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EFFECT OF SILICONE / ACRYLIC PSA BLENDS ON SKIN PERMEATION

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Introduction

Rate and extent of skin permeation from drug-in-adhesive (DIA) transdermal drug delivery systems (TDDS) has traditionally been attributed solely to the barrier properties of the stratum corneum, a fact that has shed a negative light on the perceived ability of these DIA products to reproducibly attain the target pharmacological doses. Modification of these stratum corneum barrier properties has been sought by incorporation into these products of chemical enhancers such as fatty acids, esters, etc...alone or in combination with polyhydric alcohols. Although effective in skin permeations enhancement, chemical modification has a significant down side potential stemming from the increasing irritation potential that accompanies higher concentrations of these. Additionally, in DIA systems, these chemical enhancers typically possess surfactant properties that detrimentally affect the pressure sensitive adhesive (psa) properties of these and thus the wear properties of the finished product.

Drug solubility modification via the blending of psa's has been shown to be as effective as chemical enhancement with the added benefit of having increased versatility in attainment of the required wear properties. PSA blends, and more specifically, blends of acrylic psa's with silicone psa's have been shown to afford the formulator the ability to manipulate the height of the initial delivery peak (burst effect), the lag time, and the length of time the product can sustain the pseudo-zero-order delivery of the permeant molecule. These performance characteristics are achieved by maximizing thermodynamic driving force with the minimal drug content by manipulation of the silicone to acrylic psa ratio.

Experimental Method

Two different drugs were evaluated in order to demonstrate the effects of varying the silicone to acrylic psa ratio. The two drugs selected, selegiline and estradiol, were picked based on their differences. Selegiline base is a volatile liquid at room temperature whereas estradiol is a solid. Selegiline doses are targeted in the area of 5-10 mg/day whereas estradiol is targeted at 0.05-0.10 mg/day both from a 10 cm^2 patch area.

The selegiline formulations were made at 12% w/w drug while varying the acrylic psa content between 15 and 60% and the silicone psa between 28 and 63%. No further excipients were used.

The estradiol formulations all contained 1.6% estradiol, 7.5% kollidon-30, 8% dipropylene glycol and 6% oleyl alcohol. The acrylic psa content was varied between 10 and 20% in conjunction with a silicone psa variation between 66.9 and 56.9% by weight in the finished product.

The diffusion rate of the drug is determined through a disc of cadaver skin. Epidermal discs from the same donor and site were used in the study to factor out inter-subject variability in permeability. The receiving solution is an isotonic saline solution with a sodium azide preservative (0.9% NaCl and 0.01% NaN_3) with a pH of 6.7. The cell is kept at a constant temperature of 32 °C and stirred continuously at ~300 rpm. The number of replicate cells per formulation in

the experiment was four. A known volume of saline was removed from the cell at specified time points. The complete contents of the receiver was removed and replaced with fresh saline to guard against solution saturation. The concentration of each sample of saline is determined through High Precision Liquid Chromatography with a detection wavelength of 220 nm.

Results and Discussion

SELEGILINE

Figure #1 shows the effect of increased ratio of silicone to acrylic psa while holding the drug concentration constant at 12% drug. As can be seen in this plot, as the ratio of silicone to acrylic psa went from 28:60 to 58:30 to 73:15, the corresponding average skin permeation rate went from 13.5 to 18.4 to 29.7 $\mu g/cm^2$ with no significant change in the shape of the permeation curve (i.e. initial peak followed by a gradual fall off to the 26 hour timepoint). Based on this performance, attaining equivalent rate and extent between the three formulations from a bioequivalence viewpoint could be achieved by varying the patch size.

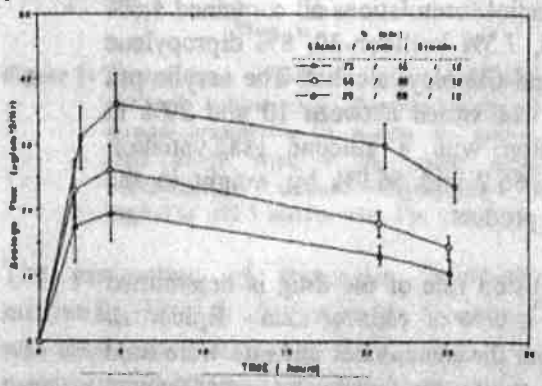

Figure 1 - Effect of Silicone to Acrylic Ratio on Selegiline Flux

ESTRADIOL

Figure #2 illustrates the in-vitro performance of the estradiol formulations where the silicone to acrylic psa ratio was varied at a constant concentration of estradiol (1.6% by weight). As shown, varying the silicone to acrylic psa ratio from 56.9:20 to 61.9:15 to 66.9:10 resulted in an average flux rate increase from 1.01 to 1.09 to 1.25 $\mu g/cm^2/hr$ with the additional effect of having altered the initial burst effect and subsequent sustenance of the pseudo-zero-order delivery profile. As can be seen in Figure #2, higher silicone to acrylic psa ratios resulted in a shift of the permeation profile from a pseudo-zero-order to a first order delivery system incapable of sustaining the targeted 84 hour delivery.

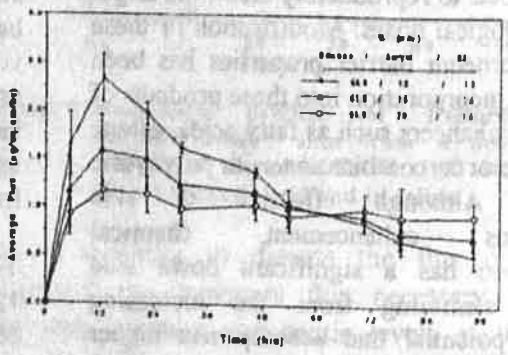

Figure 2 - Effect of Silicone to Acrylic Ratio on Estradiol Flux

Conclusion

Alteration of thermodynamic driving force in a drug-in-adhesive transdermal drug delivery system by manipulation of pressure sensitive adhesive ratios in a blend of these, specifically silicone and acrylic psa's, can have a substantial effect on the rate and extent of skin permeation for selected molecular entities. By adjusting the ratio of these, the formulator is afforded a cost-effective alternative to permeation enhancement without the deleterious effects on the physical and wear properties of the product which result from addition of large amounts of drug or surfactant-like channel enhancers.

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