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# TRANSDERMAL DRUG DELIVERY - PROBLEMS AND PROMISES

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The advantages of delivering drugs across the skin for systemic therapy are well documented (1-6), and transdermal drug delivery, on its own merits, has now become one of the fastest growing areas in drug development. The limitations and constraints of this mode of drug therapy have to be understood, however. This present article addresses such limitations and discusses the controversies surrounding these therapeutic systems. This is attempted with the hope that a good understanding and a rational approach to developing these systems will aid in early resolution of the problem(s).

Under pressure from their marketing departments, pharmaceutical companies are moving hastily to produce transdermal devices. Only with well-planned development programs that take a careful and cautious approach, transdermal technology is expected to make a significant impact on the quality of patient care.

## BACKGROUND

Transdermal therapeutic systems are self-contained, discrete dosage forms which, when applied to intact skin, deliver the drug(s) through the skin at a controlled rate to the systemic circulation. Systems typically comprise an outer covering (barrier), a drug reservoir which may have a rate-controlling membrane, a contact adhesive applied to some or all

parts of the system and the system/skin interface, and a protective layer which is removed before applying the system. The activity of these systems is defined in terms of the release rate of the drug(s) from the system.

If certain assumptions are made concerning the barrier properties of the skin, a drug's transfer rate across the skin per unit of surface area can be predicted based on the knowledge of a few physicochemical properties of the drug. The basis for these calculations is usually the drug's hydrophobic/hydrophilic partition coefficient, along with its molecular weight and water solubility (7).

## SKIN IRRITATION ISSUE

The issues of skin irritation, infection or inflammation will become more and more important as new drug entities are formulated into transdermal delivery systems. The long-term effects of putting patches on the skin have to be established. It is not the isolated case that represents the real danger, but rather the case in which a drug may cause skin irritation to a wide general population.

To qualify as an irritant, a chemical substance should evoke inflammation on initial exposure (primary irritation) or on repeated exposure (cumulative irritation). Cutaneous

irritation requires that the chemical substance penetrates through the skin barrier; if the chemical does not penetrate through the barrier, no inflammation can occur. An important concept is that virtually any chemical, including water, may qualify as an irritant; this depends largely on the circumstances of exposure to the chemical substance. As a rule of thumb, one can predict that if a chemical has the ability to penetrate the skin barrier rather efficiently, chances are it will be an irritant. It is inherent that if the molecule has a good skin permeation profile, it has to have the ability to "disrupt" the normal physiological/biochemical processes existing within the skin. And because of this, most of the skin permeation enhancers are skin irritants.

Skin should not be regarded as "leather" and neither is it just a membrane. Skin is a vital organ and, therefore, it is necessary to study and understand the biochemistry during transport in a scholarly manner. Adequate evaluation of clinical irritant reactions to chemical substances depends on a thorough understanding of all variables influencing the irritant response.

Substantial efforts have been made in recent years to study the influence of irritants on the skin (8). In 1974, Rutherford and Pawlowski (9) identified the utility of

determining the release of acid phosphatase from epidermal lysosomes or membrane coating granules as a tool for the assessment of skin irritancy. Using a histochemical technique they observed a short-term increase of epidermal lysosomal acid phosphatase activity after skin treatment with mild irritants. Prottey et al. (10), however, recently reported enhanced short-term reduction of acid phosphatase activity in human skin treated with stronger irritants. They rationalized that protein denaturation was the most probable cause for the reduced enzyme activity. Skin acid phosphatase activity may change in several ways as a consequence of contact with irritants. Some agents may directly influence the activity of this enzyme. In addition, it may also be possible that preformed acid phosphatase is released differently by irritants from latent sources as proposed by Rutherford and Powlowski (9).

Another area of major concern for scientists in transdermal drug delivery research is that of hypersensitization. In a recent symposium on transdermal delivery, a clear case of hypersensitization to clonidine as a result of skin contact was reported (11). Since very little is known about the hypersensitization potential of many of the compounds currently being evaluated for transdermal delivery, this potential must be considered before long-term clinical trials are undertaken.

Evaluation of transdermal formulations will need to be done early in the development process. Although it is likely that chronic skin contact of a great many compounds will result in isolated cases of hypersensitization, this however, should not deter their further development.

Finally, of no less importance are the issues of infection and erythema. Along with skin irritation and hypersensitization potential, these need to be evaluated at a very early stage of development. Because the area of application remains occluded, patches worn for extended periods of time may also cause microbial growth. With an early detection of the problem(s), it may still be possible to modify the formulation (such as adding an antimicrobial agent) to alleviate adverse events.

## TOLERANCE BUILD-UP

One controversial scientific issue that surrounds the role of long-term delivery of drugs is that of tolerance. For transdermal therapeutic systems, which are primarily designed for long-term therapy, one has to address such concerns by undertaking studies where the drug is administered chronically via transdermal patches. This, of course, is easier said than done.

With chronic use of nitroglycerin, tolerance (attenuation) of nitrate effect has been demonstrated (12). How this attenuation presents clinically, how marked it is, or what the mechanism could be is not clearly understood. Data suggest that there may be a difference between hemodynamic and anti-anginal attenuation and the former (hemodynamic) is more marked. Difference between attenuation in veins and attenuation in arteries may also exist. Nor is it clear whether attenuation occurs specifically in the coronary arterial tree. It has been shown that attenuation is certainly not related to changes in nitrate blood levels and that hemodynamic attenuation occurs even when nitrate blood levels are still as high as before the attenuation occurred.

Results from the chronic studies undertaken to date with transdermal nitroglycerin patches, like the results from the acute studies, vary (13,14,15,16,17,18,19). One major problem with the studies reported to date is the use of relatively low doses of transdermal preparations and one or two common dose levels for all patients, rather than titration or individualization of dosage. All trials undertaken so far are small, with variable clinical design and population profiles. The need for well-planned study designs applying rigorous protocols in larger, better-defined populations, is long overdue. Concerns for tolerance to transdermal nitroglycerin will

persist and dose-ranging and nitrate-free intervals, two potential methods of dealing with the problem, need to be assessed before conclusions can be drawn as to the proper mode of use for transdermal nitroglycerin. In the meantime, physicians need to individualize therapy and use clinical judgement until more definitive, scientific results become available.

## ZERO-ORDER OR NOT?

Results from recent clinical studies (20) have shown that drug delivery from transdermal nitroglycerin patches approach zero-order kinetics, analogous to a constant-rate i.v. infusion, and steady-state plasma levels are obtained within two hours and are maintained for more than 24 hours. But for patients at risk of tolerance development to the drug, researchers have questioned the zero-order input concept for chronic therapy. They suggest that because in such cases intermittent use of nitroglycerin patches may be necessary, one could alternatively design transdermal systems that can be programmed to deliver the drug not at a zero-order rate, but as is dictated by patient need. Transdermal nicotine, as another example, may not need a constant input of the agent. Rather, it will be necessary to 'hit' the patient with a dose of nicotine whenever the craving for smoking arises. As more is learned about and progress is made in the area of

iontophoresis, it may be possible to develop a transdermal system that incorporates a disposable battery and even a disposable circuit wafer capable of programming the application of sufficient current, as the patient need arises, to drive drug molecules through the skin.

With the recent advances in chronopharmacology (21) and the clearly established role that circadian rhythms (22) play in eliciting dramatic circadian variation from physical or chemical stimulae, it may indeed be inappropriate to administer a drug continuously at a zero-order rate over a prolonged period. Because of such circadian rhythms the absorption, metabolism and effects of medication are likely to vary predictably with administration time. Ritschel, et. al., have shown (23) that for the analgesic meperidine, both drug disposition and clinical response change during 24 hours due to circadian rhythm and diurnal variation, and that higher meperidine doses may be required during the night to achieve the same level of pain relief as during the day. For drugs that are very potent and demonstrate circadian variability, zero-order drug delivery may not be the best choice. Within the past 2-3 years, a number of pharmaceutical companies, particularly in Europe, and bioengineering industries, mainly in the United States, have begun to sponsor extensive clinical studies involving hundreds of patients to determine the optimal time of

drug administration. Once the chronopharmacokinetics of the drug are determined it may be possible to design transdermal systems that can be programmed to deliver the drug as dictated by chronopharmacology.

Zero-order input implies that one will achieve sustained and controlled blood levels. A recent study (24) with long-acting ACE inhibitors has, however, raised the question: Are flatter (blood levels) better? It was observed that the shorter-acting ACE inhibitor, captopril, induced only brief decrements in mean arterial pressure each time the drug was administered and blood pressure rose quickly to pretreatment levels before the next scheduled dose. With the longer-acting enalapril, however, the hypotensive response was prolonged and persisted at maximal values throughout the interval between doses. Since a decline in arterial pressure can cause adverse symptoms like dizziness, patients on captopril had shorter symptomatic periods and the dizziness was not drastic enough to interfere with daily activity. With enalapril on the other hand, dizziness sometimes lasted for several hours. Enalapril also caused a significant decrease in creatinine clearance and since ACE inhibitors are known to interfere with the ability of the kidneys to secrete potassium, patients on enalapril - and not those on captopril - had elevated levels of serum potassium. Therefore, the authors suggest "other things being

equal, agents with prolonged duration of action may yield few therapeutic advantages and may significantly increase the risk of adverse effects".

## WHICH SYSTEM DESIGN TO CHOOSE?

For the immediate future, transdermal delivery systems will either be a 'monolithic' or a 'membrane-controlled' type (25). Systems such as Nitro-Dur®[1] or Nitrodisc®[2] are monolithic because they contain the drug as a semisolid solution or dispersion. These systems simply provide a convenient reservoir for the drug and leave the skin to play the role of rate-controller. Catapres®[3], Estraderm®[4] and Transderm-Scop®[5], on the other hand, are examples of a membrane-controlled system that contains a rate-controlling membrane which limits drug release and prevents overdosing.

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[1]Nitro-Dur® is the trademark for nitroglycerin, property of Key Pharmaceuticals Inc.

[2]Nitrodisc® is the trademark for nitroglycerin, property of Searle Pharmaceuticals Inc.

[3]Catapres® is the trademark for clonidine, property of Boehringer Ingelheim Ltd.

[4]Estraderm® is the trademark for estradiol, property of CIBA Pharmaceutical Company.

[5]Transderm-Scop® is the trademark for scopolamine, property of CIBA Pharmaceutical Company.

In a monolithic type device a combination of diffusivity and chemical activity of the drug in the polymer matrix governs its release. These two parameters in turn are dependent upon the molecular and structural factors of the polymer-drug matrix, which include polarity, hydrogen bonding, glass transition temperature of the polymer, and solvating or plasticizing effect of the excipients and the drug upon the polymer chains. The concentration of the diffusant drug also has a significant effect upon its release. In general, the release profile from such a device follows a typical square-foot time pattern.

For membrane controlled devices, the steady state permeation rate (J) of the diffusant (under perfect sink conditions) is proportional to its membrane-diffusivity (D), the membrane-reservoir distribution coefficient (K), the concentration gradient ($\Delta C$) between the reservoir and the fluid adjacent to the control membrane, and the control membrane thickness (l). Mathematically, one can write: $J = D K (\Delta C/l)$. In actual use, the skin may not provide the perfect sink condition, and the above relationship may not hold.

The aqueous polymer matrix developed by Key Pharmaceuticals is primarily composed of a liquid phase that is three-dimensionally stable (26). Nitroglycerin/lactose triturate is dispersed within a polymeric gel (composed of polyvinyl

pyrrolidone, a glycol, and polyvinyl alcohol) such that the solvent phase is saturated. In addition, there is an excess of nitroglycerin to serve as a reservoir that replenishes the depleted drug that has penetrated the skin (substantially from the aqueous solvent phase). No membrane or adhesive covers the matrix, and the matrix is held to the skin peripherally by a hypoallergenic microporous adhesive (Figure 1). The wet nature of the matrix surface assures good skin contact. With Nitro-Dur®II[6], which was recently introduced, Key has modified the design somewhat and the nitroglycerin is dispersed in acrylic-based polymer adhesives with a resinous cross-linking agent. The result is a much thinner and elegant patch than the original Nitro-Dur®.

Searle's Nitrodisc® (Figure 2) delivers the nitroglycerin in a similar fashion. In this device, however, the drug is dispersed in a silicone polymer matrix and is held to the skin with a peripheral adhesive foam tape (27). Like the Key system, this also has no membrane over the matrix.

Ciba's Transderm-Scop® (developed by Alza) contains scopolamine in a 5-layer laminate (backing, polyiso-

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[6]Nitro-Dur®II is the trademark for nitroglycerin, property of Key Pharmaceuticals, Inc.

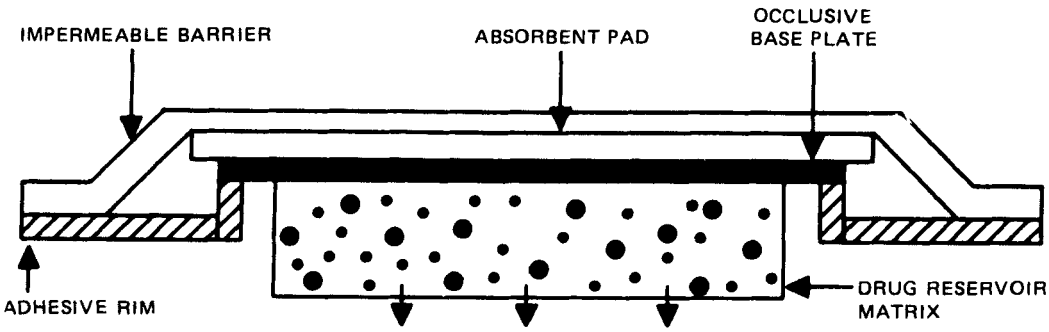


FIGURE 1 MATRIX-DIFFUSION-CONTROLLED TRANSDERMAL SYSTEM: NITRO-DUR®

(NITRO-DUR® IS THE TRADEMARK FOR MITROGLYCERIN, PROPERTY OF KEY PHARMACEUTICALS INC.)

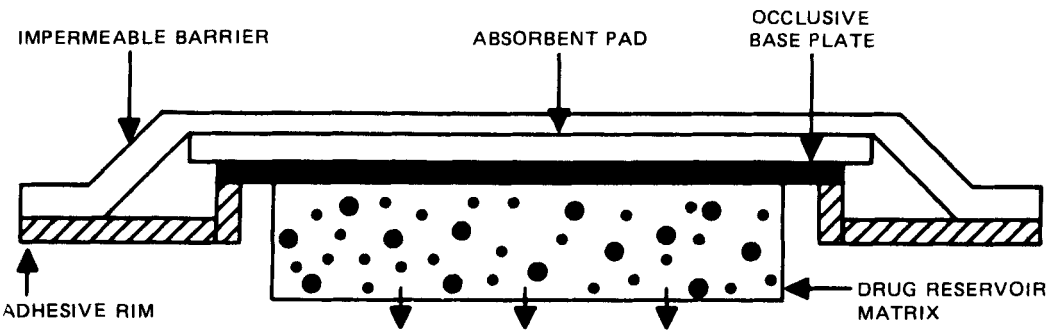


FIGURE 2 MICROSEALED (PARTITION-CONTROLLED) TRANSDERMAL SYSTEM: NITRODISC®

(NITRODISC® IS THE TRADEMARK FOR NITROGLYCERIN, PROPERTY OF SEARLE PHARMACEUTICALS INC.)

butylene/mineral oil/scopolamine as the drug reservoir, a microporous polypropylene film as the control membrane, a polyisobutylene based contact adhesive, release liner), while Transderm-Nitro®[7] (also developed by Alza) contains nitro-

[7]Transderm-Nitro® is the trademark for nitroglycerin, property of CIBA Pharmaceutical Company.

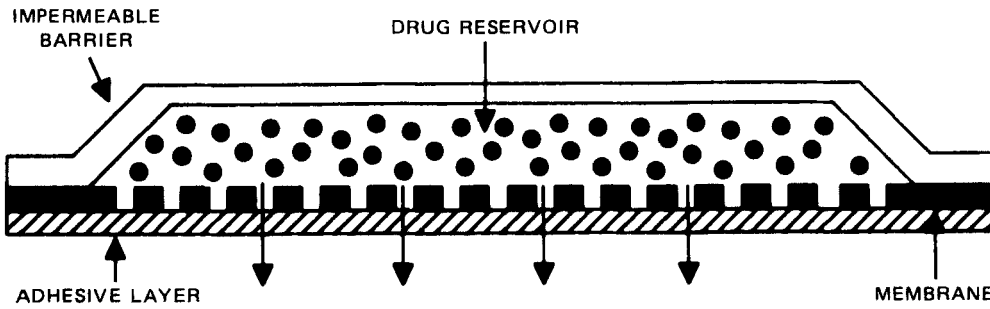


FIGURE 3 MEMBRANE-PERMEATION-CONTROLLED TRANSDERMAL SYSTEM: TRANSDERM-NITRO®

(TRANSDERM-NITRO® IS THE TRADEMARK FOR NITROGLYCERIN, PROPERTY OF CIBA PHARMACEUTICAL COMPANY)

glycerin in a fill-and-seal dosage form made up of backing, drug reservoir with nitroglycerin/lactose triturate in silicone fluid, an ethyl-vinyl acetate copolymer rate-controlling membrane, contact adhesive and protective peel-strip (Figure 3). The methods of manufacture of Transderm-Nitro® and Transderm-Scop® are somewhat different (25).

The former is the product of technologies originating in the packaging industry, referred to as form-fill-seal, and the latter system derives purely from lamination processes. Because these have been widely used by the food and cosmetic industry, it is feasible to use the two processes to produce patches under GMP regulations. With the processes of lamination, dosing of the drug reservoir and heat sealing must be refined and adapted before the overall manufacturing process

becomes general and routine. Drug delivery from both these systems is somewhat controlled by the membrane (28,29).

The recently introduced Hercon Nitroglycerin Transdermal System (NTS) is comprised of a multilayered polymeric laminate structure, in which a layer of vinyl chloride copolymer or a terpolymer containing nitroglycerin is sandwiched between two or more outer layers of polymeric films (Figure 4). The release of the drug to the surrounding medium is controlled by its selective and restricted permeability through the outer layers. An imbalance of chemical potential permits the drug to migrate continually to the surface through one or more initially inert outer layers. Pressure sensitive adhesives for attachment of the device to the skin are made up of polymeric materials such as acrylate copolymers, polysiloxanes, and polyisobutylene.

Wyeth has just entered the nitroglycerin patch market with the introduction of Deponit®[8] transdermal delivery system. A multilayered self-adhesive film, the system contains nitroglycerin in a matrix composed of lactose, plasticizer, medical

[8]Deponit® is the trademark for nitroglycerin, property of Wyeth Laboratories Inc.

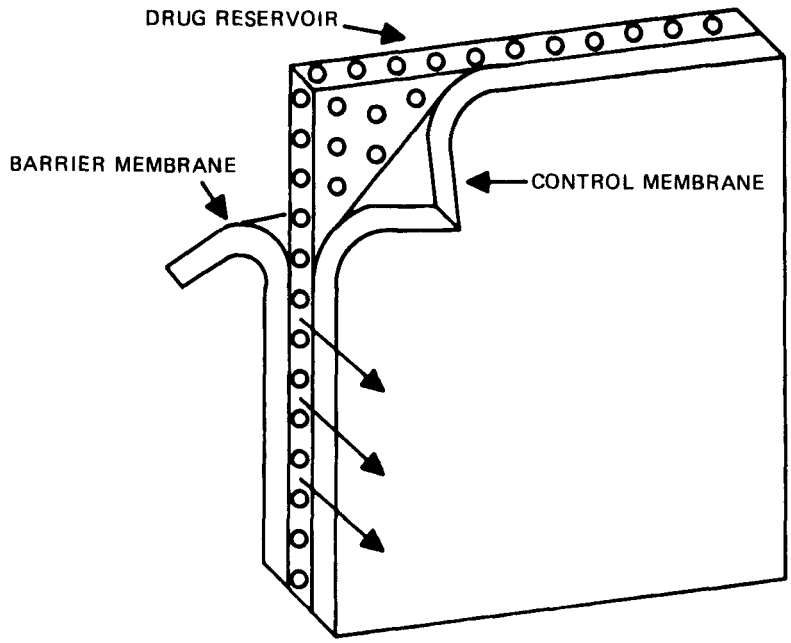


FIGURE 4 HERCON'S NITROGLYCERIN TRANSDERMAL SYSTEM

adhesive, polyisobutylene and aluminized plastic. The system is approximately 0.3 mm thick, insoluble in water, and consists of two main elements: a) a flexible, flesh-colored waterproof covering foil, and b) a multilayered adhesive film that constitutes simultaneously the drug reservoir and the release control system. The device is designed to deliver an accurate dosage with no premature release of nitroglycerin or undesired accumulation on the skin.

The designers of a new 'two-compartment' transdermal delivery system claim that in the currently available membrane-

controlled and monolithic type systems, the drug is present in a permeable active state posing problems to manufacturing, stability and performance of the delivery system. At the recently held Third International Symposium on Recent Advances in Drug Delivery (February 23-27, 1987 at Salt Lake City, Utah) these researchers claimed (30) that these limitations can be overcome by their new system, because the drug is incorporated in a stable, impermeable form. An activating agent capable of converting the impermeable drug into a permeable state is incorporated into a compartment separated from the drug by a barrier which is impermeable to both the drug in the pre-activated state and the activating substance. The barrier is breached by the user prior to administration allowing the activating substance to convert the drug into a permeable state and thereby initiating delivery. One limitation of this device would, however, be that the lag time to steady state will be somewhat longer.

The fundamental question that has to be answered before designing a transdermal system is whether delivery-rate control must be a part of the device or whether it is more desirable simply to allow the skin to act as the primary barrier to transport. To a certain extent, the degree of control desired will be dictated by the pharmacological profile of the drug. For example, for a drug like scopolamine which is very potent

and has a tendency to be absorbed through the skin rather quickly, a membrane-controlled system will limit drug release and avoid any potential overdose.

One of the limitations of transdermal drug delivery is the wide variability in skin permeability, not only between patients but also between different sites on the same patient. Because of such variabilities, certain researchers argue, it is essential that systems be designed such that the device controls the rate of drug absorption. This means that the device should present drug to the skin at a much slower rate than the skin can transport. These researchers rationalize that the concept of transdermal drug delivery rests on the premise that this mode of therapy is independent of patient's age, of the placement of the unit on the skin, and of the environment in which the patient or the unit exists (31). Device-controlled drug delivery becomes all the more necessary for a potent drug like scopolamine with a narrow therapeutic window. Figure 5 depicts the increasing number of side-effects associated with rising scopolamine blood concentrations (as reflected by urinary excretion rates) in subjects receiving 200 $\mu$g i.m. doses (32). However, prevention of motion sickness is achieved at blood levels that are much lower than those associated with the undesirable CNS effects of the drug. Understandably, therefore, scopolamine becomes a good candidate for rate-

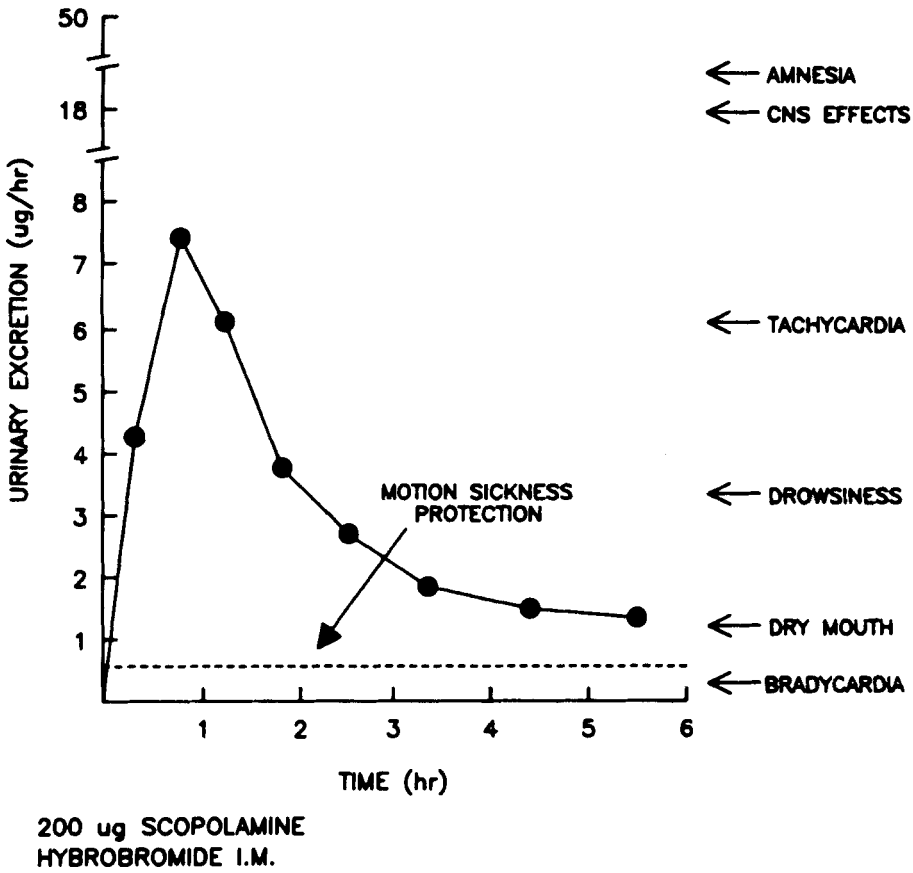


**FIGURE 5 Relationship between blood levels of scopolamine (as reflected in amount of drug excreted in urine) and pharmacologic effects. (Copyright 1987, CRC Press, Inc. Reprinted with permission from author Jane E. Shaw, ALZA Corporation).**

controlled transdermal delivery. The percutaneous absorption profiles of the drug differ widely between subjects even for the same site. Without a membrane-controlled device it becomes difficult to maintain blood levels within the narrow therapeutic window and achieve the desired selectivity, for the entire cross-section of patient population. With the membrane-

controlled Transderm-Scop®, the drug is delivered at a rate far lower than its permeation rate through the average skin and, thereby, scopolamine blood levels are precisely controlled. A recent study (33) with membrane-controlled Estraderm® showed that there was no significant difference between sites of application. The results confirm that with membrane-controlled systems one can minimize the variability.

Scientists in favor of the monolithic systems point out that although membrane-controlled systems are more sophisticated, they just don't work for 80% of the drugs available to the pharmaceutical industry today, which are suitable for transdermal delivery (34). They also suggest that manufacture of monolithic systems is inherently simpler than the manufacture of membrane-controlled systems and therefore less costly. This may or may not be true. With the monolithic systems, the drug reservoir is manufactured by dissolution of all components, including the polymer that serves as the matrix, with subsequent casting and drying (25). In some instances, the solvent may form the continuous phase of the matrix, and the process may involve mixing high viscosity fluid at elevated temperature before forming the gelled matrix either in sheet form or as a solid cylinder. Each individual unit is then punched from the sheet or sliced from the solid cylinder. Use of techniques such as injection and compression molding, common

in the plastics and rubber industries, can make these processes more efficient. However, pharmaceutical companies have been slow in adapting these technologies.

After the drug reservoir with the specified surface area is obtained, it is then assembled together with the system backing, peripheral adhesive, and protective liner -- the most labor intensive and the most expensive part of the manufacturing process. Understandably, monolithic systems of the future will be manufactured by more continuous processes such as extrusion, injection molding and laminating assembly lines.

## LAG-TIME ISSUES

The migration of a drug molecule through the skin is not instantaneous and it takes some time (referred to as 'lag time') for the drug to traverse the skin. Cooper (35) has suggested that the total lag time for transdermal medication includes not only the lag time for skin permeation but also the lag time required for the distribution of the drug in the body. Even with well-formulated systems where the adhesive carries the drug to provide the 'loading dose', this lag time may be as long as 12 hours. Furthermore, lag time to steady-state will be dependent upon the pharmacokinetics of the drug. Although

clonidine has a lag time of 8 hours, blood levels are not seen before 12 hours. Steady-state blood levels are not reached before 24 hours. This, of course, is unacceptable if the medication is needed for immediate relief. There have been suggestions that one could take a conventional dosage form (such as a tablet or capsule) as a 'bolus' dose for immediate effect, until the patch provides the necessary blood levels. This, however, will only complicate issues and may not receive the blessings of drug regulatory agencies.

The lag time becomes more pronounced if the stratum corneum acts as a 'reservoir' for the drug. Even considering modest partition characteristics, it is possible for the drug to be held back in the stratum corneum. Hydrocortisone, with a skin/water partition coefficient of approximately 10, can still be expected to be present in the stratum corneum at a level of 10% of the initial concentration 6 or 7 days postapplication (36). With more lipophilic molecules, the stratum corneum is expected to exhibit a more marked reservoir capacity. The issue is further complicated if one needs to terminate (considered to be one of the major advantages of transdermal delivery) drug input because of adverse side-effects. Drug delivery into the systemic circulation will continue from the 'depot' (stratum corneum) even after removal of the patch.

## CONCLUSION

Transdermal drug delivery is expected to become a major force in the pharmaceutical industry in the next several years. With drugs like fentanyl, codeine, testosterone, naloxone, naltrexone, nalbuphine, timolol, nadolol and numerous others under active research and expected to reach the marketplace in the very near future, the transdermal patch market will grow rapidly. Transdermal systems will provide a new means to deliver drugs in the treatment of diseased states such as hypertension, congestive heart failure, hormonal deficiency, analgesia, angina pectoris, and bronchial deficiencies. This mode of drug therapy will find particular usefulness with patients in need of night-time pulmonary relief or cardio-vascular stimulation.

The future development of transdermal delivery systems could be pursued in three different areas. First, by merely optimizing the formulation with drugs presently marketed, one might be able to achieve a suitable therapeutic blood level. Second, research with penetration enhancers should continue and long-term toxicology studies with these agents must be under-taken. Finally, drug molecules could be redesigned to achieve higher skin penetration. In addition, new manufacturing technologies that are more efficient and cost effective will

have to be developed in order to bring cost to the patient in line with more conventional routes of administration.

Iontophoresis is expected to play a major role in transdermal drug delivery. In the future it may be possible that patients will be seen wearing transdermal systems in the form of disposable, battery-operated wrist watches that will be operated and controlled by micro-chips to deliver the drug(s) at the desired rate. It may also be feasible to deliver the "not-so-potent" drugs transdermally with the help of iontophoresis. Iontophoresis will also allow the use of smaller patches which, among other things, will resolve (or at least minimize) the skin irritation problem that has so far limited the number of molecules that can be given transdermally. Some of the basic requirements of physicochemical and pharmacokinetic properties (such as low molecular weight, low dose, 'balanced' water-oil partition coefficient, relatively short biologic half-life, etc.) that a molecule must possess, before it can be considered for transdermal delivery now, may not be as important for an iontophoretically controlled device of the future.

Transdermal drug therapy will revolutionize the concept of "dose" of drug to be administered. No longer will physicians prescribe a certain "dose" of a drug, but will prescribe drugs

to be given at a certain "rate". Systems will be designed to give variable rates with variable areas. Transdermal patches with combination products such as a decongestant and an antihistamine will also become feasible.



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