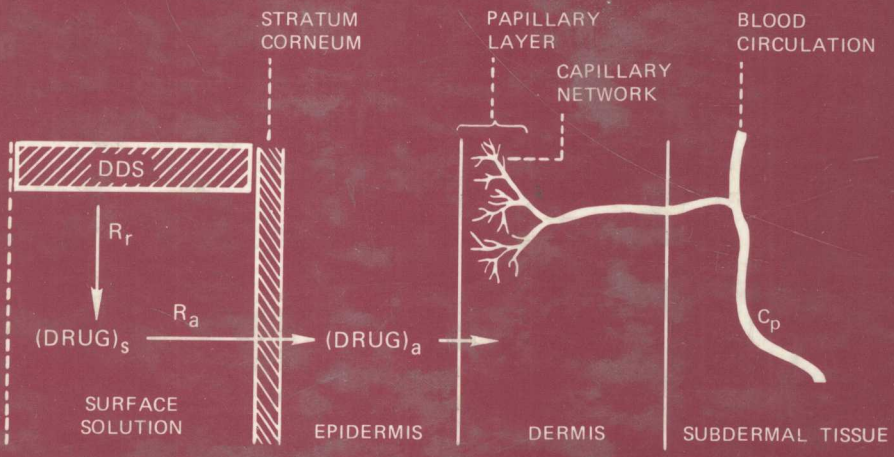
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 31

Transdermal Controlled Systemic Medications



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Advances in Transdermal Systemic Medication

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I. INTRODUCTION

Continuous intravenous administration at a programmed rate of infusion has been recognized as a superior mode of drug delivery not only to bypass hepatic "first-pass" elimination, but also to maintain a constant, prolonged, and therapeutically effective drug level in the body. A closely monitored intravenous infusion can provide the advantages of direct entry of drug into the systemic circulation and control of circulating drug levels. However, this mode of drug delivery entails certain risks and, therefore, necessitates hospitalization of the patients and close medical supervision of the medication.

Recently, there has been a growing recognition that the benefits of intravenous drug infusion can be closely duplicated, without its hazards, by using the intact skin as the port of drug administration to provide continuous transdermal drug delivery into the systemic circulation (1).

Several transdermal therapeutic systems have recently been developed for topical application on the intact skin surface aiming to achieve systemic medication. This approach was exemplified first by the development of scopolamine-releasing transdermal therapeutic system (Transderm-Scop by Ciba) for 72-hr prophylaxis or treatment of motion-induced nausea (2), and then by the successful marketing

of several nitroglycerin-releasing transdermal therapeutic systems (Deponit by Pharma-Schwarz/Lohmann, Nitrodisc by Searle, Nitro-Dur by Key, and Transderm-Nitro by Ciba), as well as an isosorbide dinitrate-releasing transdermal therapeutic system (Frandol tape by Toaeiyo, Yamanouchi) for once-a-day medication of angina pectoris (3,4), and most recently by the regulatory approval of a clonidine-releasing transdermal therapeutic system (Catapres-TTS by Boehringer Ingelheim) for weekly treatment of hypertension (4).

The intensity of interest in the potential biomedical applications of rate-controlled transdermal drug administration is further demonstrated by a substantial increase in research and development activities in many health care institutions aiming to develop patentable transdermal therapeutic systems to provide a continuous transdermal infusion of therapeutic agents for prolonged periods of time. The drug candidates evaluated have ranged from antihypertensive, antianginal, antihistamine, and anti-inflammatory agents to analgesic, antiarthritic, steroidal, and contraceptive drugs.

This chapter discusses the logic behind the concept of using intact skin as the port for continuous drug infusion as well as the historic perspective and advances in the development of rate-controlled transdermal therapeutic systems.

II. THE SKIN: SITE OF TRANSDERMAL DRUG ADMINISTRATION

The skin of an average adult body covers a surface area of approximately 2 square meters and receives about one-third of the blood circulating through the body (5). It is one of the most readily accessible organs of the human body. With a thickness of only a few millimeters (2.97 ± 0.28 mm), the skin separates the vital organs from the outside environment, serves as a protective barrier against physical, chemical or microbial attacks, acts as a thermostat in maintaining body temperature, plays a role in the regulation of the blood pressure, and protects the human body against the penetration of ultraviolet rays.

Microscopically, the skin is a multilayered organ composed of many histological layers. It is generally described in terms of three major multilaminate layers: the epidermis, the dermis, and the hypodermis (Fig. 1). The epidermis is further divided into five anatomical layers with the outermost layer of stratum corneum exposed to the external environment.

The stratum corneum consists of many layers of compacted, flattened, dehydrated, and keratinized cells. These cells are physiologically rather inactive and are continuously shed with constant

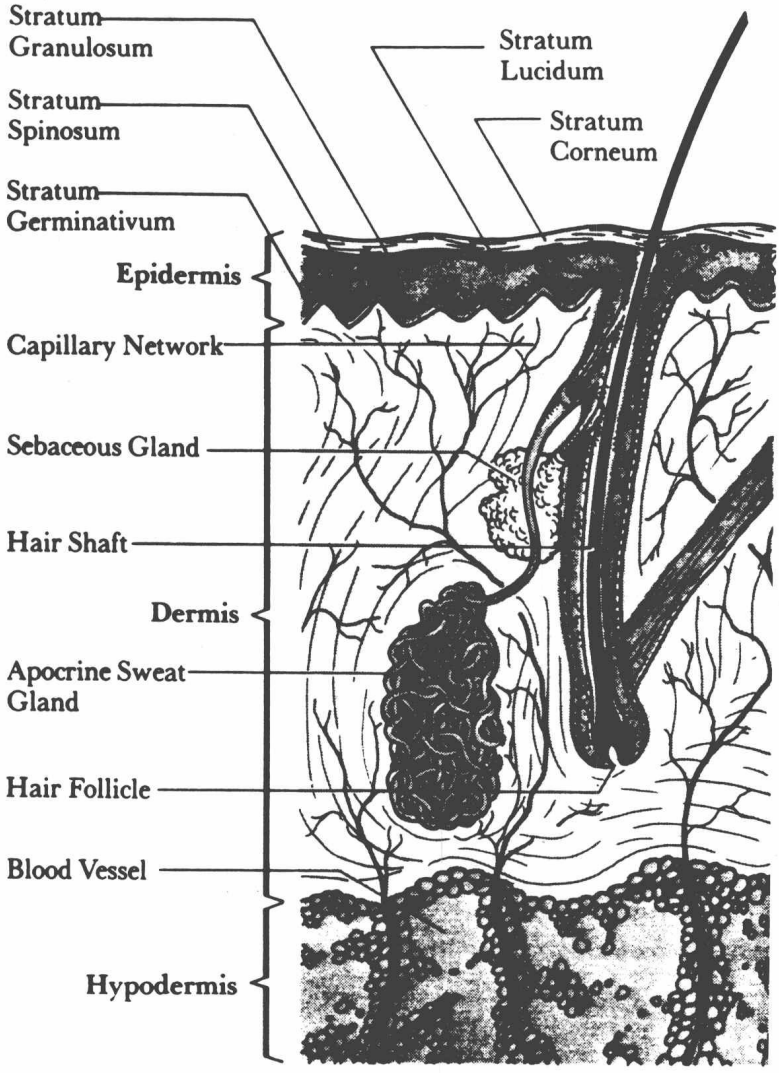

Figure 1 A cross-sectional view of human skin, showing various skin tissue layers and appendages. (From Ref. 6.)

replacement from the underlying viable epidermal tissue (6). The stratum corneum has a water content of only 20% as compared to the normal physiological level of 70%, such as in the physiologically active stratum germinativum (which is the regenerative layer of the epidermis).

The human skin surface is known to contain, on the average, 10–70 hair follicles and 200–250 sweat ducts on every square centimeter of skin area. These skin appendages, however, actually occupy, grossly, only 0.1% of the total human skin surface. Even though foreign agents, especially water-soluble ones, may be able to penetrate the skin via these skin appendages faster than through the intact area of the stratum corneum, this transappendageal route of percutaneous absorption has provided a very limited contribution to the overall kinetic profile of transdermal permeation. Therefore, the transdermal permeation of most neutral molecules at steady state can be considered as, primarily, a process of passive diffusion through the intact stratum corneum in the interfollicular region. So, for a fundamental understanding of transdermal drug infusion (7), the organization of the skin can be represented by a simplified multilayer model as shown in Figure 2.

For many decades, the skin has been commonly used as the site for the administration of dermatological drugs to achieve localized pharmacological action in the skin tissues. In such cases, the drug molecules are considered to diffuse to a target tissue in the proximity of drug application to produce their therapeutic effect before

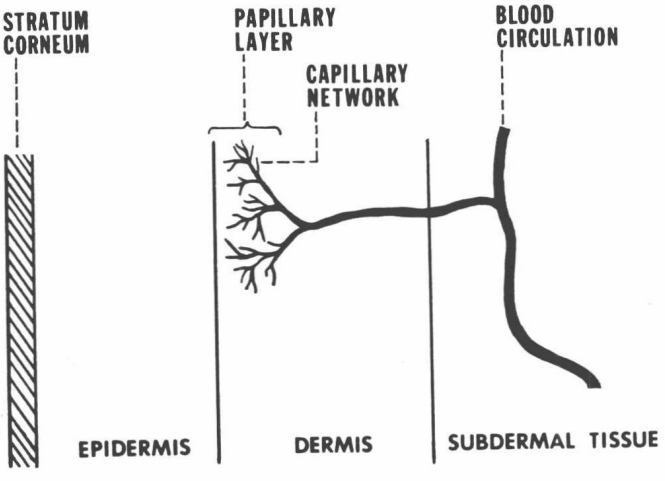

Figure 2 A simplified model of the human skin for mechanistic analysis of skin permeation. (From Ref. 7.)

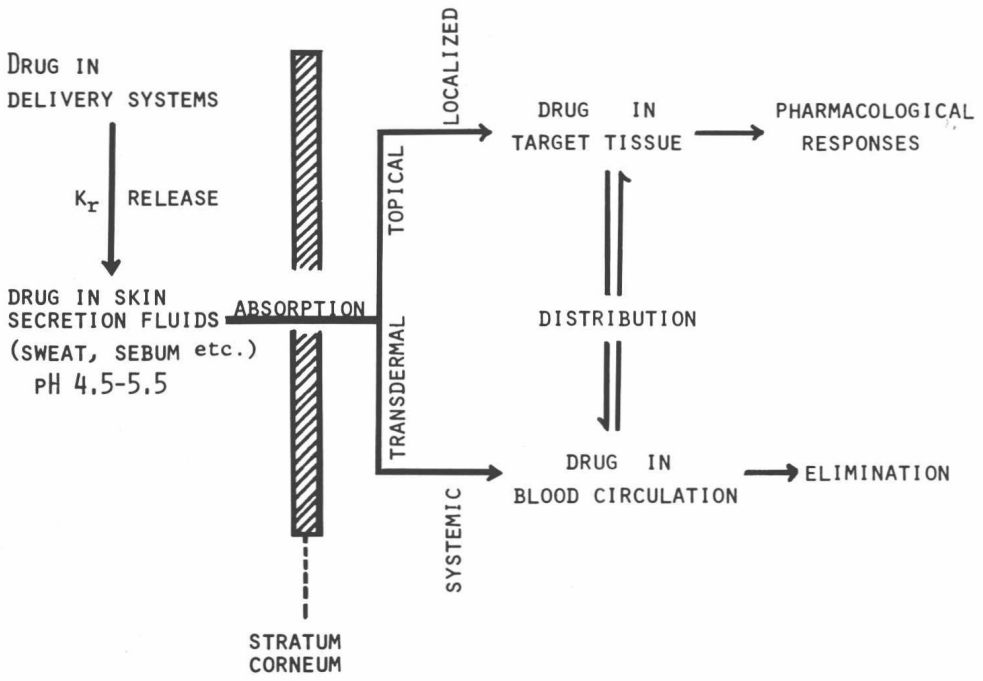

Figure 3 Schematic illustration of drug release and absorption across the skin tissues for localized therapeutic action in the tissues directly underneath the site of drug administration or for systemic medication in the tissues remote from the site of topical drug application. (From Ref. 7.)

being distributed to the blood circulation for elimination (Fig. 3). The use of hydrocortisone for dermatitis, benzoyl peroxide for acne, and neomycin for superficial infection (8) are the few examples of application.

As discussed earlier, there is increasing recognition that the skin can also serve as the port of administration for systemically active drugs (Fig. 3). In this case, the drug applied topically will be absorbed first into the blood circulation and then will be transported to target tissues, which could be rather remote from the site of drug application, to achieve its therapeutic purposes. Examples include the transdermal controlled delivery of nitroglycerin to the myocardium for the treatment of angina pectoris, of scopolamine to the vomiting center for the prevention of motion-induced

sickness, and of estradiol to various estradiol-receptor sites for the medication of postmenopausal syndromes (9–11).

III. EARLY DEVELOPMENT OF TRANSDERMAL DRUG DELIVERY

The potential of using the intact skin as the port of drug administration to the human body has been recognized for several decades, as evidenced by the development of medicated plasters for administering medication through the skin to the underlying areas. By definition, the plaster is also a drug delivery system designed for external application. It is made of adhesive material and with proper balance of cohesive strengths, the adhesive is bonded to the backing support (Fig. 4). Such a proper balance also provides good bonding to the skin when a plaster is applied and permits a clean break from the skin surface when the plaster is removed. Historically, the medicated plaster can be viewed as the first development of the idea of transdermal drug delivery. It affords protection and support by its occlusive action, and it brings medication into close contact with the skin (12).

Little is known of the historical development of medicated plasters. However, their use can be traced back at least several hundred years to ancient China. Two representative Chinese medicated plasters, which are still available for medical practice in China, are shown in Figures 5 and 6. As indicated in Tables 1 and 2, these early generations of medicated plasters tend to contain multiple ingredients of herbal drugs and are intended for localized action in the tissues directly underneath the site of application (Fig. 7).

The medicated plaster is also very popular in Japan in over-the-counter pharmaceutical dosage forms and it is also called cataplasm (13). Salonpas is a typical example (Fig. 8). Although still composed of multiple ingredients, including six therapeutically effective agents (Table 3), the formulation has been so improved that Salonpas

Figure 4 Cross-sectional view of a medicated plaster, showing various major structural components.

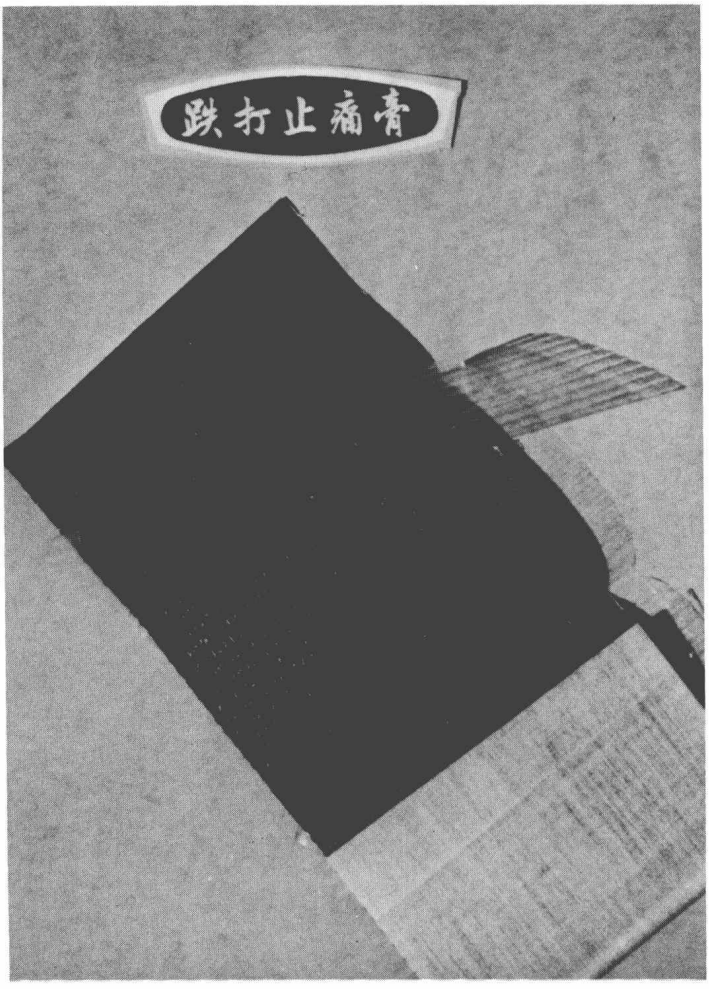

Figure 5 The Yang-Cheng medicated plaster, manufactured by the United Pharmaceutical Manufactory, Kwangchow, China, used on bruises and for its analgesic properties.

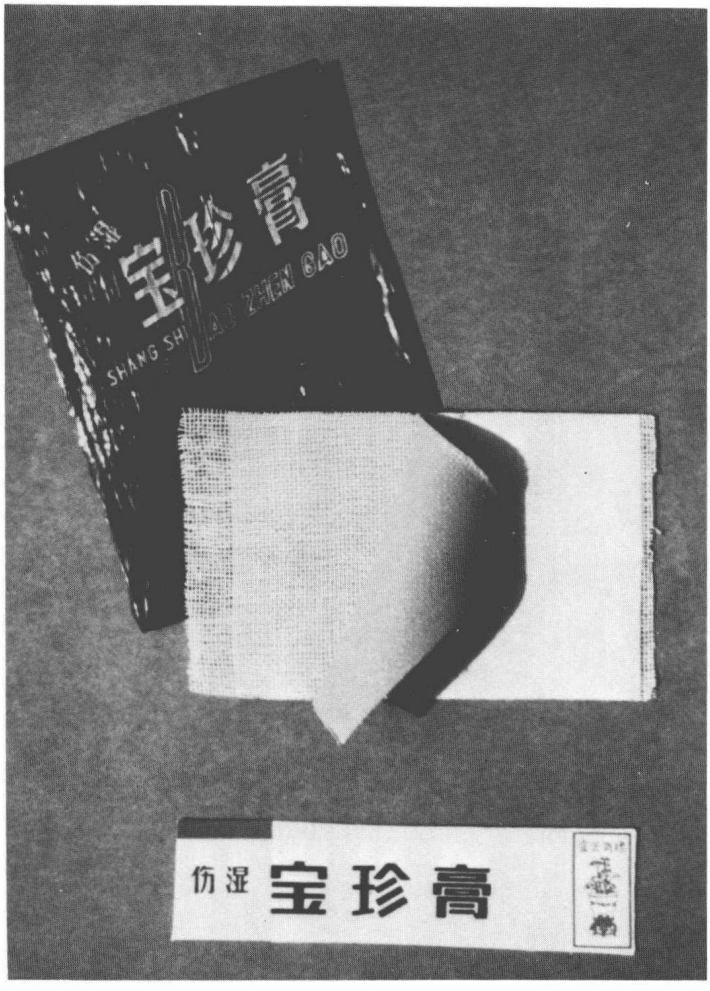

Figure 6 The Shang-Shi Bao Zhen Gao medicated plaster, manufactured by Shanghai Chinese Medicine Works, Shanghai, used for rheumatoid arthritis.

Table 1 Chinese Medicated Plaster for Bruises and as Analgesic

Main ingredients	Content (%)
Fossilia ossis mastodi	10.42
Eupolyphagasinensis walker	10.42
Sanguis draconis	4.17
Catechu	6.25
Myrrha	6.25
Rhizoma drynariae	4.17
Radix dipsaci	4.17
Flos carthami	9.17
Rhizoma rhei	8.33
Herba taraxaci	8.33
Mentholum	20.00
Methylis salicylas	8.32

Description and action: This plaster is prepared according to the dialectic therapeutics of traditional Chinese medicine. The elements of the various drugs and herbs, when applied to the skin, will penetrate into the subcutaneous tissues to stimulate circulation and produce a local analgesic effect. This plaster helps to cure inflammation of muscles and to promote the healing of bone fractures.
Indications: Bruises
Fractures
Sprains
Swelling and pains
Bad circulation of blood
Injuries and wounds
Rheumatic arthritis
Neuralgia
Limb languor
Directions: Cut a piece of desired size from the roll, remove the cellophane and apply to the affected part. Medicinal effect lasts 24 hr.