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Introduction

The "transdermal system" product concept has enjoyed a fast paced development in recent history. The term "transdermal system" applies to products that provide **controlled** delivery of drugs for **systemic** circulation rather than simple topical application of some pharmacologically active compound to the skin, especially for local effects. A transdermal system is characterized by some level of "system" control of drug delivery, and well defined "unit dose" product presentation as well as the systemic derived efficacy.

Testing transdermal systems, then, must not only address the traditional pharmaceutical dosage properties, such as potency, uniformity and purity, but also chemical and physical performance. This discussion will focus on physicochemical testing of transdermal systems.

Dissolution Performance Testing Of Transdermal Systems

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Dissolution/Release Rate/Performance Testing System Design

In addition to the characteristic "skin patch" physical format, transdermal systems distinguish themselves from other dosage forms, such as oral tablets, in their **mechanism** of drug delivery. For example, tablet dosage forms deliver drug through a series of physical and phase changes, as described below:

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                disintegration
Tablet ----------------------> Aggregates

                de-aggregation
Aggregates ------------------> Particles

                dissolution
Particles -------------------> drug in solution
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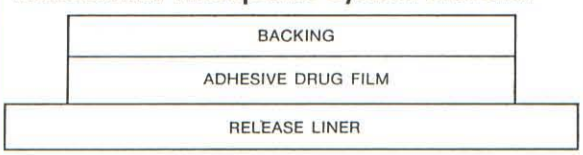
Transdermal systems release drug by various diffusion mechanisms because the drug is already "in solution" in the polymers. It is important to understand the particular mechanisms and the various system designs to develop appropriate in vitro testing.

The simplest system design is a laminate system comprised of a monolayer drug reservoir, generally with a backing film (Fig. 1).

Figure 1
Transdermal Therapeutic System Monolith

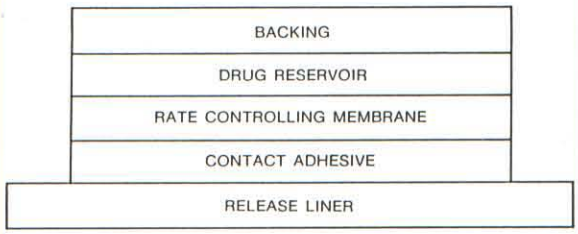


In such a system, the drug is dispersed and/or dissolved in the monolith (generally some form of polymer) and diffuses out of the system. The amount of drug released is governed by surface area, drug diffusion coefficients, monolith thickness and concentration of the drug in the polymer. Quantitative treatment of this process is defined by Fickian diffusion laws. As such, the driving force for the diffusion is the difference between drug concentrations in the polymer and the receptor solution.

The next level of complexity is the addition of a rate-controlling membrane in the system, as in Figure 2. This system also has an added adhesive layer because the rate-controlling membrane often does not have adhesive properties.

Drug release is controlled when the membrane diffusion is slower than diffusion within the reservoir.

Figure 2
Transdermal Therapeutic System Multilaminate



The expected drug delivery pattern of such a laminate system is a function of drug content in the reservoir, the relative rates of diffusion within the reservoir and through the rate-controlling membrane (generally slower diffusion in the membrane), surface area and the thickness of especially the rate-control membrane. Such a system design can yield a period of zero order rate delivery.

Such a system can also provide a bi-phasic pattern by including drug in the adhesive. Such a drug-loaded adhesive will release the drug quickly, especially relative to the controlled release of the rest of the system, providing a "burst" of drug. The particulars of the burst will be controlled by the

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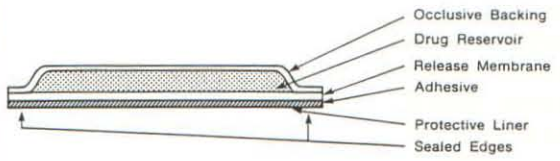
parameters of the monolith system discussed earlier.

Other transdermal systems are variations of these laminate designs. For example, one design, uses a liquid drug reservoir. Such a system, even though the liquid might be viscous, requires that the reservoir be "contained". The solution is a "form-fill-seal" (Fig. 3).

Transdermal In Vitro Methods

No matter the physical nature of the system, the theoretical drug release pattern must be estimated by various in vitro methods. Two general in vitro methods are conducted, one to challenge skin permeation, the other to control the product's development and manufacture.

Figure 3
Form-Fill-Seal System Design

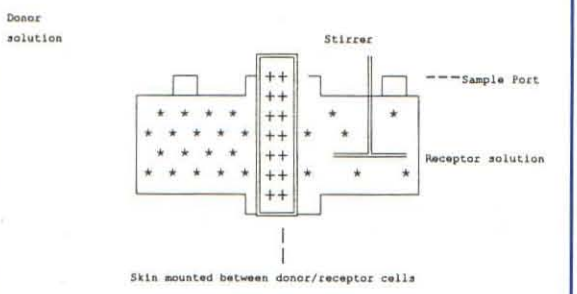


Dissolution Performance Testing Of Transdermal Systems

Skin Permeation In Vitro Method

The initial performance testing, even before the system is designed, is to determine the drug's permeation through skin. Such an in vitro test, as developed by SK Chandrasekaran[1], involves mounting various skin tissues, whole skin, epidermis or dermis, in a "diffusion cell" (Fig. 4).

Figure 4
Diffusion Cell Permeation Test



A drug solution is placed in contact with the surface of the tissue. An appropriate receptor solution is placed on the other side of the tissue and the drug is allowed to permeate through the skin tissue at controlled temperatures. The receptor solution is sampled periodically and assayed for the drug substance.

Such an experimental system allows evaluation of whether the drug is immobilized within the skin or whether there is any permeation through skin. If there is permeation, the rates can be determined and evaluated. An example of the value of such experiments was the determination of preferred skin site for placement of the scopolamine transdermal system. Skin samples from various body locations were studied for permeation rates (Fig. 5). Based on these data, the postauricular skin was selected.

Control Methods For In Vitro Performance Testing

Control methods for transdermal system performance testing must reflect various method issues. These issues ultimately define the particulars of the in vitro test method. The issues include:

- Theoretical System Design
- Temperature Effects
- Stirring Effects
- Drug Solubility/Media Effects
- Mechanical System/ Collection Format

Theoretical System Design

The in vitro method must be designed to accommodate the system design. A simple issue is that the method must accommodate the system size and basic type. Size is intuitive, but the basic type may limit options. For example, a very large laminate system could be cut into a more manageable sample aliquot because release performance is proportional to system surface area (as discussed previously); however, a form-fill-seal type system must be tested intact, regardless of size.

The method must also accommodate the system's theoretical release pattern. If the system is designed to provide a burst of drug or loading dose, the time intervals should be set to specifically capture this part of the release pattern in addition to the controlled-rate portion of the pattern. Loading-dose systems also require other considerations that will be addressed later.

Temperature Effects

Diffusion through polymers or through rate control membranes are affected by temperature. The target temperature is generally selected as 32 C or 35 C (rather than the normal 37 C used for oral dissolution testing) to better approximate the surface temperature of the skin. Temperature control throughout the test and over each test fixture (to within 0.3 C) is required for accurate and precise rate measurements. The temperature effects may be more pronounced for the rate-controlled portion of the pattern than the "uncontrolled" burst portion.

Stirring Effects

Diffusion-controlled release of a monolith type system depends on the concentration of the released drug in the receptor solution. Of more direct concern is the "apparent" concentration at the system-receptor solution interface. Poor stirring will result in a concentration gradient building at this interface, resulting in a reduction of diffusion drug flow. As stirring rates increase (to some level) the thickness and extent of this concentration gradient **decreases** to a point at which the diffusion rate controls the release pattern. Higher stirring rates would not yield any significant change in the observed release profile. The real value in stirring at levels that will not increase the rate is that minor variations in stirring will not affect the observed rates.

Drug Solubility/ Media Effects

Release of the drug into the receptor solution is directly affected by the concentration of the drug in the receptor solution in general and at the system-solution interface in particular. More correctly, however, the drug release is affected by the activity or "percent saturation" in the system and the receptor solution. As discussed earlier, this difference in concentration/activity is the driving force for the drug diffusion. Therefore water insoluble drugs reach inhibiting concentrations (percent saturation) more quickly than water soluble drugs. The particulars of the release rate mechanisms are best when they limit the drug concentration in solution to less than 10% saturation, in any collection period or vessel.

One approach that may be used is to add surfactant or organics to the aqueous receptor solution to modify the drug solubility. Though such an approach may demonstrate increased release rate measurements or limit inhibitory saturation levels, such modifiers may also "modify" the diffusion coefficients of the drug in the polymers or membranes

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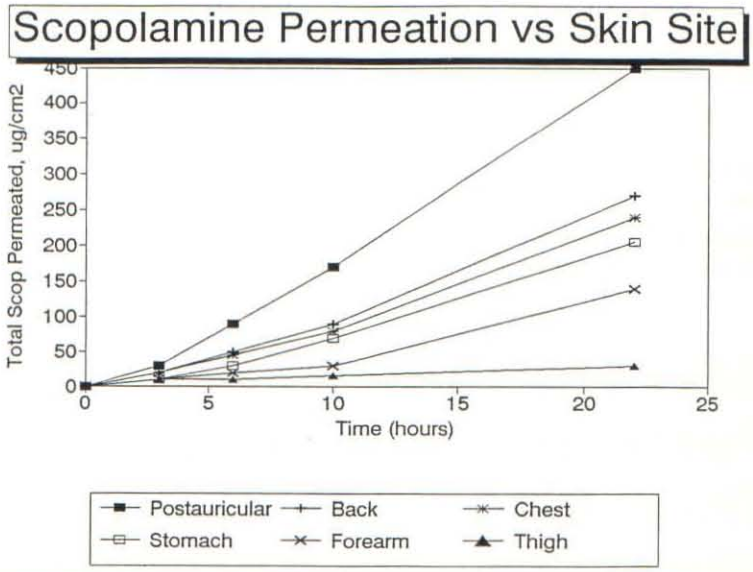
Figure 5



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and yield misleading release rates. The easiest way to limit saturation effects is to use larger volumes or shorter collection intervals. This leads to the next issue.

Mechanical System/ Collection Format

One of the more debated variables in transdermal system performance testing is the apparatus used to conduct the test. The literature presents a wide array of equipment, stirrers, shakers and the like. The USP 23 has three official apparatuses (numbers 5, 6 and 7). The diffusion cell apparatus has already been described for measuring drug permeation through the skin. Such a cell can be used also for control testing by mounting the transdermal system, such as a monolith system, in direct contact with the receptor solution (donor side not needed). The receptor solution is sampled, or sampled and replaced, at periodic intervals. The sample aliquots are submitted for drug analysis and the amounts of drug per interval are determined. More frequently, however, whole systems need larger

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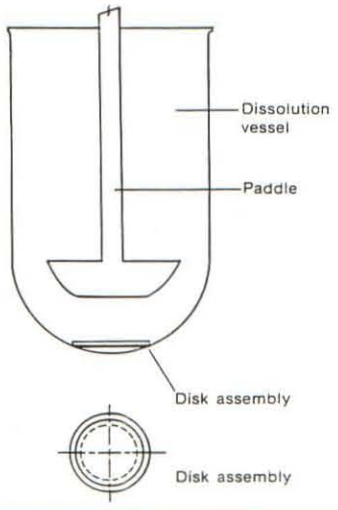
receptor solution volumes than can be accommodated by available diffusion cells, at least to meet the percent-saturation-limit requirements. Therefore, diffusion cells are not an apparatus of choice.

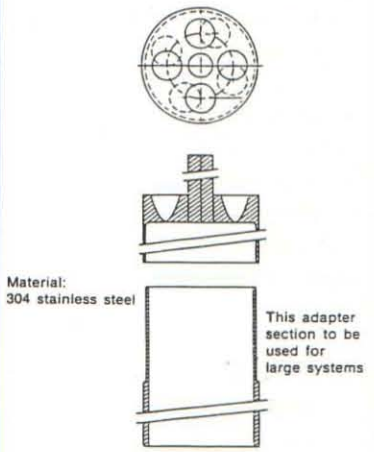
Figure 6
Paddle Over Disk



Of the more commonly used systems, the general distinguishing mechanical feature is the collection format. Collection formats are either cumulative, flow through or interval.

The cumulative collection format collects the released drug in a single container. Equipment providing cumulative collection formats are readily available in that a standard oral dissolution system can be modified to conform to USP Apparatus 5 and 6[2]. Apparatus 5 is referred to as "paddle over disk" while Apparatus 6 uses a spinning cylinder to stir the system. Sampling is by incremental "sipper" systems or flow pumps. The drug concentration in the vessel increases in a cumulative manner. See figure 6 for a diagram of the "paddle over disk." Note that the system is attached to a disk at the bottom of a standard dissolution vessel; however the physical size of the system may make its use rather impossible or may require deviations from the specified clearances. Apparatus 6 uses the same system as Apparatus 1, except the basket is replaced with the "cylinder stirring element" (Fig. 7). The transdermal system is attached to the circumference of the cylinder via occlusion with water-permeable Cuprophan, release surface to the Cuprophan, facing the receptor solution and either glued to the cylinder or held in place with "o-rings". Cuprophan is an inert porous cellulose material, available from Akzo, Enka, AG, West Germany.

Figure 7
Cylinder Stirring Equipment



Flow-through systems have small "cell volumes" and use a controlled flow of receptor solution through the cell to collect the drug. The drug released is either measured directly in the flowing solution or from a well-stirred collection vessel. This format has an advantage because the transdermal system sees a "constantly fresh" receptor solution; however the format does not have commonly available equipment and is not well represented in the literature.

Interval collection involves collecting the drug released in a series of receptor solutions, each indexed to a specific interval, USP Apparatus 7. The equipment stirs the system in the first collection vessel for a set time (collecting in a cumulative manner within the time interval), then it physically moves the transdermal system to another, fresh receptor solution for another time interval. The drug content in the various interval solutions directly reflects the release rate within the time interval. The system is held onto a "holder" of various configurations, one is currently listed in the USP, either by occlusion with Cuprophan or with inert netting in a manner similar to the USP Apparatus 6 as described above (Fig. 8 and 9). The holder then "reciprocates" the system in the receptor solution for the specified interval at about 30-60 cycles per minute with a stroke of about 2-3 cm.

Selection of the physical apparatus is often driven by d the availability of equipment. However, the decision should be made on the basis of system design (for example, burst or no burst) and the performance aspects that require measurement. If the system has a simple zero-order design yielding high rates of a drug that will not reach inhibitory percent saturation, almost any physical system/ collection format will work. However, for transdermal systems that have patterned drug release, low zero-order rates, or drugs with solubility concerns, the "interval" collection format has significant advantages. Interval collection can capture dramatically different parts of the release pattern, such as the burst, to eliminate the burst concentrations on subsequent controlled rate performance, to allow optimization of the analytical operation on dramatically different drug concentrations and to allow repetitive sampling of each interval's solution with volume-intensive analytical methods.

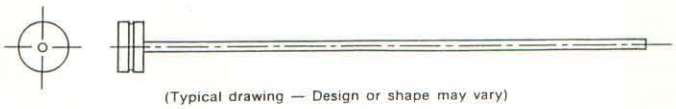
Summary

Transdermal system performance testing is an important part of both development and control. The details of performance testing require a knowledge of the system pharmaceutics, the theoretical release profile, the chemistry of the drug substance (notably aqueous solubility and diffusion constants), the particular apparatus used to agitate the system and finally, on the type of data required (cumulative, or emphasis on rate performance.)

References

1. Chandrasekaran, Michaels, Campbell Am Inst Chem Eng J 22:828-832 (1976)
2. USP 23, <724> Drug Release, pp.1793-1799, 1995

Figure 8
Reciprocating Disk Sample Holder



(Typical drawing — Design or shape may vary)

Figure 9
Apparatus for Dissolution Performance Testing of Transdermal Systems