피부침투 활성성분 운반을 위한 아젤라이산 베시클 운반체

김명훈*, 김선남[1], 김광수[2]

*캠브리지대학교 화학과, [1]나드리화장품㈜ 기술연구소, [2](주)에이티랩 기술연구소
(mhk22@cam.ac.uk, myunghunkim@ymail.com*)

Azelaic acid vesicular carrier for transdermal active ingredient delivery

Myung Hun Kim*, Seon Nam Kim[1], Kwangsoo Kim[2]
*Department of Chemisty, University of Cambridge, Cambridge, CB2 1EW, UK
[1]Technology Institute, The Nadree Co. Ltd., Pyongtaik-Si, 451-863, Korea
[2]AT LAB Co. Ltd., SNU Business Incubator#5-105, Suwon-Si, 441-853 KOREA
(mhk22@cam.ac.uk, myunghunkim@ymail.com*)

Transdermal drug delivery is a viable administration route for potent, low molecular weight therapeutic agents which cannot withstand the hostile environment of the gastro-intestinal tract and /or are subject to considerable first pass metabolism by the liver. It uses the skin as an alternative route for the delivery of systemically acting drugs. Dermal drug delivery is the topical application of drugs to the skin in the treatment of skin diseases, wherein high concentrations of drugs can be localised at the site of action, thereby reducing the systemic drug levels and side effects [1-3]. The skin covers a total surface area of approximately 1.8m^2 and provides the contact between the human body and its external environment. The stratum corneum, the outermost layer of the skin acts as the main barrier in the skin. The structure of the stratum corneum is often compared to a brick wall, with the keratin-rich corneocytes as the bricks surrounded by the mortar of the intercellular lipid lamellae. It has been generally accepted that the highly organised crystalline lipid lamellae play an essential role in the barrier properties of the stratum corneum. Many techniques have been aimed to disrupt and weaken the highly organised intercellular lipids in an attempt to enhance drug transport across the intact skin or to increase the delivery force for the permeation of drugs across this skin barrier [4-5].

Azelaic acid (1,7-heptanedicarboxyilic acid, AZA) is a naturally occurring non-toxic straight chain, saturated dicarboxylic acid derived from Pityrosporum ovale, the organism responsible for pityriasis versicolor. Azelaic acid appears to selectively influence the mechanism of hyperactive and abnormal melanocytes, but minimally influences normal skin pigmentation, freckles, nevi and senile lentigenes.

The depigmenting activity of azelaic acid appears to be mediated by an antiproliferative and cytotoxic effect on melanocytes by potent inhibition of thioredoxin reductase, an enzyme involved in mitochondrial oxidoreductase activation and DNA synthesis. The compound is also able to bind amino and carboxyl groups and may prevent the interaction of tyrosine in the active site of tyrosinase and thus function as a competitive and reversible inhibitor. Its lightening effect appears to be selective and most apparent in highly active melanocytes, with minimal

effects in normally pigmented skin.

This review describes the barrier properties of the skin, how active ingredients penetrate the skin by vesicle technique that has been used to enhance active ingredient penetration across skin.

Experimental

Ethosomes are vesicular carriers composed of hydro alcoholic or hydro/alcoholic/glycolic phospholipid in which the concentration of alcohols or their combina-tion is relatively high. In this method phospholipid, azelaic acid and other lipid materials are dissolved in ethanol in a covered vessel at room temperature by vigorous stirring with the use of mixer. Propylene glycol or other polyol is added during stirring. This mixture is heated to 300°C in a water bath. The water heated to 300°C in a separate vessel is added to the mixture, which is then stirred for 5 min in a covered vessel. The vesicle size of ethosomal formulation can be decreased to desire extend using sonication or extrusion method. Finally, the formulation is stored under refrigeration.

Results and Discussion

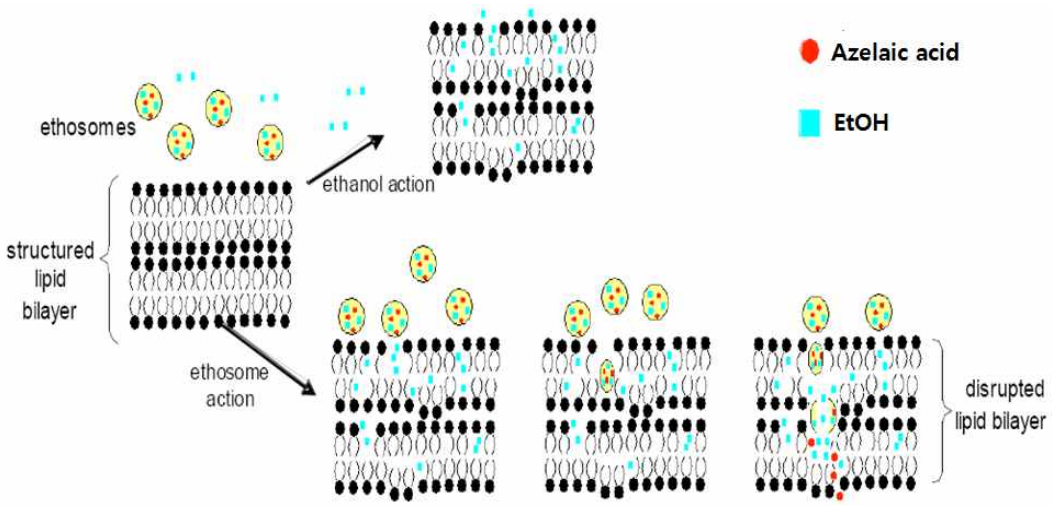


Fig. 1. Azelaic acid penetration through ethosomes.

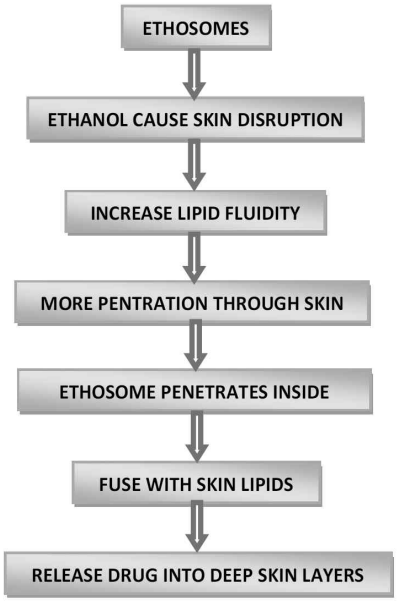
Entrapment efficiency of ethosomal vesicles was de-termined by centrifugation method. The vesicles were separated in a high speed cooling centrifuge at 20,000rpm for 90 minutes in the temperature main-tained at 4°C. The sediment and supernatant liquids were separated amount of drug in the sediment was determined by lysing the vesicles using methanol. From this, the entrapment efficiency was determined by the following equation,

Entrapment efficiency = DE / DT x 100 Where,

DE - Amount of drug in the ethosomal sediment

DT - Theoretical amount of drug used to prepare the formulation

(equal to amount of drug in supernatant liquid and in the sediment)



Scheme 1. Mechanism of action of ethosomes.

In vitro drug release study and Drug Deposition study

In vitro drug release study and Drug Deposition of ethosomal preparation was performed by Franz diffu-sion cell with artificial or biological membrane, Dialysis bag diffusion.

Storage-physical stability of ethosomes

The ability of ethosomal preparations to retain the drug (i.e., drug-retentive behavior) was checked by keeping the preparations at different temperatures, i.e., 25±2°C (room temperature, RT), 37±2°C and 45±2°C for different periods of time (1, 20, 40, 60, 80 and 120 days). The ethosomal preparations were kept in sealed vials (10ml capacity) after flushing with nitrogen. The stability of ethosomes was also determined quantitatively by monitoring size and morphology of the vesicles using DLS and TEM.

Therapeutic applications

Ethosomes, the high ethanol containing vesicles are able to penetrate the deeper layers of the skin and hence appear to be vesicles of choice for transdermal drug delivery of hydrophilic and impermeable drugs through the skin.

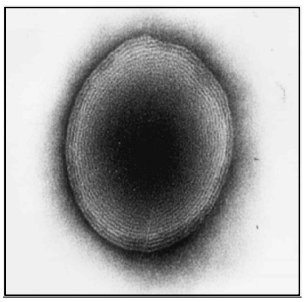


Fig. 2. Azelaic acid vesicle by cryo-TEM.

Conclusion

Transdermal route is promising alternative to drug delivery for systemic effect. Ethosomes has initiated a new area in vesicular research for transdermal drug delivery which can provide better skin permeation than liposomes. The main limiting factor of transdermal drug delivery system i.e. epidermal barrier can be overcome by ethosomes to significant extent. Application of ethosomes provides the advantages such as improved permeation through skin and targeting to deeper skin layers for various skin diseases. Ethosomes have been tested to encapsulate hydrophilic drugs, cationic drugs, proteins and peptides. Further, research in this area will allow better control over drug release in vivo and long-term safety data, allowing the therapy more effective. Thus, ethosomal formulations possess promising future in effective transdermal delivery of bioactive agents.

A detailed knowledge of the mode of action is necessary in order to assess the full potential of elastic vesicles as skin delivery vehicles, such as the delivery of large molecules or targeting certain sites and cells within the skin. This is only possible when vesicles act as carrier systems and could give rise to the development of very interesting and novel transdermal drug delivery systems. Fig. 1(vesicles being studied as carriers for skin delivery and their proposed mechanism) shows that deformable liposomes and ethosomes are better carriers for transdermal delivery when compared with liposomes and niosomes.

So, a vesicle formulation that rapidly enters the stratum corneum and remains in the deepest layers of stratum corneum releasing their drugs or proteins has useful advantages and is an important area of study to investigate such a promising approach.

Acknowledgements

This study was supported by a grant of the Korea Healthcare Technology R&D Project, Ministry of Health & Welfare in Republic of Korea (Grant No. A103017).

Reference

1. Vyas SP, Khar RK, *Transdermal drug delivery*, New Delhi, India: Vallabh Prakashan, 411-447 (2002).
2. Yie W.Chein, ***Novel drug delivery systems***. New York: Marcel Dekker, 301-380 (1992).
3. Yie W.Chein, *Transdermal controlled systemic medications*. New York: Marcel Dekker, INC. 1987.
4. J. Hadgraft, *„J. Pharm.*, **224**, 1-18 (2001).
5. Schreier H, Bouwstra J.A, *J.Controlled Release*, **30**, 1-15 (994).