 30% by weight m-pyrol in water. The entire apparatus was maintained at 32°C during the duration of the experiment. Content analysis was performed using reverse phase HPLC.

Adhesives - Acrylic copolymer adhesives with varying molecular weights were prepared by free-radical polymerization in organic solvent. Molecular weight variation was obtained by variation of monomer and/or initiator concentrations in the reaction.

Discussion

In part 1, a series of isooctyl acrylate-acrylamide-vinyl acetate (IOA/ACM/VOAc) copolymer adhesives were prepared with inherent viscosities (I.V.) ranging from 0.82 to 1.48 dl/g. These were formulated with varying levels of oleyl alcohol in such a way that the compliance of the adhesive formulations was held constant. In vitro penetration of testosterone across HMS was measured for these formulations, as well as for formulations with constant oleyl alcohol (where the compliance was allowed to vary).

Oleyl alcohol was chosen because it has shown good penetration enhancement for testosterone, and the solubility of testosterone in it is only about 6%. This is similiar to the solubility in the adhesives which was approximately 4%, which means that the addition of OA would not substantially change the relative level of saturation of drug in the adhesive formulation.

Five adhesives (see table below) were selected to span a range from low to high I.V.

Sample	I.V. [dl/g]	J x 10^5 [cm^2/dyne]	% oleyl alcohol - series 1	% oleyl alcohol - series 2
E	.82	0.631	0	4
D	.89	0.477	2	6
C	1.02	0.383	4	10
B	1.20	0.317	6	12
A	1.48	0.249	8	14

These were then formulated with 4% testosterone and oleyl alcohol levels ranging up to 14%. A linear fit of the logarithm of the shear creep as a function of oleyl alcohol level was determined for each adhesive. Two series of OA loading were selected based on these linear fits to give adhesives with the same compliance (e.g., A + 8% OA has the same shear creep compliance as D + 2% OA). Series 1 samples had a shear creep compliance of ~0.63 x 10^{-5} cm^2/dyne and series 2 samples had a shear creep of ~1.40 x 10^{-5} cm^2/dyne.

In addition, all five adhesives were formulated with 4% OA to examine the effect of changing adhesive compliance with constant penetration enhancer level.

In part 2, HMS penetration data for testosterone and IOA/ACM/VOAc adhesives was also done with two other enhancer formulations containing either terpineol or menthol as the primary component. In both cases the testosterone and enhancer concentrations were held constant, and the adhesive I.V. was varied.

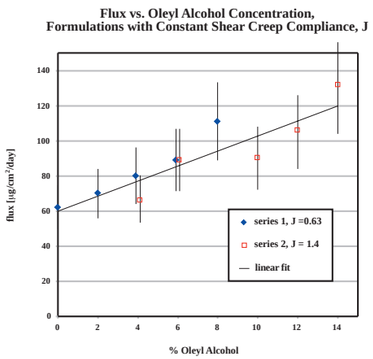
Results

Part 1 - The following table summarizes the 24 hr cumulative penetration results.

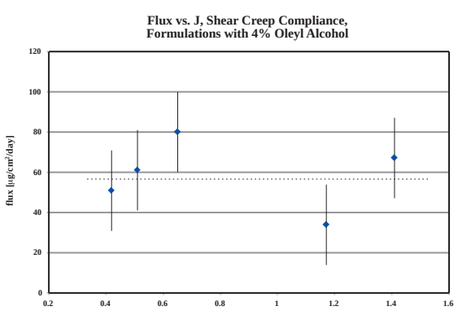
Adhesive	% oleyl alcohol	24 hr flux [µg/cm^2]	st. dev.	J x 10^5 [cm^2/dyne]
A	8	111	31	
B	6	89	25	
C	4	80	20	0.63
D	2	70	25	
E	0	62	18	
A	14	130	64	
B	12	105	36	
C	10	90	40	1.4
D	6	89	33	
E	4	67	20	
A	4	51	22	0.42
B	4	61	16	0.51
C	4	80	20	0.65
D	4	34	5	1.17
E	4	67	20	1.41

All values are averages with n=5.

There is a definite trend towards increased delivery with increasing oleyl alcohol. The delivery rate increased by approximately a factor of 2 as the oleyl alcohol level increased.

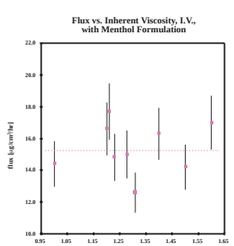


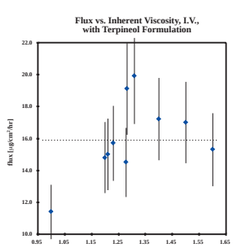
In contrast, when the oleyl alcohol level was held constant there was no observable trend in delivery rate as the formulation compliance increased from 0.4 to 1.4 x 10^{-5} cm^2/dyne.



Part 2 -
The table below shows the 24 hr penetration results.

Adhesive	IV	Flux w/Terpineol [ug/cm^2/hr]	Deviation #std. devs	Flux w/Menthol, PG [ug/cm^2/hr]	Deviation #std. devs
F					
	1.00	11.4	1.9	14.4	0.7
	1.23	15.7	0.1	14.8	0.5
	1.28	14.5	0.6	15.0	0.4
G					
	1.21	15.0	0.4	17.7	-0.7
	1.31	19.9	-1.6	12.6	1.4
H					
	1.20	14.8	0.5	16.6	-0.3
	1.28	19.1	-1.3		
	1.40	17.2	-0.5	16.3	-0.1
	1.50	17.0	-0.4	14.2	0.8
	1.60	15.3	0.3	17.0	-0.4
total average		16.0		15.4	
standard dev.		2.4		1.6	





The two enhancer combinations are seen to be equivalent. It is also apparent that all of the values for each enhancer combination are very similiar. If each group of 10 values is treated as a single population, then a standard deviation similiar to that seen for the between cell variation is obtained, and none of the individual values varies by more than 2 standard deviations from the mean. Thus, no effect on the cumulative flux is seen by changing adhesive I.V. within the range of 1.0 to 1.6 dl/g.

These results are consistent with the skin acting as a rate limiting membrane. This is based in part on the premise that the rate at which the drug can diffuse through the adhesive is much faster than the diffusion rate across the skin. This is often seen in the rapid rate of drug release in dissolution experiments where the drug is allowed to dissolve directly into a liquid medium (analogous to delivery into the bloodstream without the skin barrier). Without the rate limiting membrane, the drug release from a thin layer of adhesive can happen completely in a few hours, whereas only a fraction of the total drug is delivered over 24 hours in the penetration experiments above.

Conclusions

Within the ranges studied here, the effect of a penetration enhancer on drug flux across HMS comes entirely from its effect on the skin and/or the drug, and is not due to any plasticizing effect that it has on the adhesive. This, of course, assumes that any plasticizing effect of the enhancer does not change the ability of the adhesive to remain in skin contact during the delivery.

Glossary

IOA	isooctyl acrylate		
ACM	acrylamide	VOAc	vinyl acetate
EtOAc	ethyl acetate	IPA	isopropanol
OA	oleyl alcohol	PG	propylene glycol
HMS	hairless mouse skin	I.V.	inherent viscosity

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