Transdermal Delivery of Levonorgestrel

David R. Friend

Controlled Release and Biomedical Polymers Department, SRI International, 333 Ravenswood Avenue, Menlo Park, California 94025

I. INTRODUCTION

The transdermal route for systemic drug delivery is an accepted means for drug administration. There are a variety of advantages inherent in the transdermal route, including elimination of hepatic-first-pass effects, reduced side effects through optimization of the blood concentration-time profile, extended duration of activity, and improved patient compliance.[1] The successful introduction of several transdermal products has greatly expanded the search for drugs suitable for delivery via the transdermal route.[2] In this far-reaching search, contraceptive agents have not escaped attention. A short review article appeared in 1979, discussing the possibility of topical delivery of contraceptives.[3] While the authors of this early review concluded that delivering contraceptives transdermally would be difficult, research in transdermal delivery of contraceptives has been making steady progress.

A large number of contraceptive agents have been prepared and tested over the past 25 years. These agents are commonly administered orally in combination such that the formulation contains an estrogen and a progestin (Table I lists some typical combinations).[4] These pills are taken once a day for 21 or 22 days followed by 7 or 8 days off. Alternatively, a single entity preparation can be used continuously over the entire month (see Table I). The postcoital contraceptives (e.g., diethylstilbestrol, an estrogen) are administered 72 h postcoitus for 5 consecutive days. This review focuses on the research and development of transdermal delivery systems for the progestinal contraceptive agent levonorgestrel (LN). There also has been interest in developing combination transdermal delivery systems; some reference to these systems

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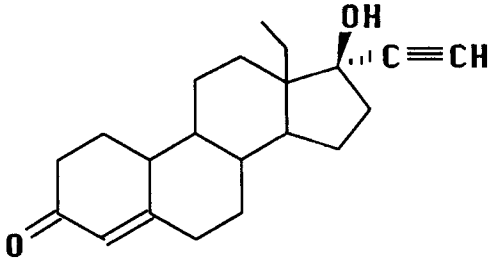
Table I
Composition of Some Typical Oral Contraceptives

Estrogen	Progestin
Combinations[a]	
Ethinyl estradiol	Norethindrone
Ethinyl estradiol	Norgestrel
Mestranol	Norethindrone
Ethinyl estradiol	Ethynodiol
Ethinyl estradiol	Norethindrone diacetate
Mestranol	Norethynodrel
Mestranol	Ethynodiol diacetate
Single-entity preparations[b]	
—	Norethindrone
—	Norgestrel

Source: From ref. 4.
[a]Combination tablets are taken 21 or 22 days and off for 7 or 8 days.
[b]Single entity preparations are taken continuously (no off period).

will be made throughout the review when relevant to the discussion of transdermal LN.



LEVONORGESTREL (LN)

The factors involved in developing a transdermal delivery system for LN (or any drug) include a consideration of skin structure, the permeability of the skin, agents that can alter the permeability of the skin (penetration enhancers), physicochemical characteristics of the drug, biological factors, device design, and in vitro and in vivo testing. Cutaneous side effects of transdermal drug delivery must also be considered. This review covers these factors as they relate specifically to delivery of LN via the transcutaneous route.

II. PERCUTANEOUS ABSORPTION

Percutaneous absorption of drugs and other chemicals has been studied in great detail for many years. Even so, a complete understanding of the factors

David R. Friend *received the Ph.D. degree from the University of California at Berkeley in 1983 while developing a colon-specific drug delivery system. He is currently a senior scientist in the Controlled Release and Biomedical Polymers Department at SRI International. His current research interests include transcutaneous drug delivery, oral drug delivery, and microencapsulation technology. He continues to study the use of prodrugs in treatment of inflammatory bowel disease as well as studying the mechanism of action of skin penetration enhancers.*

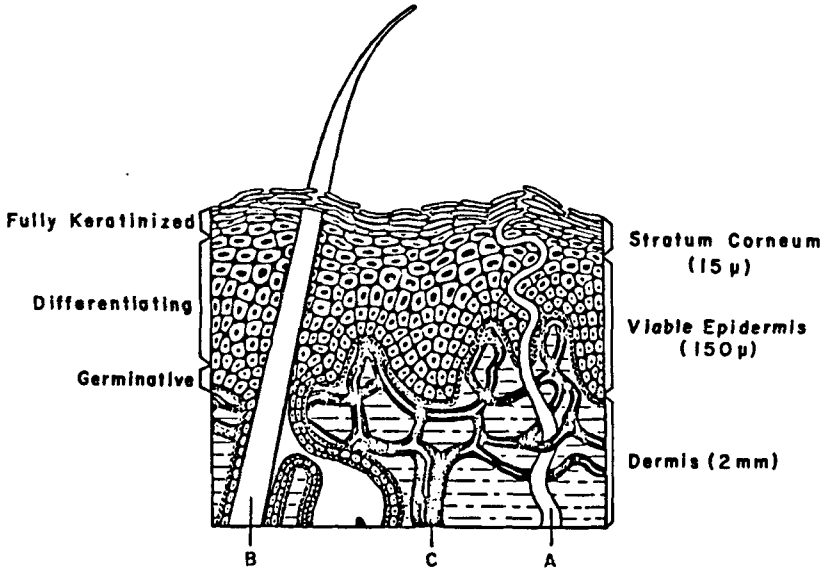


Figure 1. Schematic representation of the skin.

governing the passage of agents into and through the skin is still lacking. Drugs have been applied on the skin for treatment of a wide variety of disorders. A number of available texts present the various aspects of percutaneous absorption of drugs.[5–12] In order to better understand the limitations the human body naturally presents to those attempting to deliver drugs through the skin, the structure and function of skin and methods used to study the percutaneous absorption of drugs is reviewed briefly.

A. Skin Structure

Percutaneous absorption involves the passive diffusion of drugs across the skin. While drugs have been applied to the skin in many forms (ointments, pastes, plasters, and complex inunctions) in both Western and Eastern medicine for many years,[13,14] very little was known about diffusion of drugs through the skin. It was known by the end of the last century that lipid-soluble agents appeared to permeate the skin more rapidly than did water-soluble drugs and that the free-base form of certain biologically active agents permeated through skin while the salt form of the same agent did not. It was not until the 1950s and 1960s that the understanding of percutaneous absorption gained a firmer foothold. The past 20 years have seen the emergence of some general principles regarding drug absorption through the skin, although there is by no means consensus on the precise descriptions of these processes nor is there even a widely held description of the structure/function relationship for skin.

A general schematic representation of skin is shown in Figure 1. The surface of skin, known as the stratum corneum or the horny layer, is a dead layer of keratinized cells. It consists of 15 to 25 layers of essentially nonmetabolic cells, known as corneocytes.[15] The average thickness of the stratum corneum varies

from region to region, but is usually about 10 μm.[16] The interior of the corneocytes is densely packed with keratin fibrils.[17] The overall protein content of the stratum corneum varies from 75 to 85%, most of which is intracellular keratin. The bulk of intercellular spaces are filled with a variety of lipids. Detailed studies by Elias and Downing and Wertz, as well others, clearly indicate the importance of stratum corneum lipids in controlling the penetration of materials into the body as well as the outward movement of water.[18–27] The lipids are organized in bilayer laminate structures, which are apparently asymmetric in nature.[28] These lipids originate from the membrane-coating granules which extrude into the intercellular spaces in the upper portion of the granular layer during the process of differentiation of the epidermal keratinocyte.[29–34] Presumably, the cell membranes of the corneocytes are intact and the cells are held together by desmosomes, providing a framework for the intractable network of the stratum corneum.[35]

Traversing the stratum corneum are several other structures: hair follicles and eccrine glands. The role of hair follicles and eccrine glands in percutaneous absorption has sparked considerable debate over the past 20 years. It is now believed that for the passive diffusion of drugs across skin, these shunt (or transappendageal) routes are insignificant in most circumstances.[2]

The layer below the stratum corneum is the viable epidermis, which is a mass of living cells with no direct blood supply. The viable epidermis continually supplies the stratum corneum with new cells as corneocytes are sloughed off from the surface of the skin (desquamation). The viable epidermis is essentially a hydrogel-like proteinaceous material of variable thickness. Most of the body surface has an average epidermal thickness of 40–50 μm.[36] The microcirculation present in the skin does not begin until an approximate depth of 150–200 μm from the skin surface in what is known as the dermis or corium.[37] There is an appreciable extracellular space in the viable tissues of the epidermis. It has been estimated that the intercellular space occupies 15–18% of the total epidermal volume.[38]

The dermis is essentially an aqueous phase containing an extracellular matrix consisting of collagen fibers and elastin embedded in mucopolysaccharides. A variety of cells (fibroblasts, fibrocytes, and histiocytes) are embedded in the extracellular matrix. The capillaries extend into the upper dermis to within about 20–40 μm of the epidermis; nerves also terminate under the epidermis.[39] The dermis rests on a network of fat cells known as the subcutis, which represents a separating layer between the skin and the musculature.

B. Skin Permeability

The diffusion of drugs through the skin is a complicated process that to date has not been fully understood. The problem associated with an accurate description of skin permeation is the pathway a drug molecule follows as it passes through the diverse array of structures and chemical environments on its way to the vasculature. It is assumed that for most drugs the main resistance to skin penetration is provided by movement through the bulk of the stratum corneum, with the shunt routes playing an inconsequential role. In addition to the various components of the skin, the physicochemical prop-

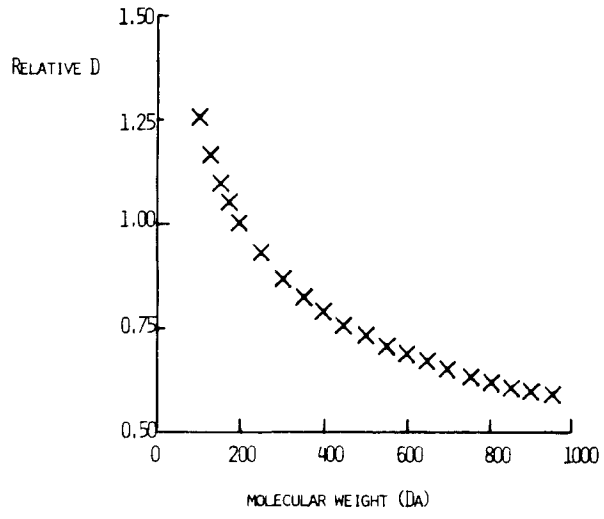


Figure 2. Idealized dependence of solute diffusion coefficient (D) upon molecular weight (M) according to Eq. (1). The ordinate expresses a relative D, normalized with respect to that of a molecule of 200 daltons. From Ref. 40.

erties of the drug can have a profound influence in the rate at which that drug diffuses across the skin.

The movement of a drug from a transdermal device or other topically applied dosage form into the vasculature can be described as a series of events:[40]

1. Drug transport within the delivery system to the device/skin interface
2. Partitioning of drug from the delivery system into the stratum corneum
3. Diffusion across the stratum corneum
4. Drug partitioning from the stratum corneum into the viable tissues
5. Transport through the viable tissues
6. Drug uptake by the microvasculature

Using such a description, it can be seen that percutaneous absorption involves the diffusion and partitioning of the drug from the device into and through the skin.

Diffusion of chemical substances through a material such as skin is governed primarily by the substance's size and by the level of interaction with the media through which diffusion is taking place.[40] Most drugs, including those currently used in contraception, are under 1000 MW. The effect of size on the diffusion in liquids can be viewed in terms of the Stokes–Einstein equation:

$$D = C M^{-1/3} \tag{1}$$

where D is the diffusion coefficient, M is the molecular weight, and C is a constant. Although not entirely accurate for diffusion through skin, this equation implies that molecular weight plays a minor role in influencing D as is shown in Figure 2. Significant deviations can occur in diffusion coefficients

Table II
In Vitro Skin Permeability Coefficients (P) of Two Homologous Groups of Steroids

Steroid	Hydroxyl Groups	Carbonyl Groups	P (cm/h × 10^6)
Progesterone	0	2	1500
Hydroxyprogesterone	1	2	600
Cortexone	1	2	450
Cortexolone	2	2	75
Cortisone	2	3	10
Cortisol	3	2	3
Estrone	1	1	3600
Estradiol	2	0	300
Estriol	3	0	40

Source: From Ref. 41.

with drugs of identical molecular weight as indicated by numerous examples in the literature.[6] This phenomenon is shown by data collected by Scheuplein et al.[41] in which the permeability coefficients (see below for definition) of a series of closely related steroids demonstrated a wide range of values (see Table II). It appears that increasing polarity of a molecule leads to significant reduction in skin permeation, perhaps through increased hydrogen bonding between polar groups on the drug and on skin substituents.

It should be noted that evaluation of D values from data derived from permeability experiments assumes a specific path length through the stratum corneum. It is not possible to account for differences in fractional area available for permeation and for tortuosity of the route taken by a particular drug molecule. Thus the values commonly referred to are apparent D values which can be useful for making relative comparisons but are probably not very precise in nature, particularly when derived from in vitro permeability experiments.[2,40]

The second important process in the percutaneous absorption of drugs is partitioning. Two partitioning steps must be considered: partitioning between the formulation into the stratum corneum and between the stratum corneum and the viable epidermis. The drug should have some affinity for the stratum corneum relative to the vehicle or transdermal device and it must also possess sufficient solubility in the aqueous environment of the viable epidermis to allow the drug to reach the microvasculature in the dermis. There is reasonably good correlation between permeability of human skin and various organic solvent/buffer partition coefficients. Drugs that partition disproportionately between an aqueous phase or nonpolar phase tend to be less skin-permeable than drugs that partition into both phases. Common organic solvents used in partitioning experiments are heptane,[42] 1-octanol,[43] benzene,[44] ether,[45] isopropyl myristate (IPM),[46] and mineral oil.[47] The relationship of the permeability coefficients and mineral oil/water partition coefficients for a group of drugs is shown in Figure 3.

Guy and Hadgraft have developed a kinetic model to describe the delivery of drugs across skin.[48–53] Such models can be used to observe the effects of changing various parameters on the delivery of a drug into plasma over time.

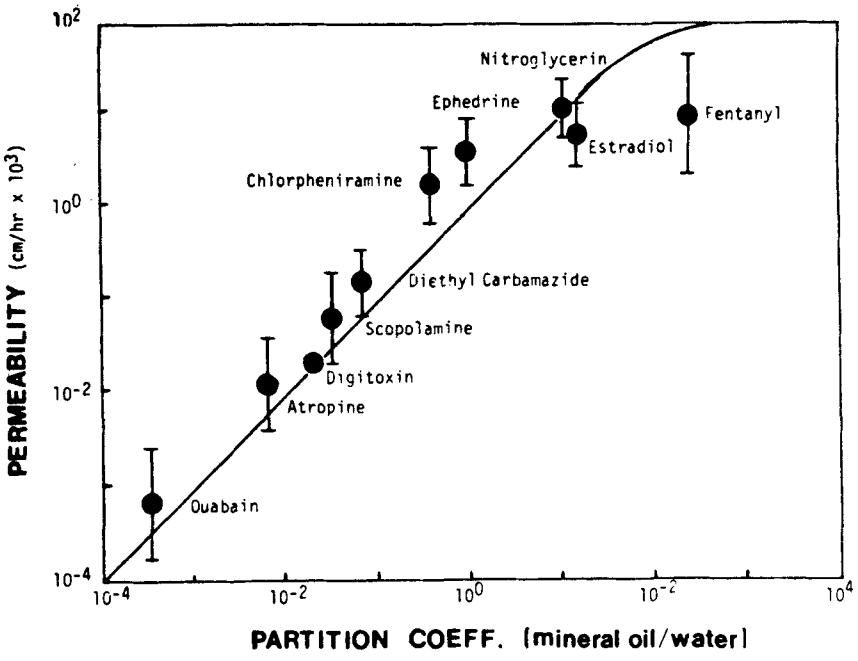


Figure 3. Variation of transdermal permeability with mineral oil/water partition coefficient. From Ref. 47.

For instance, it is possible to demonstrate that the requirements for absorption of a lipophilic drug (and promotion of the absorption of such a compound) are different than for a hydrophilic drug. In fact, if the kinetics of the transport step between the stratum corneum to the viable epidermis is relatively slow (less favorable), then the interfacial transfer of the drug from the horny layer into the viable tissues can be the rate-limiting step in absorption of that drug. Such a consideration is important for contraceptive drugs, and LN in particular, as they are relatively hydrophobic.

A number of standard relationships are used to describe the permeability of drugs through skin. While the basis for these relationships can be very complex, it has been found that the amount of drug permeating through skin can be described in a reasonably straightforward manner. The amount of drug appearing in the receptor phase when using Franz-type diffusion cells with an infinite dose can be described with the following relationship:

$$M_t = (K_m C_s) \cdot \left[D_s t/\delta - \delta/6 - 2\delta/\pi^2 \cdot \sum_{i=1}^{\infty} (-1)^n/n^2 \cdot e(-D\, n^2\pi^2 t/\delta^2) \right] \quad (2)$$

where M_t is the amount of drug passing through a unit area of the skin in time t from a drug saturated delivery system or reservoir at concentration C_s. K_m is the skin/vehicle partition coefficient, D_s is diffusion coefficient, and δ is the skin thickness. Again, it should be stated that D_s is the apparent diffusion

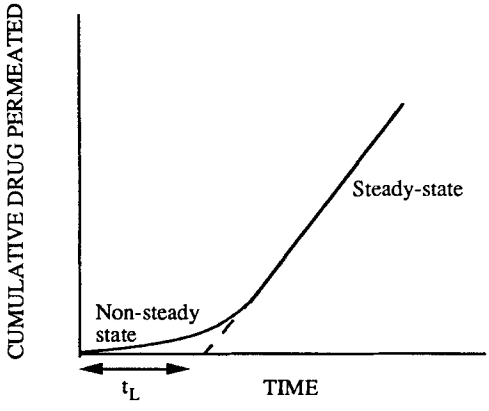


Figure 4. Schematic representation of the standard permeation profile (amount of drug permeated through the skin as a function of time), which is obtained using a two-compartment diffusion cell. The intercept of the steady state line on the time axis is the lag time.

coefficient and that the values as used here represent the net properties of the various strata of the skin. Using Eq. (2), it is possible to schematically represent the appearance of drug in the receptor fluid of in vitro permeation cells (Fig. 4). At first, the permeation of drug through skin gradually increases until a steady state condition is reached where $t \rightarrow \infty$ so that Eq. (2) can be rewritten as:

$$M_t = K_m D_s C_s / \delta \, (t - \delta^2/6D_s) \tag{3}$$

which describes the amount of drug penetrating per unit time under steady state conditions (the linear portion of the curve in Fig. 4). The steady state flux is obtained from Eq. (3) by differentiating M_t with respect to t:

$$dM_t/dt = K_m D_s C_s / \delta. \tag{4}$$

The lag time t_L can be used to estimate D_s by extrapolating the linear portion of the cumulative penetration curve (Fig. 4) to the axis where drug release = 0, such that:

$$t_L = \delta^2/6D_s \tag{5}$$

where D_s is an apparent value because of assumptions concerning the thickness of the skin and the effective permeation pathway through the skin.

It is quite common to express $K_m D_s/\delta$ of Eq. (4) as a single term called the permeability coefficient P such that:

$$dM_t/dt = PC_s. \tag{6}$$

Using a composite term such as a permeability coefficient, it is easier to describe the relative effects of changes in a formulation as it is difficult to separate out changes in diffusivity, partitioning, and the effective path length.

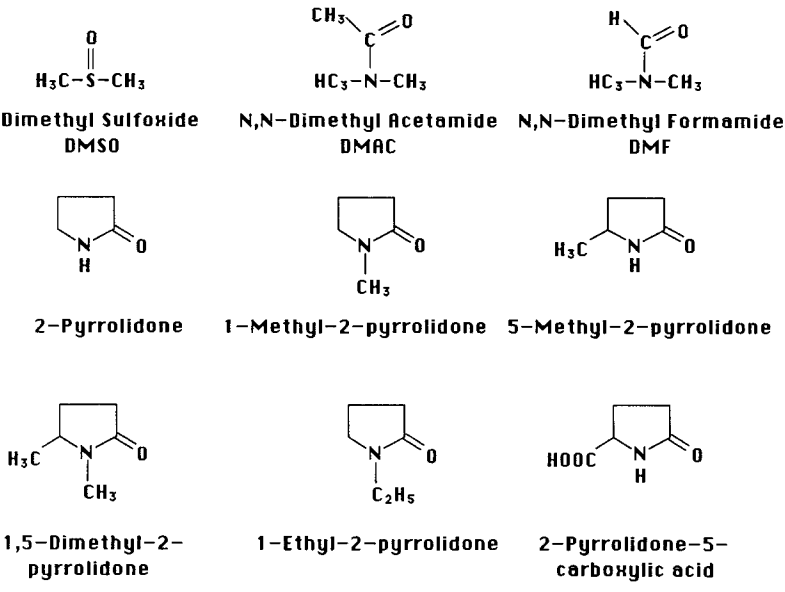


Figure 5. Structures of various chemical penetration enhancers.

It should also be noted that the driving force for diffusion across skin is the thermodynamic activity of the drug in the vehicle or transdermal device. Under most circumstances, the maximum driving force is obtained from saturated solutions or suspensions. At saturation, the drug has unit activity in the vehicle which means that in the absence of specific vehicle/skin interactions, the flux of a drug from saturated vehicles, regardless of the solubility in the vehicles, will be equivalent.[54] This principle can be used to evaluate the penetration-enhancing effect of various vehicles by using drug-saturated solutions of different vehicles and observing differences in flux. This assumes that dissolution of the drug from the suspended crystals is not rate limiting; in other words, diffusion through the skin is rate-limiting, which is usually the case.

C. Penetration Enhancers

The use of chemicals or other perturbations to increase the diffusion of drugs through human skin has been studied in some detail.[55–60] A large number of reports have been published describing the effect of various chemicals on the percutaneous absorption of drugs. However, far fewer studies have been conducted on the mechanism of action of chemical enhancers. Figures 5 and 6 show the structure of a number of the more well known enhancers. These chemicals include dimethyl sulfoxide (DMSO), decylmethyl sulfoxide, dimethyl acetamide, and dimethyl formamide; various pyrrolidones, dimethyl-*m*-toluamide, urea, ethyl acetate (EtAc), 1-dodecylazacycloheptan-2-one (laurocapram[1]), oleic acid, and ethanol (EtOH). Despite the emer-

[1]Available as Azone® from Nelson Research, Irvine, CA.

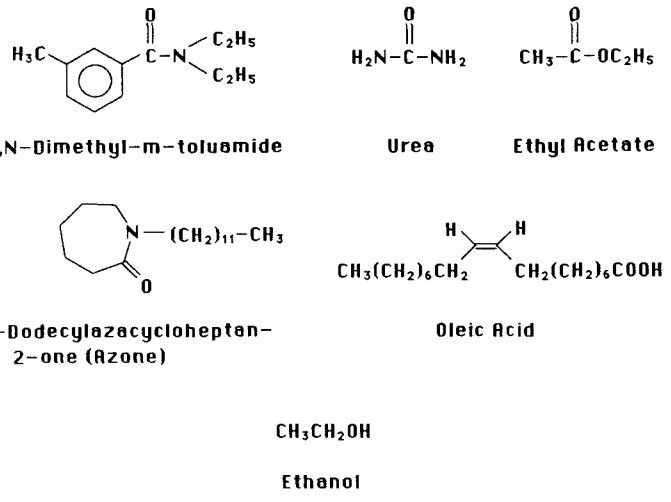


Figure 6. Structures of various chemical penetration enhancers.

gence (or re-emergence) of iontophoresis[61–64] and phonophoresis[65–67] as means to enhance the percutaneous absorption of drugs, most effort to date has focused on chemical enhancers.

The mechanism by which enhancers function is still largely unknown although application of physical techniques[68] such as differential scanning calorimetry, infrared spectroscopy (including attenuated total reflectance methods), transepidermal water loss measurements, electron spin resonance spectroscopy, and x-ray diffraction are helping to increase our understanding. Enhancers can increase flux in essentially three ways: (1) by reducing the diffusional resistance of the skin, (2) by enhancing partitioning of the drug into the skin, or (3) a combination of the two. It is not within the scope of this article to discuss the current status of chemical enhancers except where relevant to the delivery of contraceptive agents. Of more relevance to the design and performance of transdermal dosage forms is the acceptability and safety of chemical enhancers.

The use of chemicals in transdermal devices very often leads to irritation which is usually enhanced by the occlusive nature of the system. An irritant is essentially any agent, physical or chemical, that is capable of producing cell damage if applied for sufficient time and in sufficient concentration.[69] However, cell damage is not always a prerequisite for irritancy to develop[70–72]; furthermore, there is a current need to improve or refine the definition of irritant.[70] More will be said about irritation in a later section, using specific examples. Other areas of concern with respect to cutaneous side effects are contact allergy, contact urticaria, photoirritancy, and photoallergy.

III. PERCUTANEOUS ABSORPTION OF LEVONOGESTREL

Levonorgestrel is a potent progestational steroid capable of suppressing ovulation at a delivery rate as low as 20 μg/day from vaginal devices.[73] Orally, LN is effective when administered at 75 μg/day.[4] A low daily dose requirement is one of the biological criteria that must be considered prior to initiating a

research program in transdermal drug delivery. A complete list of the biological criteria used to evaluate transdermal candidates follows.[74]

1. The drug must be potent, requiring a parenteral daily dose of milligrams or less.
2. Drugs subject to extensive hepatic first-pass effects on oral dosing may benefit by transdermal delivery.
3. Drugs with short (rather than long) biological half-lives are most appropriate (this is true for essentially all sustained or prolonged release dosage forms).
4. The drug should not elicit a major cutaneous irritant or allergic response. It is possible that a transdermal dosage form lead to a mild irritant response, including sensitization.
5. Due to the constant delivery profile obtained from most transdermal dosage forms, it is important to monitor the possible induction of tolerance, as has been suggested to occur with transdermal nitroglycerin dosage forms.
6. The drug should not be subject to cutaneous metabolism within the viable epidermis or to degradation by surface microorganisms.

The physicochemical criteria for drug selection are essentially the molecular weight of the drug and specific drug-skin interactions as they relate to the drug's ability to diffuse through the skin and the skin/vehicle partition coefficient (and in some cases the stratum corneum/viable epidermis partition coefficient) (see Sect. II. B).

A. In Vitro Skin Permeability of Levonorgestrel

The goal of in vitro permeability experiments is to determine if the drug under consideration can be formulated to allow sufficient amounts of drug to reach the systemic circulation over an acceptable period of time. Therefore, some criteria must be used to evaluate the data collected in such experiments. In the case of LN, the target delivery rate is about 35 μg/day, or about twice the minimum rate known to prevent estrus in women. In addition to increasing the permeation rate through skin, the active surface area of the patch can be increased to deliver more drug. In the case of contraception, it is desirable to work toward as small a patch as possible. This would permit preparation of a discrete delivery system that would ideally have high user acceptance. These devices will be worn chronically where patient compliance is essential. The patch size used as a guideline in evaluating various formulations was 5 cm^2. This would require a delivery rate of LN of 0.3 $\mu g/cm^2$ h in vivo.

Until recently, there was little information regarding the skin permeation characteristics of LN. An early study did investigate the percutaneous absorption of *d*-norgestrel (levonorgestrel) in vivo in hairless mice and guinea pigs (see Sect. III B).

Experiments conducted using full-thickness rat skin indicated that LN possessed insufficient skin permeability to permit formulation without a penetration enhancer. Therefore, a series of chemical solvents were investigated for their ability to enhance the percutaneous absorption of LN. The enhancer of note investigated was ethanol (EtOH), because of its known penetration-

Table III
Steady-State Flux of LN Through Rat Skin From EtOH/H_2O

Donor Phase	t_L (h)	J_{LN} ($\mu g/cm^2$ h)
H_2O	22	0.01
EtOH/H_2O (2:8) (v/v)	20	0.02
EtOH/H_2O (6:4) (v/v)	20	0.06
EtOH/H_2O (4:6) (v/v)	19	0.06
EtOH/H_2O (2:8) (v/v)	20	0.06
EtOH	21	0.06

Source: From ref. 80.

enhancing properties when used with a number of drugs, including 17β-estradiol.[75–79] For example, the flux of estradiol through human skin in vitro from an EtOH/H_2O (7:3) donor solution saturated with estradiol was about 20-fold greater than from a donor of H_2O only (saturated with estradiol).[79]

Mixtures of EtOH and H_2O were tested as penetration-enhancing solvents with rat skin.[80] The results (t_L and J_{LN}) are shown in Table III. It can be seen that the flux of LN (J_{LN}) reached a maximum at a 0.4 volume fraction of EtOH in H_2O. J_{LN} was measured from a neat EtOH donor phase (saturated with LN) with human cadaver skin to gain some insight into the permeability of human skin. J_{LN} was found to 3 to 4 times less permeable than in rat skin; in human cadaver skin t_L also had a much greater effect.[80] This result was not unexpected as human skin is generally less permeable than is rodent skin.[81–85] J_{LN} (0.02 $\mu g/cm^2$ h) through human skin from EtOH was too low by about tenfold to prepare a 5-cm^2 device.

Because EtOH was relatively ineffectual as an enhancer for LN, a variety of other alkanols were investigated for their ability to enhance transdermal delivery of LN.[80] Using the relationship observed between rat skin and human cadaver skin with EtOH as an enhancer, a target J_{LN} of 1.0 $\mu g/cm^2$ h was used as a guideline for all the additional work with rat skin. When a series of alkanols from methanol to 1-octanol was tested as enhancers, 1-butanol gave a J_{LN} of 0.75 $\mu g/cm^2$ h at steady state; the other alkanols with longer and shorter alkyl chains were less effective at enhancing J_{LN}. While J_{LN} was enhanced considerably by 1-butanol, it was not pursued further due to potential problems of skin irritation and systemic toxicity.

Another potential penetration enhancer tested for its ability to increase J_{LN} was ethyl acetate (EtAc). This common organic solvent was found to increase J_{LN} significantly relative to EtOH.[86] The results obtained using EtAc, EtOH, and H_2O as enhancers with excised rat skin are shown in Figure 7. J_{LN} at steady state was about 1.0 $\mu g/cm^2$ h (about 17 times greater than from neat EtOH and about 100 greater than from H_2O). These in vitro permeability studies were extended to include hairless mouse skin, hairless guinea pig skin, and human cadaver skin.[87] The results of these experiments are summarized in Table IV. As expected, there was considerable variation in J_{LN}, depending on the skin type used. Hairless mouse skin was more permeable than the other skins. In general, all the rodent skins were more permeable than human skin under the influence of EtAc and EtOH. The flux of EtAc (J_{EtAc}) and EtOH (J_{EtOH}) were also both much higher in the rodent skins than in human skin. When the cumulative amount of LN delivered through the

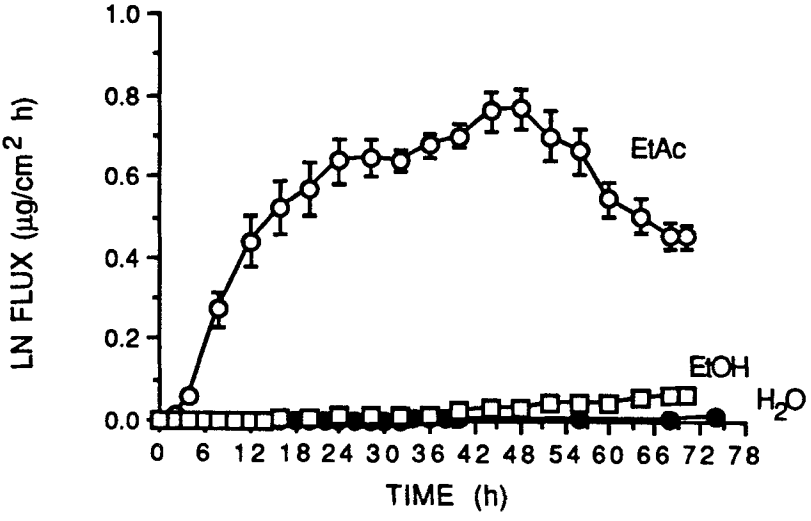


Figure 7. Transdermal flux of LN through rat skin from saturated solution of EtAc, EtOH, and H_2O. Error bars indicate mean standard errors. From Ref. 86.

Table IV
Lag Times and Steady-State Fluxes of Levonorgestrel, Ethyl Acetate, and Ethanol Through Rat Skin, Hairless Mouse Skin, Hairless Guinea Pig Skin, and Human Skin

		Lag Time (h)			Steady-state Flux		
Skin Type	Vehicle (vol %)	LN	EtAc	EtOH	LN (μg/cm² h)	EtAc (mg/cm² h)	EtOH (mg/em² h)
Rat	EtOH	16	NA[a]	20	0.06	NA	ND[c]
	EtAc/EtOH (0.3:0.7)	16	16	22	1.2	3	7
	EtAc/EtOH (0.5:0.5)	20	12	14	3.5	5	9
	EtAc/EtOH (0.7:0.3)	20	8	12	3.0	10	9
	EtAc	14	8	NA	1.0	12	NA
HM	EtAc/EtOH (0.3:0.7)	6[b]	6	8	4.4[b]	8	20
	EtAc/EtOH (0.5:0.5)	4[b]	6	4	10	13	16
	EtAc/EtOH (0.7:0.3)	6[b]	6	8	4.1[b]	18	17
HGP	EtAc/EtOH (0.3:0.7)	20[b]	20	22[b]	1.1	1	4[b]
	EtAc/EtOH (0.5:0.5)	12	10	12	1.3	3	4
	EtAc/EtOH (0.7:0.3)	12	8	16	2.3	7	11
Human	EtOH	32	NA	12	0.03	NA	1.5
	EtAc/EtOH (0.3:0.7)	22	18	12	0.08	0.3	1.1
	EtAc/EtOH (0.5:0.5)	22	20	12	0.12	0.5	1.0
	EtAc/EtOH (0.7:0.3)	22	20	12	0.12	0.5	1.1
	EtAc	26	24	NA	0.20	0.5	NA
	EtAc (PEG 400)	26	20	NA	0.25	0.5	NA

[a]NA = not applicable.
[b]Steady-state conditions were not reached.
[c]ND = not determined.
Source: From Ref. 87.

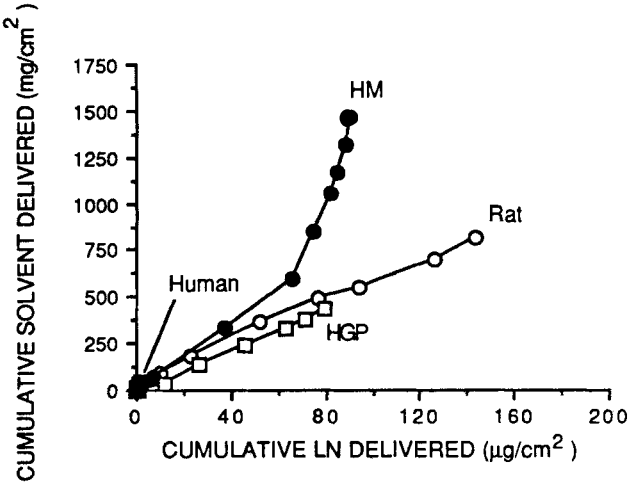


Figure 8 Relationship between cumulative LN delivered and cumulative total solvent delivered through rat skin, hairless mouse (HM) skin, hairless guinea pig (HGP) skin, and human skin using a donor vehicle of EtAc/EtOH (0.7:0.3).

various skins is plotted against the cumulative amount of total solvent delivered, a linear correlation is seen. This is shown in Figure 8 for the EtAc/EtOH (0.7:0.3) donor vehicle. There is a deviation from this relationship for the hairless mouse skin that cannot be easily explained. With the EtAc/EtOH enhancer vehicles, there was a significant drop in flux over time that could not be changed by replacement of the donor vehicle with fresh material.

From the data in Table IV, it can be seen that J_{LN} through human skin was much lower than was observed through the rodent skins. At steady state, J_{LN} was about 0.2 μg/cm^2 h. The target flux of LN through human skin was about 0.3 μg/cm^2 h; therefore, using EtAc as an enhancer, the device would need to be 7.5 cm^2 to deliver adequate amounts of LN. There is considerable variation in drug absorption depending on the body site as well as wide intersubject variation. Thus, the values and guidelines suggested herein are only approximations. Nonetheless, it appears that EtAc can be used to deliver LN in sufficient amounts from a relatively small patch. Further discussions regarding the use of EtAc in a transdermal device as well as potential skin irritation caused by EtAc are found later in this review.

The effect of EtAc on the percutaneous absorption of LN has been investigated in more detail.[88] The hairless mouse data presented in Table IV was supplemented with additional in vitro percutaneous absorption experiments using H_2O, EtOH, and several other cosolvents (oleic acid and isopropyl myristate). Using the thickness of the hairless mouse skin (0.026 cm) and the t_L from cumulative release plots as shown in Figure 3, the diffusion coefficients D_s and the skin/vehicle partition coefficients K_m were obtained using Eqs. (4) and (5). D_s and K_m for the various vehicles tested on hairless mouse skin are shown in Table V. These results indicate that between H_2O and the EtOH and EtAc containing vehicles, there is a relatively large increase in D_s; there was no difference in D_s for the EtOH and EtAC vehicles. The differences in J_{LN} observed between the EtOH, EtAc/EtOH, and the EtAc vehicles appears to be roughly correlated with K_m. The vehicles in which oleic acid and iso-

Table V
Diffusion Coefficients (D_s) and Partition Coefficients (K_m) for Permeation of LN Through Hairless Mouse Skin from the Vehicles Tested

Vehicle	LN Solubility at 32°C (mg/mL)	D_s ($cm^2/h \times 10^5$)	K_m
H_2O	0.001	0.70	74
EtOH	8.8	5.6	0.085
EtAc/EtOH (0.3:0.7)	13.7	5.6	0.18
EtAc/EtOH (0.5:0.5)	15.7	5.6	0.35
EtAc/EtOH (0.7:0.3)	15.8	5.6	0.14
EtAc	8.0	5.6	0.29
EtAc/OA (0.5:0.5)	6.9	2.8	0.18
EtAc/IMP (0.5:0.5)	4.7	2.8	0.23
EtAc/EtOH/OA (0.475: 0.475:0.05)	15.3	3.8	0.45
EtOH/OA (0.95:0.05)	8.5	1.1	2.4

Source: From Ref. 88.

propyl myristate were added had somewhat smaller values for D_s. The addition of oleic acid to either a EtAc/EtOH (0.5:0.5) or EtOH increased K_m, indicating that oleic acid was increasing the partitioning of LN between the skin and the vehicle.[88]

L-α-Amino acids have been shown to be effective penetration enhancers for LN as well.[89] Fifteen L-α-amino acids were tested and found to enhance the rate of penetration of LN through hairless mouse skin. Addition of a number of L-α-amino acids (tryptophan, alanine, arginine, proline, serine, glycine, isoleucine, leucine, and valine) in an ethanolic vehicle increased J_{LN} up to 16-fold relative to the ethanolic vehicle without any amino acid. The maximum J_{LN} through hairless mouse skin was found to be about 3.1 $\mu g/cm^2$ h from isoleucine adjusted to the isoelectric pH. This flux is still less than that observed through hairless mouse skin (over 10 $\mu g/cm^2$ h) using EtAc/EtOH (0.5:0.5, v/v) as the enhancer under in vitro conditions.[87]

B. In Vitro Skin Permeability of Prodrug Derivatives of Levonorgestrel

Prodrugs are often used to modify the physicochemical properties of drugs to improve dermal penetration.[90–93] The basis for using prodrugs is generally related to solubility properties in that drugs of lower melting point generally are more soluble in both lipophilic and hydrophilic environments. In other words, such compounds have greater biphasic solubility properties. There is a known correlation between the melting point of a drug and its skin permeability, as shown in Figure 9. It is relatively easy to lower the melting point of drugs by preparing derivatives (prodrugs). Using this approach, partitioning of the drug in the skin leads to increased skin permeability. Diffusion through the skin is actually reduced slightly due to the larger size of the prodrug relative to the free drug assuming that introduction of the promoiety neither influences nor alters interactions with the skin. The promoiety must be removed through either chemical or enzymatic means as it passes through the skin or upon entry into the systemic circulation.

The prodrug approach has been used to increase the percutaneous absorption of LN.[94] Two avenues were followed in designing prodrugs of LN. The

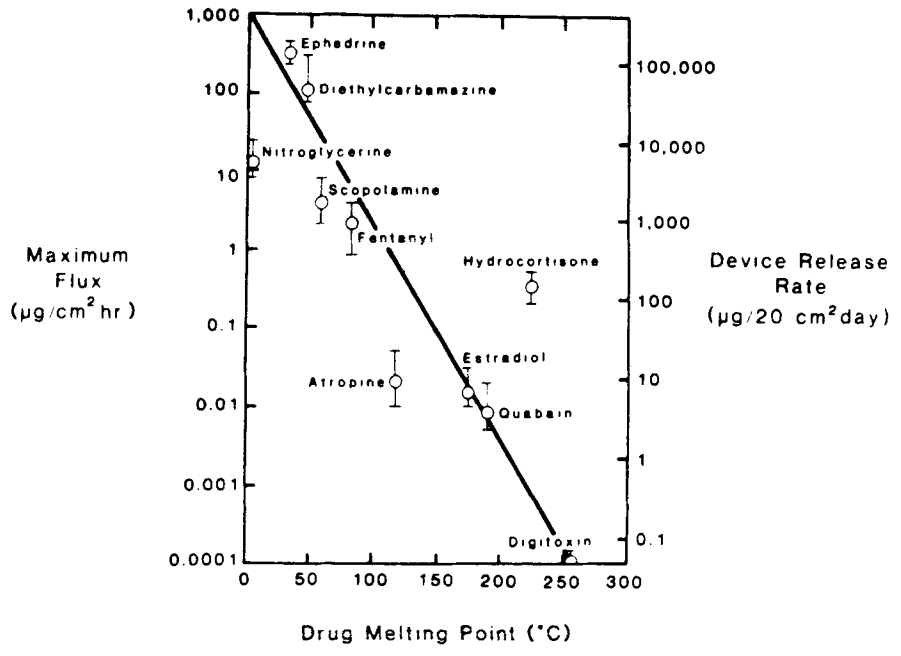
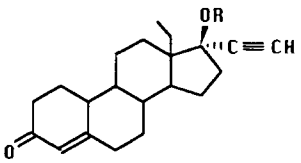


Figure 9. Transdermal fluxes of various drugs through human skin plotted against drug melting point. From Ref. 91.

first involved preparation of simple esters of LN in order to lower the melting point while the second involved preparation of prodrugs of increased hydrophilicity and lower melting point. The structure of the four prodrugs tested is shown in Figure 10. The flux of the hydrophilic prodrugs of LN (LN-glycidol and LN-hexanediol) through rat skin from saturated solutions of EtOH/H_2O (4:6, v/v) is shown in Figure 11 along with the flux of LN (unmodified) from the same vehicle. The transdermal flux of LN (free drug and prodrug) for the



Prodrug	R
LN-glycidol	$-CO-O-CH_2-CHOH-CH_2OH$
LN-hexanediol	$-CO-O-(CH_2)_4-CHOH-CH_2OH$
LN-hexanoate	$-CO-(CH_2)_4CH_3$
LN-pentanoate	$-CO-(CH_2)_3CH_3$

Figure 10. Name and structure of LN prodrugs tested for skin permeability in vitro.

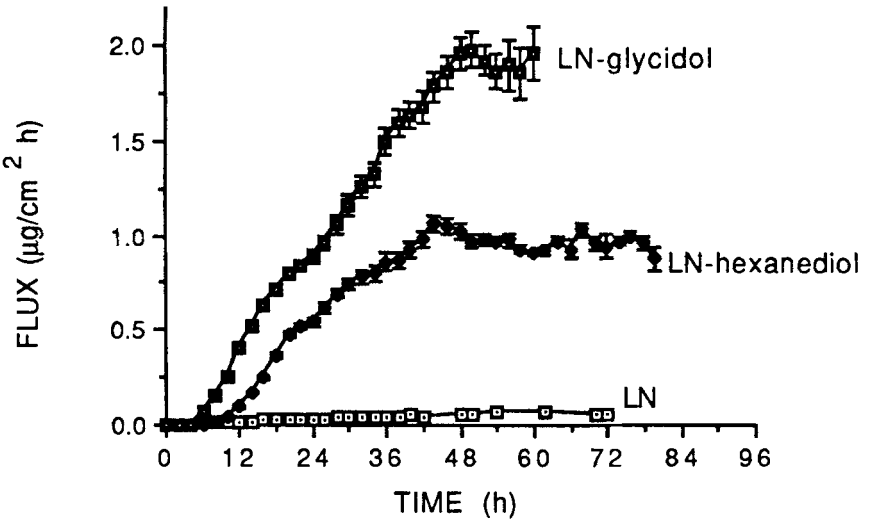


Figure 11. Flux of LN (as prodrugs and free LN) through rat skins in vitro from LN-glycidol (n = 5), LN-hexanediol (n = 4), and LN (unmodified), n = 4). The donor phase (EtOH/H_2O, 4:6) was saturated with excess solid prodrug. Error bars indicate mean standard errors. From Ref. 94.

glycidol prodrugs was 1.95 μg/cm^2 h (32-fold increase over free LN) while that of the hexanediol prodrug was about 1.0 μg/cm^2 h (17-fold increase over free LN). Both prodrug and free drug were detected in the receptor medium (about 20% of the prodrug was hydrolyzed at the later time points tested). There was also some hydrolysis in the donor medium (about 4% of the total drug species in solution). Both prodrugs are hydrolytically unstable and therefore would require formulation in devices free of water.

The simple ester derivatives of LN also showed increased skin permeability relative to free LN (see Fig. 12). In this case, the flux enhancement was not as great as was observed with the hydrophilic prodrugs. The results with the prodrugs support the contention that partitioning of LN from the lipid-rich stratum corneum into the aqueous viable epidermis may be a rate-limiting process. The log octanol/water partition coefficient of LN is 3.7 while that of the LN-glycidol was less (log K = 3.2).[94] The partition coefficients of the other three prodrugs were actually higher than free LN, indicating that partitioning may be only one factor in determining the transdermal flux of LN through skin and that octanol/water partition coefficients may not always directly correlate with skin permeability.

The prodrug approach offers considerable versatility in solving problems such as low skin permeability. There are limits to the use of penetration enhancers [only EtOH is currently approved for use by the Food and Drug Administration (FDA)]. Recently, the prodrug approach has fallen into disfavor due to the position that prodrugs are considered new drugs, and as such are subject to considerable regulatory scrutiny. However, such scrutiny should be borne when a prodrug makes it possible to prepare a safe and effective drug delivery system. For example, the flux enhancement observed from LN-glycidol in EtOH/H_2O (4:6) makes the preparation of a 7-day ther-

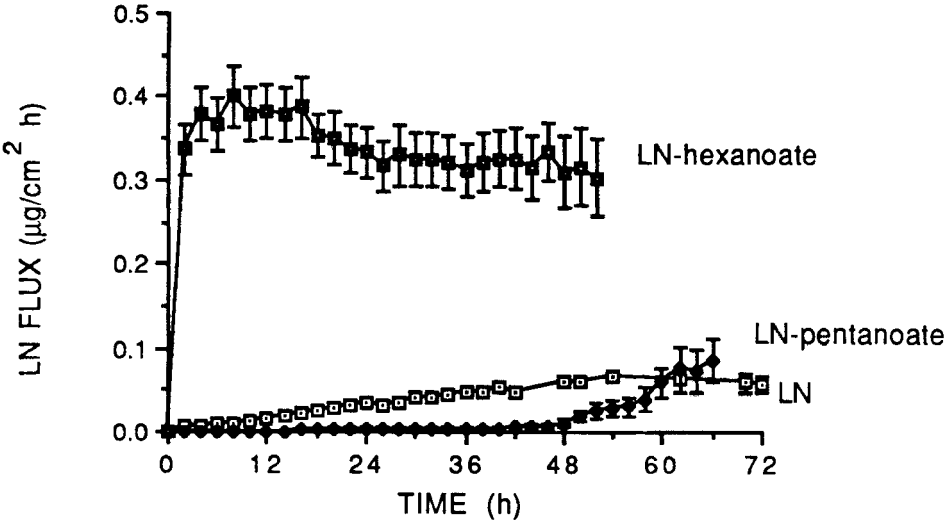


Figure 12. Flux of LN (as prodrug and free drug LN) through rat skins in vitro from LN-hexanoate (n = 6), LN-pentanoate (n = 3) and LN (unmodified, n = 4). Donor phase for LN-hexanoate was EtOH/H_2O (0.62:0.38); donor phase for LN-pentanoate was neat EtOH. Error bars indicate mean standard errors. From Ref. 94.

apeutic transdermal system for LN quite feasible using an FDA-approved enhancer.

C. In Vivo Skin Permeability of Levonorgestrel

Very few studies have been performed to assess the skin permeability of LN under in vivo conditions. LN was evaluated in a study using guinea pigs and hairless mice on the cutaneous penetration of sex steroid hormones.[95] Several vehicles were evaluated: a water/oil emulsion, an oil/water emulsion, and a fatty base. It was found that the penetration of LN was greatest from the oil/water emulsion.

More recently, in vivo percutaneous absorption of LN has been studied from transdermal delivery systems in both rabbits and humans. These studies are discussed in the following section.

IV. TRANSDERMAL DELIVERY SYSTEMS FOR LEVONORGESTREL

Transdermal systemic drug delivery systems have been under development since the middle 1970s. Over the past 15 years, three types of patch formulations have evolved: membrane-controlled devices, diffusion-controlled devices (matrix systems), and the microseal system.[96] For a drug that requires codelivery of an enhancer or enhancers, a reservoir is often a prerequisite. It may also be desirable to control the delivery of the enhancers to the skin to moderate the permeability properties of the skin. Therefore, a membrane-based delivery system was investigated for the codelivery of LN and EtAc/EtOH. Several other delivery systems have been under development recently for the

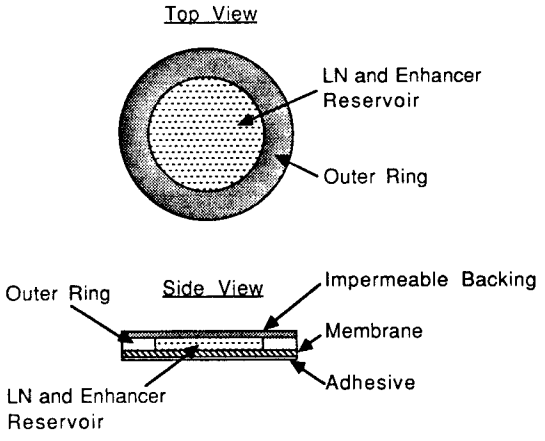


Figure 13. Schematic of a transdermal delivery device used to codeliver LN, EtAc, and EtOH to the skin. Active surface area = 5.0 cm^2; reservoir contains 0.5 mL of enhancer solvent saturated with excess LN. The membrane is composed of EVAc varied from 7.5 to 25% VAc at a thickness of 50 ± 10 μm or 100 ± 10 μm.

controlled release of both LN (a progestin) and 17β-estradiol (an estrogen). Such delivery systems are based on combination therapy used in oral contraceptives. Examples of these delivery systems are presented with respect to delivery of LN from the formulations.

The delivery of LN from a transdermal patch has been explored using EtAc and EtOH as penetration enhancers. As noted above, the percutaneous absorption of LN through human skin is such that a potent penetration enhancer must be formulated into the transdermal patch. The requirement for codelivery of EtAc and EtOH from a transdermal patch indicated that a reservoir-type system as shown in Figure 13 was required. Therefore, a membrane capable of retaining the drug/enhancer suspension and capable of controlling delivery of drug and/or enhancer to the skin was developed. Preliminary screening of a variety of membranes indicated that ethylene vinyl acetate (EVAc) copolymers were able to control the delivery of EtAc and EtOH to the skin.[97]

The EVAc membranes were incorporated into devices designed to deliver LN over 24 h. These membrane-type devices were prepared by a heat-sealing procedure as outlined in Figure 14.[98] The devices were evaluated for release of LN, EtAc, and EtOH under skin conditions and when supported on excised rat skin. The membranes tested were EVAc [12% vinyl acetate (VAc) to 25% VAc content] at either 50 or 100 μm thicknesses. The release rate of LN from the devices was dependent on the VAc content of EVAc membranes and membrane thickness (Fig. 15). It has been shown that for most low molecular weight chemicals, the permeability of EVAc membranes increases with increasing VAc content.[99,100] Delivery of EtAc from the devices was very rapid over the first 4 to 8 h; the 12% VAc content membrane tested sustained the release of EtAc to a greater extent than did the other membranes (15%, 18%, and 25% VAc content; see Fig. 15). Release of EtOH from these devices is also shown in Figure 15. The 12% VAc membrane released EtOH more slowly

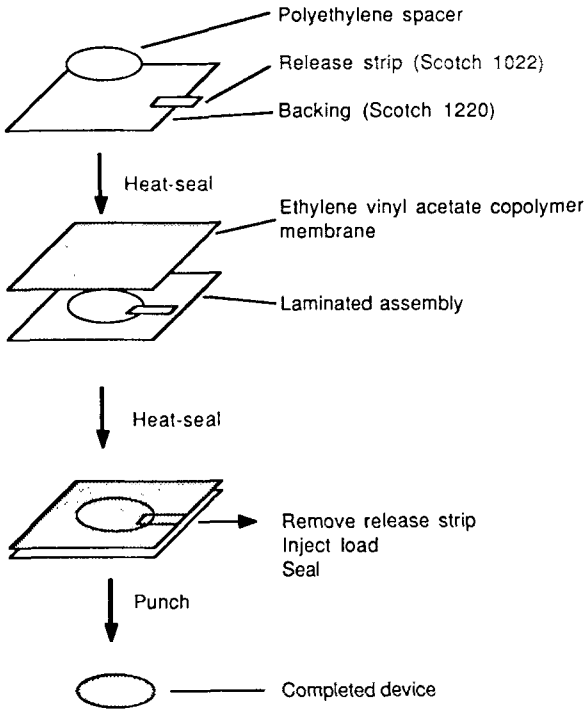


Figure 14. Schematic for preparation of transdermal devices for LN. From Ref. 98.

over time than did the higher VAc content membranes. These same devices were tested for their ability to codeliver LN, EtAC, and EtOH while supported on full-thickness rat skin in vitro.[98] Delivery of LN, EtAc, and EtOH from transdermal devices (25% VAc content, 100 ± 10 μm thick) through rat skin is shown in Figure 16. Flux of LN reached a maximum at about 16 h and slowly diminished until a new patch was placed on the skins at 24 h. The flux of LN increased after the new patches were in place although total delivery of LN over the second 24-h period was less than that of the first 24-h period. The reasons for this are unclear: it appears that the skin exhibited increased barrier properties toward all species released from the device. Solvent flux from these devices is also shown in Figure 16. Maximum solvent flux was reached at about 8 h; solvent flux was negligible by 24 h. Devices using progressively less permeable membranes (18%, 15%, and 12% VAc content EVAc membranes) were tested in the same manner. The flux data from these experiments are shown in Figures 17–19. The devices formulated with 15% and 12% VAc content membranes exhibited lower solvent delivery which in turn led to lower drug flux. The relationship between solvent delivery and drug delivery from the four formulations is shown in Figure 20. From this relationship, it appears that LN delivery is directly related to the amount of solvent delivered to the skin. This relationship holds until solvent release diminishes at which time drug continues to be released into the receptor phase. These results suggest that LN follows the concentration gradient of the solvent in the skin and when solvent delivery drops, release of LN from the skin continues due to drug retained in the horny layer (reservoir effect).[101]

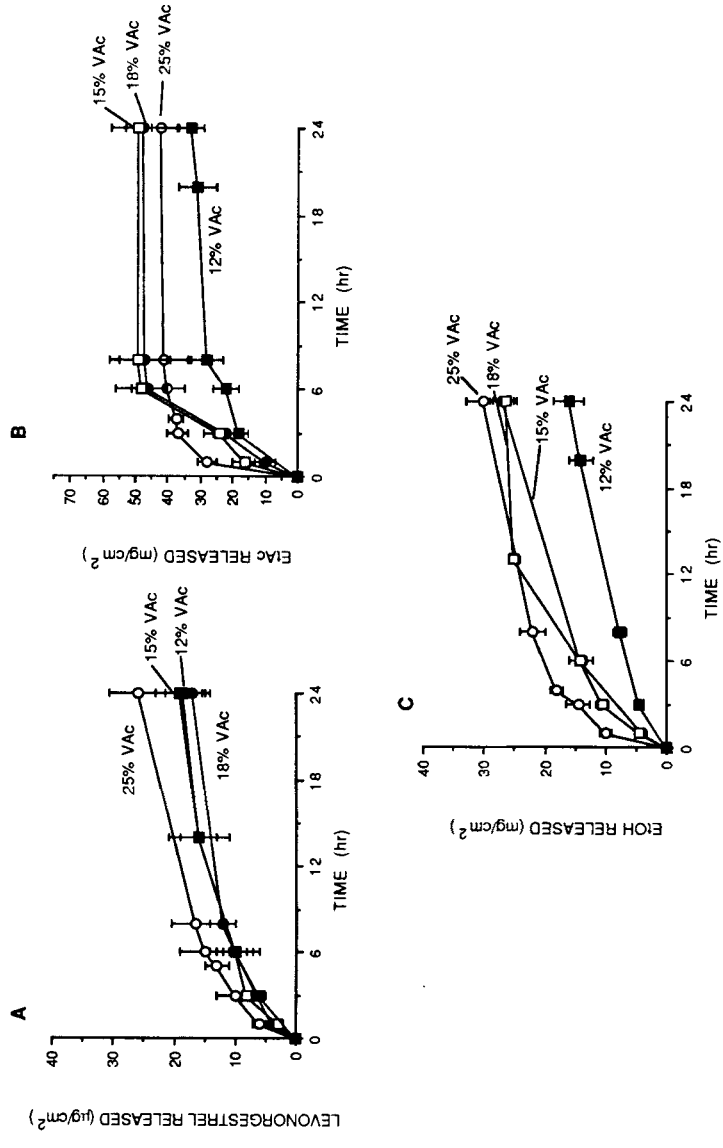


Figure 15. Cumulative release of LN (A), EtAc (B), and EtOH (C) from transdermal devices (5 cm^2) containing 0.5 mL of a LN-saturated reservoir of EtAc/EtOH (0.7:0.3, v/v). The membranes tested were EVAc at 100 ± 10 μm thickness with VAc contents of 12%, 15%, 18%, and 25%. Error bars represent the high and low values obtained (n = 3). From Ref. 98.

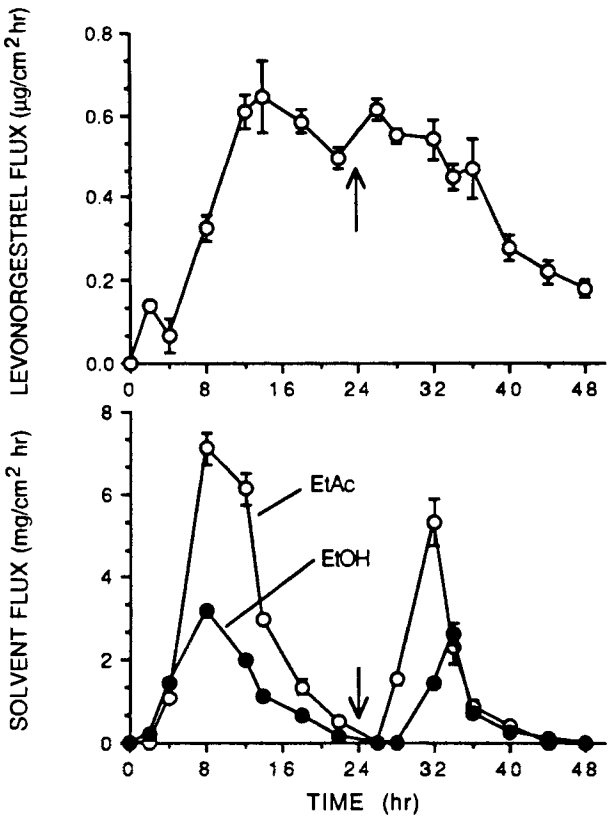


Figure 16. Release of LN, EtAc, and EtOH from transdermal devices (EVAc membranes, 25% VAc content, 100 ± 10 μm thick). The arrow indicates when the devices were removed and new devices placed on the rat skin. Error bars represent SEM (n = 4). From Ref. 98.

These devices were also tested in vivo using rabbits to assess the ability of the patches to deliver LN.[102] The devices were placed on the dorsal area of rabbits, which were shaved with mechanical clippers. In Figure 21, the plasma levels of LN are shown following application of transdermal patches (EVAc membrane, 12% VAc content, 100 ± 10 μm thick) on different sites for three consecutive days. The plasma level expected from constant delivery of LN at a rate of 35 μg/d, as assessed by a constant infusion experiment, is also shown in Figure 21. It is clear that delivery of LN was nonconstant from these devices. The higher plasma levels observed following application of the patches at 24 and 48 h could be due to increased cutaneous blood flow following removal of the patch. This additional blood flow could result in increased clearance of LN from the skin.

A more restrictive EVAc membrane (9% VAc; 50 μm thick) was tested using neat EtAc as the enhancer. The plasma levels of LN following application of these devices are shown in Figure 22. The devices delivered LN at a much more constant rate over time. Based on the data from a constant infusion experiment,[102] these devices delivered LN at a rate of 70 to 100 μg/day. This corresponds to a delivery rate of 0.6 to 0.8 μg/cm² h from the 5 cm² devices.

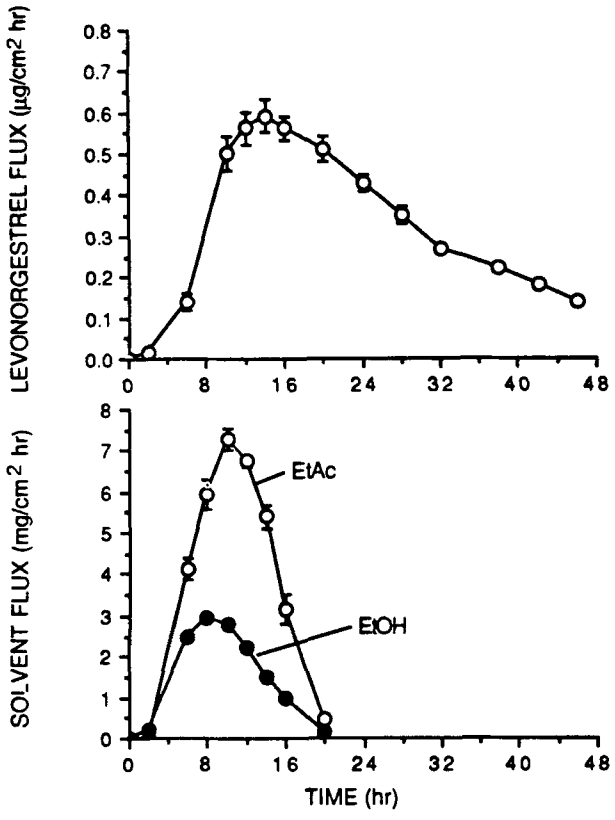


Figure 17. Release of LN, EtAc, and EtOH from transdermal devices (EVAc membranes, 18% VAc content, 100 ± 10 μm thick). Error bars represent SEM (n = 4). From Ref. 98.

Extrapolation of these results to humans is difficult. Most mammals, including rabbits, have skin which is more permeable than is human skin.[81–85] Because of this, delivery of LN from the devices tested would probably be lower than was observed in the rabbits. Until clinical experiments are performed using the delivery system described,[102] it is difficult to predict the ideal membrane, patch size, or exact enhancer composition required to deliver LN at 35 μg/day in women. However, these preliminary experiments indicate that it should be feasible to prepare a relatively small transdermal system for delivery of LN. The skin irritation of these devices is discussed below in the section on cutaneous effects of transdermal delivery systems.

The microreservoir system has been adapted for delivery of contraceptive steroids.[103–105] The delivery system is designed to deliver estradiol (ED) and LN from a once-a-week formulation. In this case, the target delivery rate of LN from the patch is 20 μg/d (roughly half that required in the LN-only system described above). A chemical found to have some penetration-enhancing effect for both ED and LN was isopropyl myristate. This material, when dissolved in the adhesive layer of the microreservoir system, was found to enhance the skin permeation of both estradiol and LN (see Table VI). The

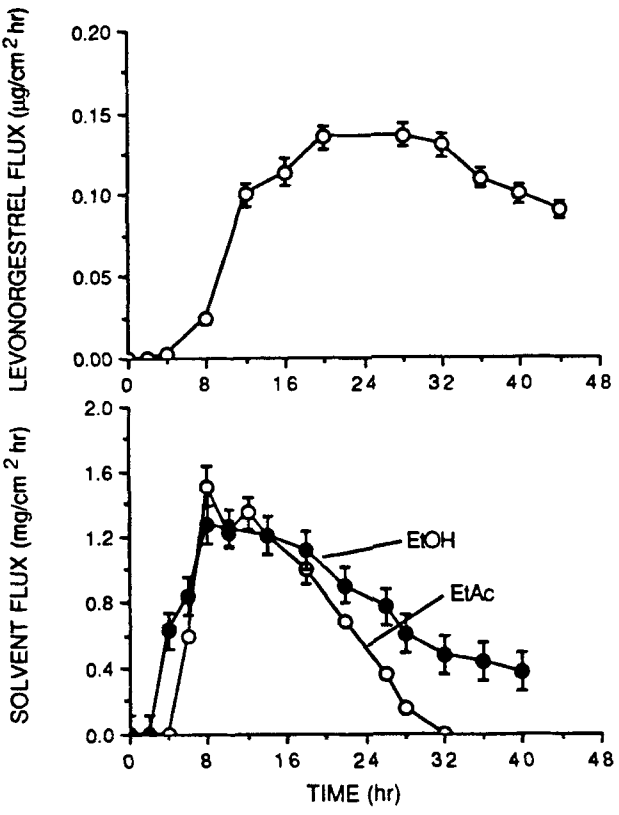


Figure 18. Release of LN, EtAc, and EtOH from transdermal devices (EVAc membranes, 15% VAc content, 100 ± 10 μm thick). Error bars represent SEM (n = 4). From Ref. 98.

absolute delivery rate of LN is quite high in the absence of enhancers in the studies summarized in Table VI. For example, the flux of LN through human cadaver skin from EtOH (saturated with LN) has been measured at 0.03 μg/cm² h (see Table IV)[99] whereas the flux of LN through human cadaver skin from the microreservoir devices (no enhancer) was measured at 10 times that amount (0.31 μg/cm² h). Why there is a tenfold difference in flux in these two cases is not known.

The delivery of LN from the microreservoir patches was evaluated in a Phase I clinical study. The plasma levels of LN following application of these patches in groups of 6 women are shown Figure 23. Unfortunately, the enhancer(s) used in this formulation is not identified in the brief report describing the clinical trial. The devices were found to deliver LN at about 0.12 μg/cm² h, which was very close to the in vitro skin permeation rate.[104,105] The patches were reportedly well tolerated with no significant dermatoxicity observed; however, values from a Draize evaluation[106] were not reported.

Another combination delivery system designed to deliver both ED and LN simultaneously has been developed.[107–109] This delivery system is similar to the reservoir-type delivery systems except that the membrane is macroporous and hence is non-rate-limiting with respect to drug or enhancer. Thus, this

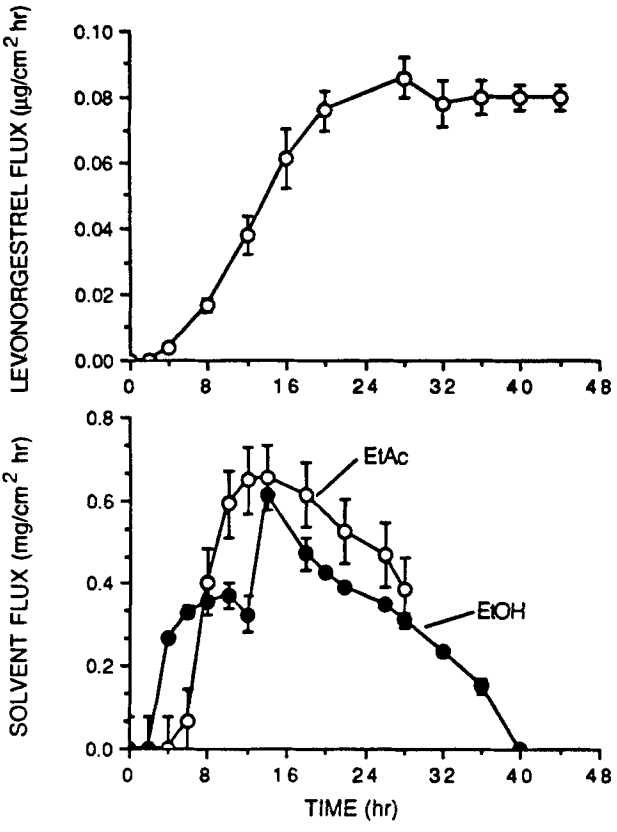


Figure 19. Release of LN, EtAc, and EtOH from transdermal devices (EVAc membranes, 12% VAc content, 100 ± 10 μm thick). Error bars represent SEM (n = 4). From Ref. 98.

type of delivery system behaves essentially as a matrix-type system with respect to drug release kinetics. This device can incorporate encapsulated drugs such that release of drug to the skin can be controlled by release of the drug from the microcapsules.

Data on delivery of LN from the patches using the macroporous membrane device indicates that a delivery rate of over 2 μg/cm² h is possible in rabbits. This system used EtOH as a penetration enhancer, which was added to the reservoir. This rate is almost 17 times greater than was observed in human clinical trial described above. Relative to the transdermal delivery of LN using membrane-moderated devices with EtAc as an enhancer (see Fig. 22), the macroporous membrane devices delivered 2.5 times as much LN (2.0 μg/cm² h vs. 0.8 μg/cm² h) over a 24 h period. The higher delivery rate from the macroporous system was obtained in rabbits treated with a chemical depilatory, which can lead to significant increases in the absorption of drugs through skin treated in such a manner.[110] In fact, large variations in absorption (up to 15-fold) are observed following application of a depilation agent. When chemicals are applied along with EtOH following depilation, absorption has been increased up to 6.2 times relative to untreated skin.[110]

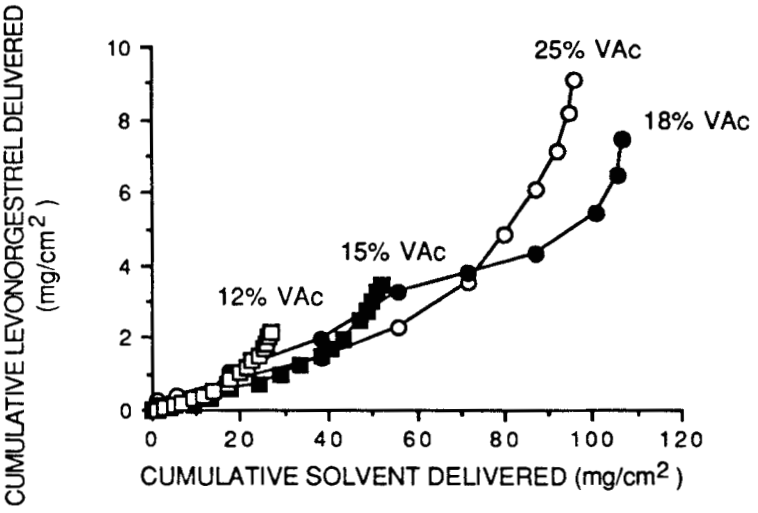


Figure 20. Relationship between cumulative solvent delivered through rat skin and cumulative LN delivered from devices (12%, 15%, 18%, and 25% VAc content EVAc membranes, 100 ± 10 μm). From Ref. 98.

V. CUTANEOUS EFFECTS OF TRANSDERMAL LEVONORGESTREL

A problem associated with the use of transdermal patches is the cutaneous side effects produced by the delivery system. The toxicological implications of transdermal drug delivery systems have recently been reviewed.[111,112] Most transdermal systems are mild contact irritants; however, this irritation is in-

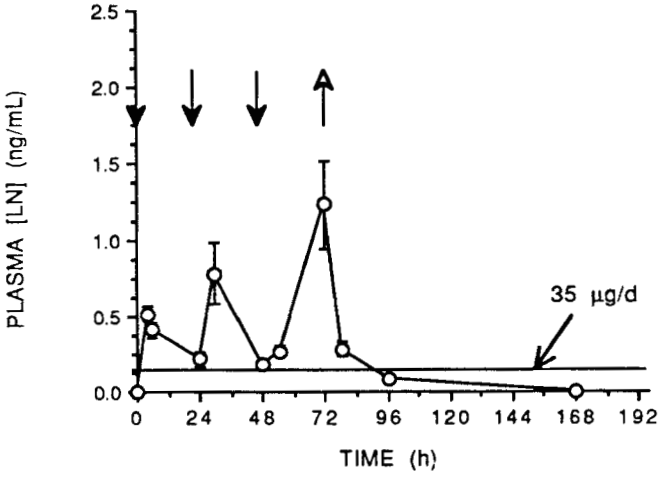


Figure 21. Plasma concentration of LN in rabbits (2–3 kg) after application of transdermal patches (EVAc membrane, 12% VAc content, 100 ± 10 μm thick) at t = 0, 24, and 48 h, as indicated by the arrows. The last patch was removed at 72 h. The surface area of the patches was 5.0 cm^2; the reservoir contained 0.5 mL of a gelled solution of EtAc/EtOH (7:3, v/v) which was saturated with excess LN. Error bars are SEM (n = 4). From Ref. 102.

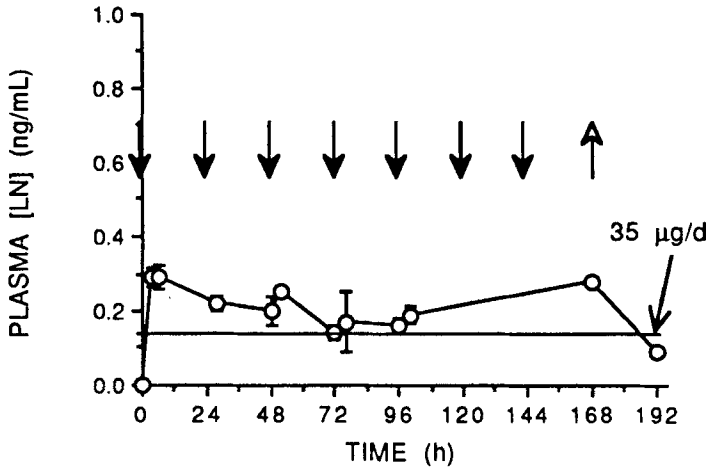


Figure 22. Plasma concentration of LN in rabbits (2–3 kg) after application of transdermal patches (EVAc membrane, 9% VAc content, 50 ± 10 µm thick) at t = 0, 24, 48 h, 72, 96, 120, and 144 h, as shown by the arrows. The last patch was removed at 168 h. The surface area of the patches was 5.0 cm^2; the reservoir contained 0.5 mL of a gelled solution of EtAc which was saturated with excess LN. Error bars are SEM (n = 4). From Ref. 102.

significant in the majority of users. As described in this review, transdermal delivery systems for contraceptives use chemical enhancers that can exacerbate cutaneous responses to occlusive transdermal delivery systems.

The experimental transdermal delivery systems for LN have not been fully characterized with respect to skin irritation. Indeed, it is unlikely that these systems will be free of cutaneous side effects. Some data are available on the delivery system using EtAc and EtAc/EtOH as enhancers. A major concern with using EtAc as a skin penetration enhancer is its ability to cause irritation

Table VI
Effect of Isopropyl myristate (IPM) in Adhesive Layer on Skin Permeation and Lag Time Profiles of Estradiol (ED) and Levonorgestrel from Transdermal Patches[a]

Adhesive Composition[b]	Permeation Rates[c]		Lag Times (h ± SD)	
	ED	LN	ED	LN
No adhesive	0.27 ± 0.048	0.31 ± 0.049	14.5 ± 1.85	32.5 ± 6.22
Adhesive	0.26 ± 0.051	0.16 ± 0.028	12.4 ± 1.10	29.8 ± 3.45
Adhesive with IPM				
0.5 M	0.036 ± 0.054	0.22 ± 0.037	19.8 ± 2.10	28.9 ± 4.56
1.0 M	0.48 ± 0.066	0.43 ± 0.072	22.0 ± 2.92	36.6 ± 7.01
1.5 M	0.50 ± 0.069	0.45 ± 0.072	18.9 ± 2.22	33.2 ± 6.72
2.0 M	0.47 ± 0.050	0.46 ± 0.066	20.6 ± 2.79	32.8 ± 6.60

[a]Devices were fabricated from a formula which contained 5% (w/w) of LN and 2.5% (w/w) of ED dispersed in separate microreservoir compartments (10% w/w) containing 40% (v/v) polyethylene glycol 400 solution.

[b]Enhancer incorporated adhesive layer (16 µm thick).

[c]Permeation rate expressed as µg/cm^2 h ± SD.

Source: From Ref. 103.

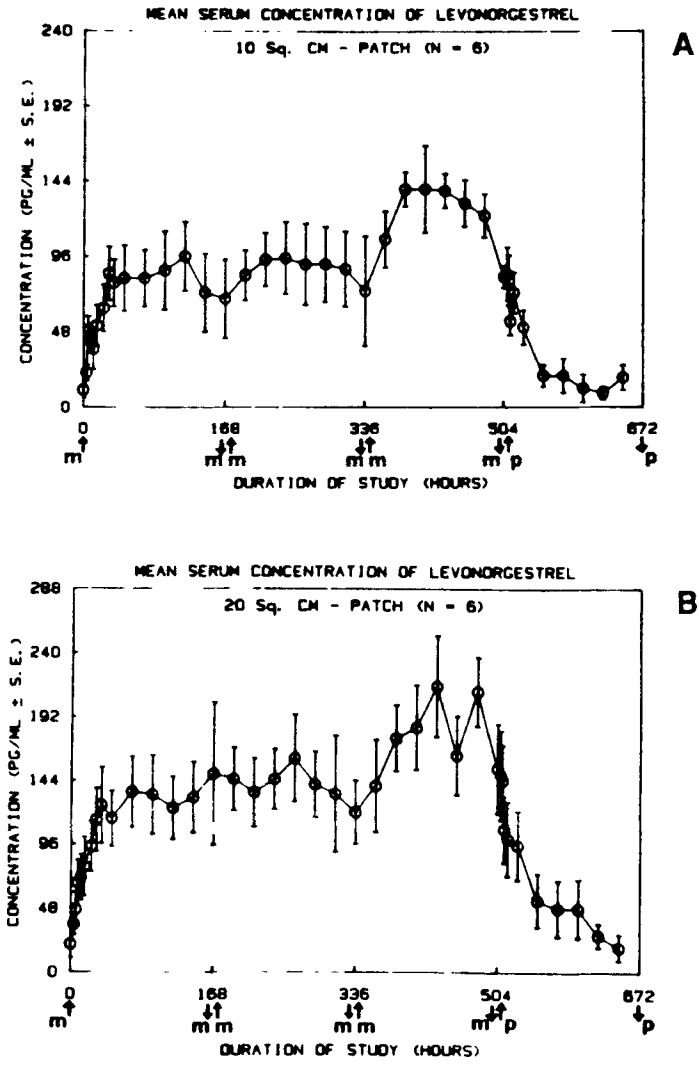


Figure 23. Mean serum concentration of LN in women (n = 6) from microreservoir patches delivering LN and ED from patches (A: 10 cm^2; B: 20 cm^2) applied once-a week for 3 weeks. From Ref. 94.

under occlusion. The irritation of the devices tested in vivo in rabbits was evaluated for cutaneous side effects. The application sites were examined visually and graded for irritation (erythema and edema) according to the Draize method;[106] the sites were also examined histologically. Devices using EtAc/EtOH or EtAc as penetration enhancers produced mild erythema and very mild edema. The average erythema scores were 1.5 to 1.7 following removal of the patches after a 24 h application; edema scores averaged 0.5 to 0.6. Some adhesive was found to remain on the skin following removal of the patches. Placebo patches (no enhancer in the reservoir) gave irritation scores of about 1.0 (erythema) following removal of the patches. However,

the irritation at the sites increased to 1.2–1.4 at 24 and 48 h, respectively, following removal of the placebo patches. The increase in irritation was probably due to residual adhesive remaining on the site. Histological evaluation of the application sites confirmed the visual assessments.

While topical irritation is the most common problem associated with the use of transdermal delivery systems, other side effects are possible. Contact allergy is probably the second most common area for concern although its reported incidence is much less frequent than irritation. Transdermal LN will be used chronically; hence, the potential for development of sensitization must be considered. Contact urticaria, which is characterized by a short-lived reaction of rapid onset consisting of swelling and itching, is another potential problem associated with transdermal delivery systems. However, no cases of contact urticaria involving transdermal delivery systems have been reported.[111] Photoirritancy and photoallergy may, in theory, represent a potential problem in transdermal drug delivery. However, the systems are generally light-impermeable and are almost always worn under clothing.

VI. CONCLUSIONS

Transdermal delivery of contraceptives has been a goal of researchers in this field for many years. In fact, patents were filed in Europe by Organon Laboratories in 1969 for a plaster containing contraceptive agents.[114] However, no transdermal contraceptive has become available commercially. Clearly, there is a need for improved forms of contraception, particularly in third world countries.

There are issues that remain to be resolved with transdermal contraceptives. It may be better to pursue a once-a-week delivery system; however, because these systems will require an enhancer, cumulative irritation will undoubltly be of concern. The Estraderm delivery system for ED is a 3.5-d patch that uses EtOH as an enhancer. This formulation is irritating to a number of users.[115–117] Obviously, the longer a patch is worn, the greater is the chance for contact irritation to develop.

Another issue is the use of a combination system (estrogen, progestin) or an single entity system (progestin only). There are greater technical challenges to developing a combination system in that each drug would need to be delivered at its own rate with each requiring its own penetration enhancer. If such a system can be developed, however, it would need to be worn for only 3 weeks followed by one week off.

The development of a transdermal delivery system for LN requires a very potent enhancer. EtAc may prove to be a very useful chemical penetration enhancer for LN. It is Generally Recognized as Safe (GRAS) and is a very mild contact irritant, even when evaluated in the 21-d cumulative irritation assay in humans.[118] It is very low in toxicity as well: LD_{50} for acute oral toxicity is 5.6 g/kg and 3–5 g/kg for subcutaneous toxicity.[119] However, long-term stability of a patch containing EtAc must be addressed before a delivery system using EtAc can be considered a viable clinical candidate.

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