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Transdermal Delivery of Estradiol and Norethindrone Acetate: Effect of Vehicles and Pressure Sensitive Adhesive Matrix

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ABSTRACT – Addition of 30% propylene glycol was required to maintain sink condition in the evaluation of percutaneous absorption of estradiol and norethindrone acetate. The permeability of estradiol was higher in silicone and SIS adhesives. However, estradiol was crystallized in silicone, SIS, and SBS adhesive matrix. The permeability ratio of estradiol or norethindrone acetate from acrylic pressure sensitive adhesives varied widely depending on the functional group of the acrylic adhesives. PEO grafting to acrylic adhesive seemed to change physicochemical property of acrylic adhesive and increased the permeability of estradiol and norethindrone acetate significantly. On the contrary, highly cross-linked enhancer compatible acrylic adhesive decreased the permeability of both estradiol and norethindrone acetate. Span® 20 provided the highest enhancing effect on the permeability of both estradiol and norethindrone acetate followed by oleic acid and Crovol® EP40. The permeability of the drugs from the developed system was comparable to that from commercial Combitran®, although significantly lower amount of estradiol and norethindrone acetate were loaded in the developed system.

Key words – estradiol, norethindrone acetate, transdermal, pressure sensitive adhesive, enhancer

Extended life expectancy, more frequent use of radiotherapy and anti-cancer drugs, the main causes of menopause, have made menopause an important social issue. Most women in developed countries are expected to spend a third of their lives postmenopausally.[1] These postmenopaused women are at high risk for coronary heart disease (CHD), osteoporosis and many other symptoms. In order to prevent these diseases and other menopausal symptoms, hormone replacement therapy (HRT) has been widely used.[2-4] Epidemiological studies consistently found that estrogen showed positive effects on various risk factors for CHD and preventing osteoporosis in postmenopausal women.[5-6]

Estrogen has been mostly administered orally; however, it undergoes substantial conversion to inactive metabolites in the gastrointestinal tract and first-pass hepatic metabolism.[7] These undesired side effects can be offset by using transdermal administration which can also attenuate the fluctuating hormone levels resulting from oral therapy. The transdermal estrogen replacement therapy is also reported to have fewer risk of developing diabetes, fibrinolysis, and gastrointestinal adverse effect.[7-9] Although estrogen replacement therapy has been the effective way of preventing various postmenopausal symptoms, estrogen is known to increase the risk of developing endometrial hyperplasia and cancer.[10] The same report claimed that continuous administration of progestin was required to reduce the risk of cancer development.

Despite various advantages of transdermal delivery system, drugs used in transdermal delivery are often limited because of the outermost layer of the skin, stratum corneum. Although this layer is only 20-25 μm thick, it provides a very effective barrier towards penetration of the drug. To overcome this barrier property of stratum corneum and to increase the permeation of a drug across the skin, various physical and chemical methods have been used. Currently, the most widely used approach to drug permeation-enhancement across stratum corneum barrier is the use of chemical penetration enhancers.[11] In addition to the penetration enhancers, the skin permeation of estradiol could be affected by the pressure sensitive adhesives (PSA). The PSA fulfills the adhesion-to-skin function and serves as the formulation foundation. The selection of appropriate PSA matrix is important in designing transdermal drug delivery system, since it is well known that the physicochemical properties of PSA can affect significantly the flux of a drug from PSA across the skin.[12-14]

The purpose of this study was to investigate the effects of various vehicles and pressure sensitive adhesive matrices (PSA) on the percutaneous absorption of estradiol and norethindrone acetate across the hairless mouse skin to develop

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combination patch for HRT.

Experimental

Materials

17β-estradiol and norethindrone acetate were purchased from Sigma Chemical Co. (St. Louis, MO). Propylene glycol laurate (Lauroglycol®), ethoxydiglycol USP (Transcutol®) were obtained from Gatteposse Korea (Seoul, Korea). Oleyl alcohol, PEG-20 evening primrose glycerides (Crovol® EP40) and refined oleyl alcohol (Novol®) were obtained from Croda Inc. (Parsippany, NJ). Sorbitan monolaurate (Span® 20) was purchased from Aldrich Chemical Co. (Milwaukee, WI). Polyoxyethylene sorbitan monolaurate (Tween® 20) was purchased from Yakuri Pure Chemicals Co. (Osaka, Japan). Oleic acid, and isopropyl myristate (IPM) were purchased from Junsei Chemical Co. (Tokyo, Japan). Polystyrene-polybutadiene-polystyrene (SBS) and acrylic pressure sensitive adhesive solutions in organic solvents were obtained from National Starch and Chemical Company (Bridgewater, NJ). Polyisobutylene (PIB) (Vistanex LM-MH, Vistanex MML-100) were obtained from Jeil Pharm. Co. (Seoul, Korea). Polystyrene-polyisoprene-polystyrene (SIS) and silicone pressure sensitive adhesive was obtained from Shell Chemicals (Stanlow, UK) and Dow Corning (Midland, MI), respectively. Combitran® was obtained locally. All other chemicals were reagent grade or above and were used without further purification.

Preparation of adhesive matrices

SBS, silicone or acrylic adhesive solution in organic solvent mixture was mixed with 17β-estradiol and/or norethindrone acetate solution in ethyl acetate with or without enhancer according to the study protocol. In case of SIS and PIB, all components are dissolved in a mixture of chloroform and hexane. Pressure sensitive adhesive matrix was prepared by casting the above solutions on polyester release liner using a casting knife. It was set at room temperature for 20 minutes and was subsequently oven-dried at 90°C for about 20 minutes to remove the residual organic solvents. The dried film with the thickness of 50 μm was laminated onto a backing film.

Penetration studies

A flow-through diffusion cell system, the preparation of hairless mouse skins, procedure of the penetration studies, and data reduction methods have been described in an earlier study.[15] 30% of propylene glycol was added to receiver cell medium. The penetration samples were collected at predetermined time interval.

Analytical conditions

The HPLC method was used to analyze 17β-estradiol and norethindrone acetate. A reverse-phase column (Alltima C8, Alltech Ass., IL) was used. The column temperature was maintained at 30°C by a thin foil temperature controller (CH1445, Systec, MN). The flow rate was 1 ml/min. The wavelengths of UV detector for analyzing 17β-estradiol and norethindrone acetate were 200 nm and 240 nm, respectively. The composition of mobile phase was acetonitrile/water/phosphoric acid (650/350/1).

Results and Discussion

Effect of receiver cell medium

When pH 7.4 phosphate buffer was used as receiver cell medium, it was not possible to maintain sink condition due to very low aqueous solubility of norethindrone acetate and estradiol and obtained extremely low permeability of both drugs. To increase the solubility of the drugs in the receiver cell medium, 30% of propylene glycol was added to the receiver cell medium. It did not show any unusual permeation pattern after adding propylene glycol, such as unusual and abrupt increase in the permeation rate with time.

Effect of pressure sensitive adhesives on the permeation of drugs

The effect of PSA matrix on the permeation of estradiol was investigated using SBS, PIB, SIS, silicone and acrylic adhesive matrices. As shown in Figure 1, the permeability of estradiol was higher in silicone and SIS adhesives. However, estradiol crystallized in silicone adhesive matrix right after the prep-

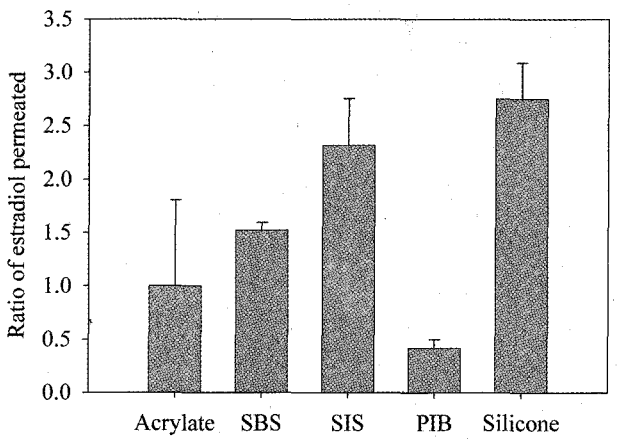

Figure 1–Effect of the types of pressure sensitive adhesive on the permeation of estradiol across hairless mouse skin. (Each bar shows the ratio of cumulative amount of estradiol permeated in 44 h using acrylic adhesive as a control).

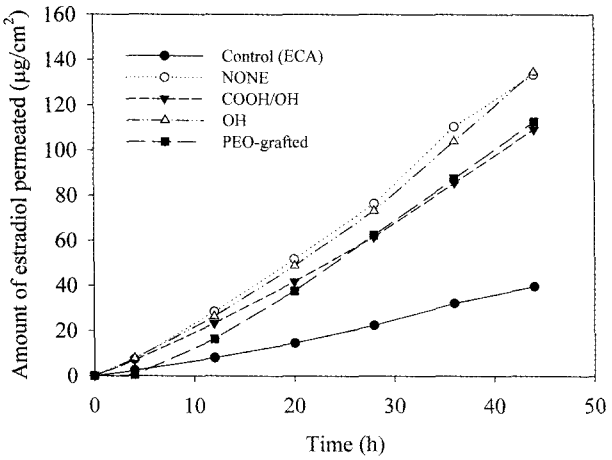

Figure 2–Effect of the functional groups of the acrylic adhesive on the permeation of estradiol.

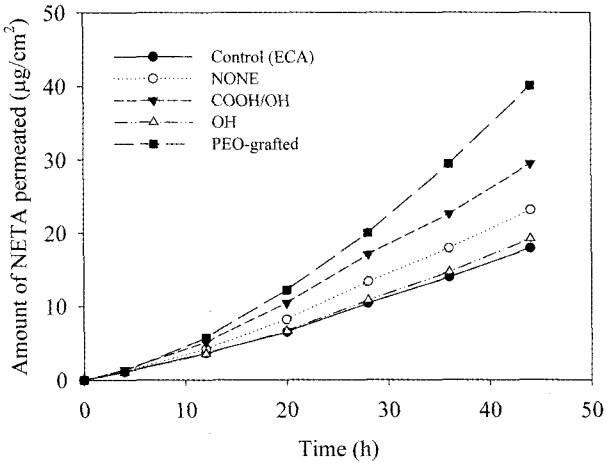

Figure 3–Effect of the functional groups of the acrylic adhesive on the permeation of norethindrone acetate (NETA).

aration, and it also crystallized in SIS and SBS adhesives after a while. It indicates that estradiol has very low solubility in silicone, SIS, and SBS PSA. Although PIB is known to be a non-polar PSA together with SIS and SBS, it provided the lowest permeability among tested adhesives. Based on crystallization characteristics and permeability across the skin, acrylic adhesives with several functional groups were chosen for further study.

Figure 2 shows the effect of various functional groups of acrylic PSA on the permeation of estradiol across the hairless mouse skin. The permeability of estradiol from acrylic pressure sensitive adhesives varied widely depending on the functional group of acrylic adhesives. These results clearly indicate that the nature of pressure sensitive adhesive, such as polarity, glass transition temperature, viscosity, degree of cross-linking, plays an important role in determining permeability of a drug.[12-14] It is interesting to note that the typical acrylic adhesives with hydroxyl functional groups, hydroxyl and carboxyl functional groups, the acrylic adhesive without functional groups, and polyethylene oxide (PEO)-grafted acrylic adhesive provided higher permeability than the highly cross-linked enhancer compatible acrylic adhesive (ECA) used as a control. The enhancers sometimes can act as a plasticizer and it may change the viscoelastic property of the adhesive matrix, causing cold flow. One of the approaches to minimize the plasticizing effect of enhancers is to cross-link the polymer chain of the adhesive. As can be seen in Figure 2, however, the highly cross-linked enhancer compatible acrylic adhesive showed fairly low permeability, indicating that cross-linking greatly reduced the permeability of estradiol.

Based on the permeability and crystallization characteristics of estradiol, acrylic adhesives were chosen for the permeability study of norethindrone acetate. Figure 3 shows the effect of various adhesive matrices on the permeation of norethindrone acetate across the hairless mouse skin. The permeability of norethindrone acetate from acrylic PSA also varied widely depending on the functional group of acrylic adhesives. It is interesting to note that the PEO-grafted acrylic adhesive showed the highest permeability of norethindrone acetate. The results indicate that PEO grafting to acrylic adhesive changed physicochemical property of acrylic adhesive and other polymer chains may also be used to modify permeation characteristics of PSA. It also suggested that modification of acrylic chain configuration is worthwhile approach to obtain better permeation profile of the drugs. The highly cross-linked enhancer compatible acrylic adhesive again showed the lowest permeability, indicating that cross-linking greatly reduced the permeability of norethindrone acetate as was the case in estradiol. Based on permeability ratio, tack and peel properties of the prepared matrix, the PEO-grafted acrylic adhesive was chosen for further study with permeation enhancers. Although acrylic adhesive with hydroxyl functional group and one without functional group provided higher permeation rate of estradiol, they failed to provide high enough permeability of norethindrone acetate.

Effect of enhancers on the permeation of drugs

One of the major obstacles to the development of transdermal delivery systems is the low permeation rate of the drugs through the skin. It is well known that chemical enhancers such as oleic acid, Transcutol® have been used to increase the delivery rate of a drug through the skin.[14,19] An appropriate

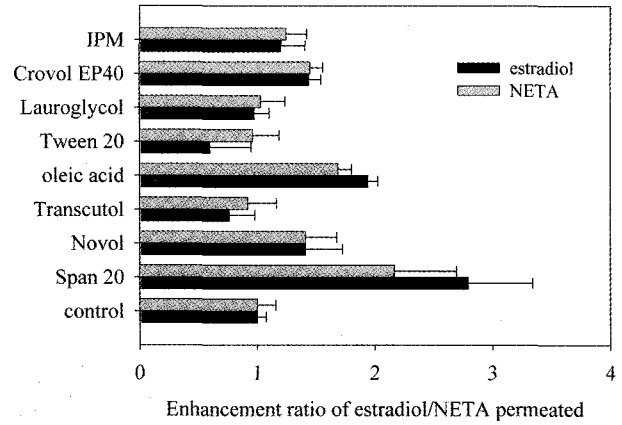

Figure 4–The effect of various enhancers on the permeation of estradiol and norethindrone acetate (NETA) across hairless mouse skin from the PEO-grafted acrylic adhesive. Each bar shows the ratio of cumulative amount of estradiol permeated in 44 h using acrylic adhesive as a control.

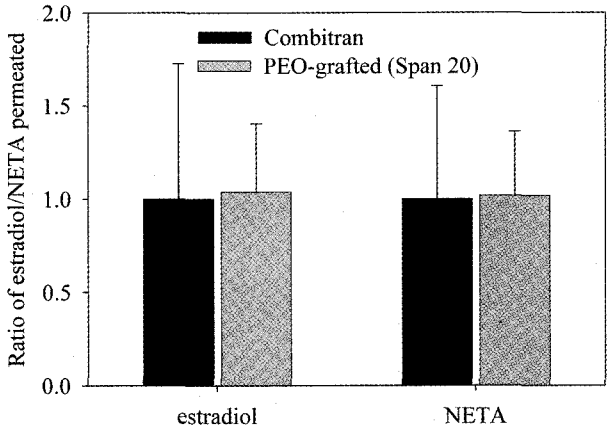

Figure 5–Comparison of the amounts of estradiol and norethindrone acetate (NETA) permeated across the hairless mouse skin from the developed system containing Span® 20 as a permeation enhancer with those from commercial Combitran®. Each bar shows the ratio of cumulative amount of estradiol permeated in 44 h using Combitran® as a control.

chemical enhancer often not only acts as a plasticizer in the adhesive, increasing the mobility of the drug in the adhesive, but also modifies the structure of the skin to ease the permeation of the drug. To further increase the permeability of estradiol and norethindrone acetate, the effect of some permeation enhancers on the permeation of estradiol and norethindrone acetate across the hairless mouse skin from PEO-grafted acrylic adhesive matrix was investigated (Figure 4). The amount of each enhancer tested was 11.8% of the weight of acrylic adhesive matrix. As can be seen in Figure 4, Span® 20 provided the highest enhancing effect on the permeability of both estradiol and norethindrone acetate followed by oleic acid and Crovol® EP40. However, the incorporation of Tween® 20, Transcutol® or Lauroglycol® into the PEO-grafted acrylic adhesive matrix had no the enhancing effect or even decreased the permeability.

Based on enhancing effect of the tested permeation enhancers, appropriate amount of estradiol (0.54%) and norethindrone acetate (2.48%) were formulated in PEO-grafted acrylic PSA including Span® 20 as a permeation enhancer. The permeability of estradiol and norethindrone acetate from the developed system was compared with those from commercial Combitran®. As can be seen in Figure 5, the permeation of the drugs from the newly developed system was similar to that from Combitran®. It should be noted, however, that the drug concentrations in our system were lower than those of Combitran®. The estradiol and norethindrone acetate content per unit area (cm^2) were 0.372 mg and 0.18 mg for Combitran®, and 0.035 mg and 0.16 mg for our system, respectively. The results confirm the superiority of the newly developed system for estradiol and norethindrone acetate.

Acknowledgments

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