

## ABSTRACT

In-vitro permeation studies were performed to investigate the feasibility of utilizing acrylic pressure sensitive adhesives (PSAs), which are comprised of two varying monomer ratios, to control the permeation rate and delivery profile of hormones from drug-in-adhesive transdermal drug delivery systems (TDDSs). The monomers selected for the acrylic PSA composition varied in their associated  $T_g$ , and are referred to as either soft (< -10°C) or hard (> -5°C) monomers. The permeation studies were performed with TDDSs consisting of drug, acrylic PSA, silicone PSA, co-solvent(s) and polyvinylpyrrolidone (PVP) [1] [2]. The results of the studies conducted were both surprising and unexpected, but correlative to previous in-vitro studies conducted with d-Amphetamine Base [3], which utilized similar acrylic monomers comprising backing film layers. The results indicate manipulation of the permeation rate and delivery profile was determined to be induced by the acrylic PSA monomer ratios, as historically seen by manipulation of the ratio between the acrylic PSA and silicone PSA concentrations in the drug-in-adhesive matrix. Finally, drug solubility in the drug-in-adhesive matrix was also noted to be influenced by the varying monomer ratios of the acrylic PSAs.

## I. PURPOSE

This investigation was initiated to establish formulary parameters for the delivery of hormones from TDDSs, which could then be utilized as a foundation for initiating future formulation development of other drugs in TDDSs. The parameters to be explored were drug permeation rate and delivery profile, as well as solubility, for a single drug-in-adhesive matrix. The hormone drug selected for incorporation into each drug-in-adhesive matrix was either an Estrogen, Progesterin or Androgen. All in-vitro permeation studies were conducted without a control TDDS, as that the outcome of each experiment was strictly dependent on the monomeric composition of each acrylic PSA utilized for the particular study. Although the three parameters previously mentioned deal strictly with the individual drug, it was theorized the outcome of these studies would help define the future formulary work for similar and dissimilar active ingredients.

## II. EXPERIMENTAL METHODS

### A. Formulations

#### Drug Permeation / Profile : Study 1

Three non-functional / non-reactive acrylic PSAs, differing only in their monomer ratios, were formulated into a drug-in-adhesive matrix to determine which acrylic PSA controlled the permeation rate and delivery profile of Estrogen released from the TDDSs. The drug concentration was held at 2% while the silicone PSA to acrylic PSA ratio was 3:1 for the drug-in-adhesive matrix. The drug-in-adhesive matrix also included a unsaturated fatty alcohol and PVP at 6% and 10%, respectively. The dried drug-in-adhesive matrices had a coat weight of 10mg/cm<sup>2</sup>.

#### Drug Permeation / Profile : Study 2

Three non-functional / non-reactive acrylic PSAs, differing only in their monomer ratios, were formulated into a drug-in-adhesive matrix to determine which acrylic PSA controlled the permeation rate and delivery profile of Progesterin released from the TDDSs. The drug concentration was held at 2% while the silicone PSA to acrylic PSA ratio was 3:1 for the drug-in-adhesive matrix. The drug-in-adhesive matrix also included a unsaturated fatty alcohol and PVP at 6% and 10%, respectively. The dried drug-in-adhesive matrices had coat weights of 10mg/cm<sup>2</sup>.

#### Drug Permeation / Profile : Study 3

Two non-functional / non-reactive acrylic PSAs, differing only in their monomer ratios, were formulated into a drug-in-adhesive matrix to determine which acrylic PSA controlled the permeation rate and delivery profile of Androgen released from the TDDSs. The drug concentration was held at 2%, while the silicone PSA and acrylic PSA ratio was 4:3 for the drug-in adhesive matrix. Each drug-in-adhesive matrix also included an unsaturated fatty alcohol, a dihydric alcohol and PVP at 6%, 8% and 10%, respectively. The dried drug in-adhesive matrices had coat weights of 10mg/cm<sup>2</sup>.

### B. In-Vitro Permeation Studies

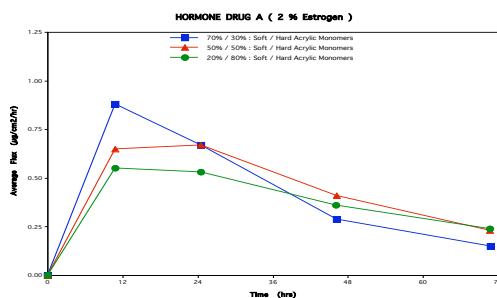
Determination of the permeation properties of the described formulations were conducted on a modified Franz Diffusion Cell through a disc of stratum corneum obtained from human cadaver skin. The formulations were die punched, mounted on the disc, and placed on the cell, which contained an isotonic saline solution. The cells were stored at 32°C for the duration of each permeation study while having the solution stirred at a constant rate of approximately 300 rpm. Samples of the solution were taken during the course of each study (approximately 72 hours) to determine the permeation characteristics for each formulation. The drug concentrations in each cell were determined by HPLC. Finally, all formulations were run with a population of n=5 for each permeation study.

## III. DISCUSSION OF RESULTS

### A. Drug Permeation / Profile : Study 1

Figure 1 illustrates the graphical representation of the results for the three non-functional/non-reactive acrylic PSAs incorporated into the drug-in-adhesive TDDSs and their effect on the in-vitro delivery of an Estrogen drug. The three acrylic PSAs were comprised of polymerized hard and soft non-functional monomers in ratios of 3:7, 1:1 and 4:1. It was surmised that no effect should have been noted in the delivery profiles between three acrylic PSAs utilized in the TDDSs based on their non-reactive properties and total solubility for the drug at 2% concentration. Further investigations will need to be conducted to explore the cause and effect of the "dump and die" profile caused by the higher amount of the soft acrylic monomer (70%) in the acrylic PSA composition compared to the similar results obtained from the 1:1 and 1:4 ratios of soft to hard monomers comprising the two other acrylic PSAs. Finally, future in-vitro permeation investigation will be required to determine whether the non-zero order delivery profile of all three platforms is formulary or drug concentration dependent.

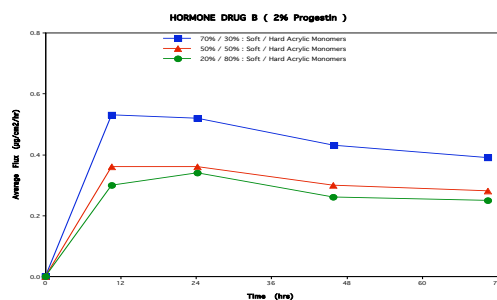
FIGURE 1



### B. Drug Permeation / Profile : Study 2

Based on the results of Study 1, Study 2 was conducted to investigate the permeation rate and delivery profile of a Progesterin drug when incorporated into the same drug-in-adhesive matrices. Figure 2 illustrates the permeation profile for the three formulations. Similar to the previous results illustrated in Study 1, the use of a higher amount of soft monomer (70%) in the acrylic PSA composition resulted in a higher permeation of the drug. Furthermore, similar in-vitro permeation profiles were obtained with either the 1:1 or 4:1 ratios of hard to soft monomers comprising the acrylic PSA composition. Finally, the results of Study 2 indicate that all three drug-in-adhesive matrices rendered near zero order delivery profiles regardless of the acrylic PSA monomeric composition.

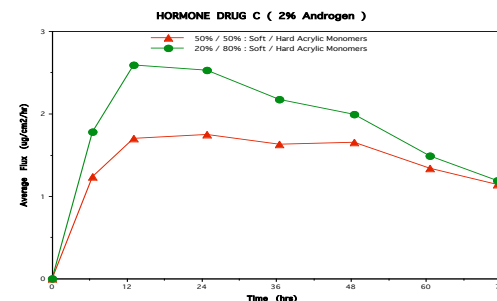
FIGURE 2



### C. Drug Permeation / Profile : Study 3

Figure 3 illustrates the permeation rate and delivery profile for variation of soft and hard monomers comprising two acrylic PSAs utilized in Studies 1 and 2, with an Androgen as the drug. The graphical presentation indicates that permeation rate of the drug increases with the higher amount of hard monomer, while the delivery profile approaches near-zero order and lower permeation as the soft monomer increases in the acrylic PSA. The results of this study are inverse of those attained from the use of Estrogen or Progesterin as the incorporated drug in the active adhesive matrix.

FIGURE 3



## IV. CONCLUSION

The results of the three in-vitro permeation studies indicate compositional manipulation of the acrylic PSA allows flexibility to attain a desired permeation rate and delivery profile for the drugs selected. Utilizing acrylic PSAs, comprised of two differing  $T_g$  monomers, enhances the experimental design with which the formulator can develop TDDSs. As previously discussed, the three parameters evaluated were drug permeation rate, delivery profile and solubility. All explored studies suggest the simple manipulation of monomeric ratios, in the composition of the acrylic PSAs, influences both the permeation rate and delivery profile of the drug from the TDDS. A visual evaluation of each studies drug to recrystallize (exposed atmospheric condition) in the drug-in-adhesive matrix indicated that i) Studies 1 and 2 TDDSs had no observed crystals after 28 days and ii) Study 3 TDDSs had crystals in the 1:1 hard to soft monomer ratio composition of the acrylic PSA, while the 4:1 ratio of hard to soft monomer ratio acrylic PSA was crystal free after 28 days. These results indicate that further evaluation is needed to determine individual drug saturation points in each acrylic PSA comprised of only hard and soft monomers. Furthermore, this same experimental design has been conducted with other drug entities, to verify and confirm applicability for TDDSs. Finally, further investigative work is being conducted to evaluate variations of two monomer acrylic PSA compositions comprised of only hard and soft monomers.

## V. REFERENCES

- [1] Miranda J. and Sablitsky S.; Solubility Parameter Based Drug Delivery System and Method for Altering Drug Saturation Concentration: US Patent 5,474,783.
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- [3] Kanios, D., Hartwig, R., Adams, R. S.; Controlled In-Vitro Permeation and Profile from Transdermal Drug Delivery Systems Utilizing Acrylic Polymer Backing Films: AAPS 2003