경피흡수의 개선을 위한 약물 전달체로서의 대사

조 애 리 (덕성여대)

Liposomes as topical drug carriers for improved dermal delivery

Ae-Ri Cho Lee[1], Byung-Lak Ahn[2], Moon-Kyung Kim[2] and Chang-Koo Shim[2]

1) College of Pharmacy, Duksung Women's University, Ssangmun-dong, Dobong-ku, Seoul 132-714, Korea

2) College of Pharmacy, Seoul National University, Shinlim-dong, Kwanak-ku, Seoul 151-742, Korea

Introduction

Until recently, most of the topical formulations for treating skin diseases are simple ointment, cream or gel. Our experience tells that most of the time, we get better cure after having a subcutaneous injection rather than having a topical application for skin diseases such as bacterial or viral infectious diseases or inflammation, etc.

The reason we couldn't get a proper treatment after conventional topical application can be summarized into two important aspects as follows:

1. Not enough skin penetration of a drug to reach the diseased skin tissue through the stratum corneum, the diffusional barrier.
2. Rapid clearance of drug from the diseased skin site and reach the systemic circulation resulted in short duration of activity and undesired side effects.

To improve these problems with conventional topical formulations, several drug carrier systems have been developed. Among them, Liposomes have shown the enhanced dermal delivery of active therapeutic agent with less systemic absorption. Many experimental results showed a sufficient level of drug in cutaneous structures and continuous local therapeutic effect with liposomal formulation. In this presentation, I will briefly discuss the characteristics of liposome, mechanism of enhanced dermal delivery, comparative studies of liposomes and conventional dermal dosage forms and their promising clinical applications.

Characteristics of liposome

Liposomes are artificial lipid-membrane vesicles which came from the understanding of our cellular membrane composition, mainly phospholipid and cholesterol which are the only water insoluble compounds in our body except

inorganic salts. In 1961, it was first discovered that phospholipids spontaneously form closed fluid-filled vesicles when they are mixed in suitable concentrations with water (Bangham, 1963). Initially they were used to study ion transport across cell membranes but later were evaluated as drug delivery systems. Liposomes can be prepared in various ways and their sizes can be controlled by choosing the preparation method. There are multilamellar large vesicles (MLV) with a size range of 0.1 to 5 to 10 > μm, large unilamellar vesicles (LUV), > 0.06 μm and small unilamellar vesicles (SUV), 0.02 to 0.05 μm (Schafer-Korting, 1989). Drugs can be incorporated into the interior of liposomes. Hydrophilic drugs are entrapped in the internal water phase, whereas lipophilic drugs can be incorportaed into the phospholipid membrane.

Mechanism of enhanced dermal delivery

Skin is composed of three distinguished layers: stratum corneum, epidermis and dermis. Stratum corneum is a very lipophilic membrane and is composed of about 20 layers of horney cell layers. The startum corneum lipids consist principally of ceramides (40%), cholesterol (25%), fatty acids (25%) and cholesteryl sulfate (10%). These lipids are arranged in multiple intercellular lamellae that provide an efficient water barrier because of the crystalline array of the straight and predominantly saturated lipid chains (Downing, 1987). So, it functions as a major diffusion barrier for most of the drug substances. Meanwhile epidermis and dermis is a hydrophilic membrane and has a high metabolizing activity. So, in transdermal drug delivery, first drug should pass through the physical barrier membrane, stratum corneum, and then permeate the chemical barrier, viable dermis layer.

One of the most prescribed antibiotics for skin infectious diseases, Aminoglycosides which is a very hydrophilic drug has a difficulty to permeate through the stratum corneum. By incorporating this hydrophilic drug into the lipophilic phospholipid membrane, the permeability coefficient of the drug through the skin membrane can be increased by enhancing the partition coefficient and diffusion coefficient of aminoglycosides. Also, the restricted permeability of phospholipid membranes, liposomes can serve as controllable time dependant release systems for drugs.

Masini and coworkers investigated the in vitro absorption and in vivo distribution of C^{14}-Tretinoin in liposomes where H^{3}-phosphatidylcholine dipalmitoyl, DPPC, were incorporated in the phospholipid phase and in a conventional alcoholic gel. In epidermis and dermis, the percentages of tretinoin found were significantly higher with liposomes than with the gel (Masini, 1993). However, phospholipid itself can not penetrate deep into the skin strata. Liposomes impregnated the stratum corneum and a partial dissociation occurs beteen tretinoin and phosphatidylcholine and in the dermis. Tretinoin diffused

alone. Eventhough, there is a lot of conterversy whether liposome can penetrate through the deep skin or not, most of the studies strongly demonstrate that phospholipid serve as an useful vehicle for drug transport and might enhance the partitioning of drug into the skin strata and provide the needed physicochemical environment for transfer of drug into the skin (Weiner, 1989). The penetration enhancing effect of phospholipid itself also has been reported (Drejer, 1992).

Comparative studies of liposomes and conventional dosage forms

C^{14}-labeled triamcinolone acetonide, encapsulated in MLV was applied to rabbits. Drug levels were compared with those obtained with identical doses administered in a lotion and in a gel. With the liposomal preparation, drug concentrations in epidermis and dermis increased threefold to fivefold (Mezei, 1980 & 1982).

The kinetics and extent of uptake of cyclosporin (CSA) in various strata of human cadaver skin upon topical application of oil-in-water emulsion and four liposomal systems were determined by in vitro diffusion cell experiments (Egbaria, 1991). The accumulation of CSA in the stratum corneum at 24 h is in the order : 'skin lipid liposome' MLV >'skin lipid liposome LUV > Phospholipid MLV > phospholipid LUV > emulsion. The total amount of drug in the deeper skin strata at 24 h is in the order : phospholipid MLV > 'skin lipid 'MLV > phospholipid LUV > skin lipid LUV > emulsion. This information provides us a very useful tool to control the drug depositing site. For treating the superficial cutaneous infection such as Impetigo or Erysipelas, 'skin lipid liposome' multilamellar vesicles might be preferable.

Promising clinical application

Alopecia, hair loss, is a common side effect of anti-cancer drugs. Its prevention can improve patient adaption to chemotherapy. Balsari and coworkers (Balsari,1994) reported very encouriging experimental result. In 31 of 45 young rats treated intraperitoneally with doxorubicin,alopecia was completely prevented by topical treatment of the skin with liposome-incorporated anti-doxorubicin monoclonal antibody. They strongly suggest that liposome-entrpped monoclonal antibodies are capable of penetrating the stratum corneum of the skin without losing their function.

The topical steroids have been the major breakthrough in the management of skin disorders and have been the most commonly correctly prescribed for eczema and psoriasis. However, if they are misprescribed or abused, side effects are inevitable. Since corticosteroids are powerful immuno-suppressants, it certainly worsen the infectious disease of the skin. The potential side- effects of topical steroids is atrophy of viable skin, perioral dermatitis and exacerbation of

rosacea.

Penetration kinetics of liposomal hydrocortisone in human skin was studied by Wohlrab and coworkers (Wohlrab ,1987). With the liposomal form, a considerably better concentration-time profile was obtained in the individual layers of human skin than with the corresponding Hydrocortisone ointment. The pronounced carrier ability of liposomes for hydrocortisone holds promise for an increase in its therapeutic efficacy, thus reducing unwanted side effects of the topical glucocorticoid therapy.

In burn wound management, frequent application of creams and ointments require cleaning to remove residue, resulting in increased patients discomfort. Price and coworkers (Price, 1992) reported that in burn wounds, tobramycin incorporated into liposomes remain at the site of burn tissue. And low systemic absorption of the liposomes was confirmed by the low levels of radioactivity measured in peripheral organs such as blood, liver, spleen and kidney, etc. The total recovered dose in the liver or kidney is less than 2 % of applied dose while the majority (>90 percent) of radioactivity was remained at the burn site. Since aminoglycisodes causes a serious nephro-toxicity and oto-toxicity, we can decrease these side effects by using topical liposomal formulation.

Summary

Liposomes may provide the needed physicochemical environment for transfer of drug into the skin. The liposomal formulation could provide a reservoir for the drug and permit its sustained and regular release into the skin. Prolonged release from liposomal delivery systems might be useful in the treatment of a variety of skin diseases.

References

A.L. Balsari, D.Molelli, S. Manard, U. Veronesi and M.I. Colnaghi, *FASEB J.*, 1994, 8: 226-230

A.D. Bangham, *Adv. Lipid Res.*, 1963, 1: 65-104

D.T. Downing, M.E. Stewart, P.W. Wertz, S.W. Colton, W.Abraham, J.S. Strauss, *J. Invest. Dermatology* , 1987, 88: 2s-6s

K. Drejer, A. Vaag, K. Bech, P. Hansen, AR. Sorensen and N. Mygind, *Diabet. Med.*,1992, 9: 335-340

K. Egbaria, C. Ramachandran and N. Weiner, *Skin Pharmacol.*, 1991,4: 21-28

H.C. Korting, P. Blecher , M. Schafer-Korting and A. Wendel, *J. Am. Acad. Dermatology*, 1991, 25: 1068-1071

V. Masini, F. Bonte, A. Meybeck and J. Wepierre, *J. Pharm. Sci.*,1993, 82: 17-21

M. Mezei and V. Gulasekharam, *Life Sciences*, 1980, 26: 1473-147

M. Meizei and V. Gulasekharam, *J. Pharm. Pharmacol.*, 1982, 34: 473-474

C.I. Price, J. W. Horton and C.R. Baxter, *Gynecology & Obstetrics*, 1992, 174: 414-418

H. Schreier and J. Bouwstra, *J. Controlled Release*, 1994, 30: 1-15

N. Weiner, N. Williams, G. Birch, C. ramachandran, C. Shipman and G. Flynn, *Antimicrobial Agents and Chemotherapy*, 1989, 33: 1217-1221

W. Wohlrab and J. Lasch, *Dermatologica*, 1987, 174: 18-22