약물 경피 흡수시 *In vivo* 와 *In vitro* 에서의 상관관계

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Dynamic Control of Transdermal Drug Delivery

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Introduction

In the past, we commonly believed that the skin was a virtually impermeable barrier to foreign compounds including drugs. However due to the recent advances in transdermal therapeutic systems, the skin barrier may be controlled physically and/or chemically by enhancing the permeability without damaging the structure of skin.

Since 1982, several transdermal delivery systems have been successfully introduced in the market for administering systemically active drugs through the intact skin. The drugs used clinically in the transdermal delivery formulations are scopolamine for motion sickness, nitroglycerin and isosorbide dinitrate for angina pectoris, clonidine for hypertension, estradiol for hormone deficiency of menopause and osteoporosis, fentanyl for pain control and nicotine for smoking cessation. When the transdermal patch is applied on the skin, the drug molecules continuously penetrate through the skin to reach the systemic circulation, resulting that the drug concentration in the blood remains constant for many hours or even days during the medication. Once-a-day or once-a-week patches have significantly improved the patient compliance. This is particularly the case in transdermal delivery of nitroglycerin used to control chest pain associated with heart diseases.

Dynamic Control of Blood Concentration

In spite of wide application of transdermal drug delivery, we have yet clear evidence demonstrating that the constant and continuous infusion of the drug into the blood circulation is ideal for medication. For instance, nitroglycerin patches rapidly become ineffective if they are worn 24 hours a day. This is probably due to a tolerance to the drug which is continuously introduced to the body. Some studies have shown that the tolerance also develops in patients who take it in pill form but to a lesser degree, possibly because the pills do not deliver an even and continuous flow of the drug in the blood. This finding may suggest that when patients removed their patches

overnight, they may not build up a tolerance to nitroglycerin. Therefore, the continuous delivery of drugs may not always be ideal. The issue on tolerance for transdermal drug delivery has justified the attention paid to the risk of constant concentration in the blood during a long period of the treatment.

Another important time-dependent phenomenon is the circadian rhythm of our body functions. It is well known that biochemical messengers such as hormones, transmitters and growth factors, have a circadian periodicity in the frequency and the magnitude of these secretory episodes. Therefore the transdermal drug delivery system must be optimized by considering the time-dependent phenomena in our body systems.

Maintaining glucose homeostasis with exogenous insulin for diabetes patients is also subject to the timed-variation of glucose level in the blood. The control of blood sugar cannot be achieved with a fixed concentration of insulin. We may need to develop novel transdermal delivery which can control a variety of time-dependent blood concentration to maximize the therapeutic efficacy.

Drug Transport through the Skin

The skin is a heterogeneous membrane consisting of the stratum corneum, the viable epidermis and dermis. The multilayer structure of the skin efficiently protects the body against the entry of foreign compounds. The stratum corneum is the major physical barrier for passage of most drugs, although the viable skin may act as a metabolic barrier for some drugs. It is essential, for developing transdermal drug delivery, to minimize the diffusion resistance of the stratum corneum. Literature survey indicates that the diffusion coefficient across the stratum corneum is usually 10^{-10} to 10^{-11} cm^2/s for many drugs with molecular weights of 200 to 400 Da, while the diffusion coefficient across the viable skin is approximately 1000 times greater than that across the stratum corneum[4]. If we assume the thickness of the stratum corneum is 20 micrometers, the lag time in the skin penetration is approximately the order of 10 hours. The long lag time occurred in the skin permeation may give difficulty in the dynamic control of the drug concentration in the blood following transdermal delivery.

In the start-up period after the onset of transdermal medication, we may control the lag time by introducing the coadministration with other delivery systems. In the system-off period, however, the coadministration may be ineffective. We can use penetration enhancers like ethanol to wash quickly out the drug molecules in the skin. The patch with adhesive layer is also

useful for making the lag time shorter; the surface layers of the stratum corneum, which contain a large quantity of the drug molecules, are stripped off when the patch is removed[1]. The drug molecules accumulated in the skin cause the reservoir effect after the removal of the patch. Not only the dissolved molecules but rather the bound molecules contribute to this reservoir function of the skin. The skin binding may occur to some extent in the stratum corneum and viable skin.

The enzymatic activity in the skin is effective for enhancing skin permeability[2]. By the chemical modification of the parent drug, the prodrug may dissolve in the surface layers of skin at a concentration much higher than that for the parent drug. The prodrug is then bioconverted to the parent drug in the viable skin. We recently found that the lag time appeared in the skin penetration of estradiol was significantly reduced by the use of estradiol esters[3].

Several mechanical methods have been proposed for enhancing the permeability of drugs through skin[4]: iontophoresis, phonophoresis, pulsed laser light, electroporation and thermal patch. These approaches, if optimized, can enhance the steady state permeability as well as dynamically control transdermal delivery. Under iontophoretic delivery, the mode of application of the electric field seemed to play a critical role in controlling the time-course of the plasma concentration[5]. We also found that the phonophoresis appreciably increased the skin permeability of prednisolone; the degree of enhancement was markedly influenced by the period of application of ultrasonic energy[6]. Thermal patches may also enhance the skin permeability although the enhancement factor is not remarkable comparing to iontophoresis and phonophoresis. Among the mechanical methods proposed, the iontophoresis may be most promising for the dynamic control of transdermal drug delivery. Due to a variety of operating factors in iontophoretic transdermal delivery, we may achieve versatile dynamic control of the blood concentration if the pharmacokinetics of the drug is known for elimination and distribution in the body.

Pharmacokinetic Model

We have recently developed a general pharmacokinetic model for transdermal drug delivery which takes into account the dynamic control of the drug concentration in the blood[5,7]. The model parameters are determined from the in vitro and in vivo experiments. The pharmacokinetic model successfully predicted the time-course of the blood concentration following a

variety of transdermal drug delivery systems including iontophoresis. The model enables us to understand quantitatively that the drug concentration in the blood after transdermal delivery is determined by the balance between the permeation rate across the skin and the elimination / distribution rate in the body[7]. When the drug has a short elimination half-life such as nitroglycerin, the time course of the blood concentration is wholly controlled by the skin permeation. Under these conditions, the dynamic control may be possible by the design of the transdermal delivery system. On the other hand, when the drug has a long half-life such as clonidine and levonorgestrel, the dynamic control of the blood concentration may not be achieved by the system design.

Summary

The penetration rate of drugs across the skin may be controlled in a time-dependent manner by enhancing skin permeability as well as by making the lag time shorter. However the dynamic control in the blood concentration may be limited to the drugs which have a short elimination half-life in the body. For the drugs without tendency of skin binding, the pulsed transdermal delivery to meet the circadian rhythm may be realized by the application of the electric field.

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