Transdermal therapeutic systems: a review

Patients and consumers will ultimately decide which products are the winners in the market for transdermal therapeutic systems (TTS).

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Two decades ago, scopolamine was the first drug to be marketed in the form of a transdermal therapeutic system (TTS). Since then, the market share of this innovative dosage form has been growing constantly, and products have been launched in all major markets of the world. However, the number of drugs that can be delivered transdermally is more limited than was originally expected in the pioneering times of the late 1980s. The most prominent product successes to be named are clonidine, oestradiol, fentanyl, nicotine, nitroglycerine, norethisterone acetate, testosterone and tulobuterol.

In the 1990s, a solid knowledge-base of the opportunities and limitations for transdermal drug delivery has been gathered (1,2). While a large number of publications can be found in the fields of theoretical models and experimental investigations, know-how about the industrial development and large-scale production of TTS is more or less completely in the hands of a limited number of specialised companies.

TTS basics

The main permeation barrier for most drugs is the stratum corneum, which is typically only 10-15 µm thick and consists of several layers of non-viable cornified cells. The interspaces between these corneocytes are filled with several lipid bi-layers, and the whole construction is similar to bricks and mortar. Several specialised pathways, like hair follicles and the ducts of different glands, interrupt this barrier but are rarely involved in the absorption of drugs to a noteworthy extent (3). The intercellular lipid bi-layers are the most important lipophilic pathway for drug absorption. This lipid barrier more or less dictates the physico-chemical characteristics of a drug to be a candidate for transdermal absorption. The following parameters should ideally be within the listed ranges:

- Molecular weight <1000 daltons and preferably <500 daltons,
- Melting point <200°C,
- Log partition coefficient octanol/water between 0.0 and 2.0, and
- No or few polar centres, like carboxylic groups or zwitter ionic structures.

The kinetic half-life of the drug should not exceed 6-8 hours, since transdermal delivery in effect mimics an intravenous drip infusion. The distinction between local or systemic delivery via the transdermal route in principle only depends on the question of whether therapeutically-effective plasma levels of a drug are obtained or not. The main advantages of transdermal over oral drug delivery can be seen as the possibility to maintain therapy with drugs having only a short biological half-life, and to avoid the chemically aggressive conditions of the gastrointestinal tract and the hepatic first-pass effect. Furthermore, medication regimens can be simplified and patient compliance can be improved. Especially with conventional oral forms, plasma peaks typically occur shortly after intake. For potent drugs with a
narrow therapeutic window, side effects or even adverse effects may be related to these peaks. With oral forms, patients often have to be titrated carefully to this type of drug. Transdermal systems offer the possibility to avoid undesirable plasma peaks as a result of the smooth onset of delivery (4).

On the basis of cosmetic appeal, and especially patient-comfort, a system size of 50 cm² is, in most cases, the upper limit for a TTS. A transdermal dosage of 5–20 mg per day is usually the maximum feasible. Once-a-day, twice-weekly or seven-day applications are best correlated with human routines.

Within the last decade, the construction of marketed transdermal systems has undergone a number of significant improvements. The historical approach to TTS construction includes a drug-containing reservoir (for example, a solution or semi-solid preparation of the drug) with an adjacent release rate-controlling membrane to provide zero-order release. An additional adhesive layer is used to affix this system to the skin (Figure 1a). Ongoing functional integration (Figures 1b and 1c) finally resulted in a monolithic matrix system without a membrane - as is the case with many modern systems (Figure 1d). The drug-releasing matrix directly contacts the skin and has self-adhesive properties at the same time. The whole application area is available for drug delivery, so that these systems can be smaller in size. Thus, developmental efforts and innovative formulation strategies have enabled a high degree of functional integration into a simplified system construction.

Special techniques

Penetration enhancers, liposomes and prodrugs

Since many drugs lack the ideal physico-chemical properties to be absorbed via the transdermal route, chemical penetration enhancers attract much interest in the field of TTS development. Numerous compounds have been described in the literature (5). In the classical sense, enhancers work on the lipid bi-layers in the stratum corneum by, for example, disordering of the lipids, widening of polar pathways or increased solubility of the drug within the barrier - all of which result in accelerated diffusion of the drug through the skin. These effects should be transient and reversible. A large number of the enhancers known today lack the necessary toxicological data (for example, GRAS status). The risk of skin irritation usually increases in parallel with the degree of effectiveness; thus, chemical enhancement may be an essential tool in a limited number of cases and should be used with care. A strong permeation-enhancing effect can result from skin occlusion by impermeable backing layers. Hydration and swelling of the stratum corneum goes hand-in-hand with increased permeability for most polar and non-polar drugs.

Liposomes have often been proposed as vehicles for dermal and transdermal delivery of the enclosed drugs. There is evidence for liposomes being supportive during drug incorporation into the upper layers of the stratum corneum - not to forget that liposome formulations typically include surfactants which are usually also enhancers. Today, it is generally accepted that liposomes do not permeate the skin intact as a complete entity.

The use of more lipophilic prodrugs is another strategy to improve the transdermal absorption of inappropriate molecules. Lipophilic esterification of carboxylic groups, or acetylation of primary and secondary amines, can increase the transdermal absorption of a drug. Since the capacity for biotransformation in the skin is very low in comparison with the liver, any prodrug concept should be carefully verified. Considerable amounts of the prodrug might enter the systemic circulation, in contrast to oral delivery. Thus, prodrugs are a feasible concept but, in highly regulated markets, they may easily turn out as a completely new drug during development, and finally in the toxicological and clinical dossier for a transdermal dosage form.

Figure 1. Typical system constructions.

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Electric current can be employed as part of various methods to facilitate transdermal transport of drug molecules which are inappropriate for passive transport. Among these, iontophoresis and, especially, electroporation are the most frequently studied techniques (6). While iontophoresis creates an electromotive force driving charged molecules through the barrier, electroporation acts by the application of high voltage pulses in a less specific manner and transiently opens pore-like pathways in the barrier layers for compounds which would otherwise be too large or too polar.

Both techniques are promising tools for the delivery of new classes of drugs, such as peptides, small proteins or oligonucleotides. In this respect, they have to compete with advances in other fields, like nasal or transmucosal delivery. Currently, transdermal insulin therapy still seems to be beyond the scope of electrically assisted systems.

Iontophoresis can be further employed to shorten the lag-time of TTS. With passive diffusion, effective plasma levels are typically only reached after several hours. In the field of pain management and other acute therapies, rapid onset of action is required; this can be facilitated by initial iontophoresis, although the chances for real bolus delivery still appear to be limited. Currently, iontophoresis is the only technique that would enable pulsatile transdermal drug delivery in a reproducible time- and rate-controlled manner.

The development of miniaturised systems for use by outpatients is costly in terms of both scientific and regulatory aspects. At the moment, the vast number of patents in this field is in strong contrast to the market share held by electrically assisted TTS. In addition, very little information has been published on their dermal tolerability; they will probably form more of a niche market within TTS, rather than represent the next generation of transdermal system.

Phonophoresis The application of ultrasound (typically 100-1,000 kHz) is known to lower the permeation barrier of the skin for a number of chemically different compounds. Several underlying mechanisms are being hypothesised - among which is the formation of gaseous bubbles within the stratum corneum by cavitation. The potential of this kind of enhancement again appears to be limited with regard to the necessary miniaturisation of systems.

Heated devices The typical surface temperature of human skin is recognised to be 32°C. Heating can improve the transdermal absorption and shorten the lag-time of drugs, but its use is limited since temperatures above 40°C induce pain or at least discomfort for the patient. Nevertheless, progress has been made in the implementation of chemically-driven heating devices into marketable forms of TTS.

Supersaturation represents a potent means to enhance transdermal absorption, since it strongly increases the driving force with which a drug can be released from the matrix into the skin. In contrast to aqueous or organic solutions, supersaturated polymeric matrices can be kept in a meta-stable condition for a prolonged time period, in some cases even for years - that is, the whole shelf-life of the TTS. Directly supersaturating a system with a drug during manufacture adds a risk of recrystallisation of the product. Various ways to inhibit recrystallisation have been identified. Among these, thermodynamic “freezing” inside a polymer is one possibility: at storage conditions, the drug remains entrapped in the polymeric matrix whereas, during application, the drug is mobilised by thermodynamic changes in the polymeric structure.

To avoid the risk of direct supersaturation, strategies can be employed to ensure supersaturation only in situ after application to the skin, for example:
- evaporation of a drug solvent from the system (Figure 2a),
- uptake of water from the skin (Figure 2b), and
- activation of thermodynamically “frozen” drug-supersaturated islands by hydration (Figure 2c).

In particular, the uptake of water can be utilised to initiate a variety of significant increases in the thermodynamic activity of a TTS; this may even involve phase separation or phase reunion within more complex systems. A fuller understanding of these processes - especially in multi-component formulations - is worthy of further intensified research.

Future prospects

Due to their breakthrough image, sophisticated approaches such as iontophoresis and electroporation have attracted most public attention on transdermal forms in the last decade. So far, the pharmaceutical market has not reflected the strong developmental efforts in this field. Delivery of oligopeptides, oligonucleotides and other highly polar drugs has been physically demonstrated, but certain obstacles are not yet being mastered completely, for example, skin tolerability, skin pH, electrically induced degradation, unintended transport of physiological ions and enzymatic degradation in the epidermis.

At the same time, numerous galenical concepts have been invented to improve the performance and economics of classical TTS constructions, especially matrix systems. Although less spectacular, many of these inventions could be implemented for products currently on the market, as well as those entering the market over the next few years. Female - and also male - hormone replacement appears to be the segment of the TTS market with
the strongest growth. New entrants to the market can be expected in the fields of pain management, and the treatment of Alzheimer's and Parkinson's disease.

Generally-speaking, this form of drug delivery is no longer in its infancy. It has already generated a highly competitive market, with generic forms expected to follow expiry of major patents. Industry awareness of the opportunities offered by transdermal delivery in early phases of drug development is already high and will grow still further. Patients and consumers will ultimately decide which products are the winners in the TTS market - their needs and desires must be analysed and fulfilled. Systems should be small, thin, safe and reliable. Normal activities - such as showering, swimming and sport - should not be restricted; this poses a challenge in terms of choice of materials, especially adhesives and backing materials. From an industrial standpoint, new product innovations will also need to be assessed in terms of time-to-market, cost of goods and new product value.

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References