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Advances in Topical Drug Delivery Systems for Dermatological Disorders: A Comprehensive Review

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Abstract : Topical drug delivery holds immense potential for treating dermatological disorders, offering advantages over oral and parenteral routes. This review explores recent advancements and strategies in topical drug delivery systems for various skin conditions, including acne, cellulitis, atopic dermatitis, and psoriasis. Key topics covered include the skin's barrier function, drug penetration mechanisms, and novel formulations such as nanocapsules, lipid vesicles, and solid lipid nanoparticles. Additionally, promising findings from preclinical and clinical studies are discussed, highlighting the efficacy and safety of innovative topical formulations in managing dermatological disorders. This review provides valuable insights into the evolving landscape of topical drug delivery for dermatology.

IndexTerms **- Topical, Dermatological Disorders, Penetration, Nanoparticles.**

I. INTRODUCTION

The skin offers an attractive avenue for drug delivery, circumventing many limitations associated with oral, inhalation, and parenteral routes. Its unique properties have captured the interest of researchers in recent years [1]. Acting as a protective barrier, the skin regulates the passage of various chemicals, maintains moisture levels, and regulates body temperature to uphold homeostasis. Skin disorders affect nearly one-third of the global population, ranking as the fourth most prevalent category of human diseases [2].

Skin disorders, such as atopic dermatitis and psoriasis, cause significant morbidity and reduced quality of life due to symptoms like severe itching. The high prevalence and costly treatments, like biologics, add to the burden of these conditions [3].Topical treatment of skin diseases is effective but requires a deep understanding of the skin's barrier function. For centuries, the skin has been utilized worldwide to deliver drugs that are poorly soluble or have low oral bioavailability [4]. The skin comprises three layers: the epidermis (outer layer), the dermis (middle layer with connective fibers, sensory receptors, and sweat glands), and the hypodermis (subcutaneous layer with adipose tissue supporting the other two layers) [5].

Over time, technological progress has expanded our understanding of how drugs are absorbed through the skin, leading to better quality topical formulations [6]. Extensive research in the 20th and 21st centuries has advanced our knowledge of skin structure, pharmacology, toxicology, physiology, and pharmaceutical technology [7]. This research has included studies quantifying drug permeation through various skin layers, including the epidermis, human stratum corneum, and dermatome skin [8].The primary objective of this review is to evaluate different treatment strategies utilized in topical drug delivery systems to improve the absorption of therapeutic agents through the skin. Additionally, it aims to assess their effectiveness in treating skin-related disorders.

II. SKIN TARGET SITES AND BARRIERS IN SKIN EPIDERMIS

Topical drug formulations are meticulously designed to target specific skin areas, such as the dermal, epidermal, and appendageal regions, including various cells like Langerhans cells, Merkel cells, and melanocytes. The challenge lies in balancing local effectiveness with potential systemic side effects. These formulations cater to diverse therapeutic purposes, from skin whitening to pain relief and even vaccine activation [9]. Skin plays crucial roles in protection, temperature regulation, and moisture retention, with the stratum corneum acting as the primary barrier. Brody's classification divides it into basal, intermediate, and superficial zones based on keratin fibril density. Corneocytes, the outermost layer of the epidermis, undergo shedding and regeneration, influencing drug delivery dynamics [10]. Corneocytes are hexagonal cells that form the superficial zone and shed every 21 days on the hands and 7 days on the forehead. Hydration affects the SC layer, impacting corneocyte thickness and undulation. The second zone of corneocytes, with 5-10 layers, remains less affected by osmotic changes. Topical hydration alters water content, influencing protease activity in corneocyte envelopes [9], [11]. Proteins in the stratum corneum are cross-linked by disulfide bonds, providing strength, while lipids act as a functional barrier. Melanocytes, Merkel cells, and Langerhans cells,

originating from different sources, have distinct roles in the epidermal layer. Langerhans cells capture skin antigens and migrate to lymph nodes to activate T-cells against infections, while Merkel cells are touch-sensitive cells [12], [13].

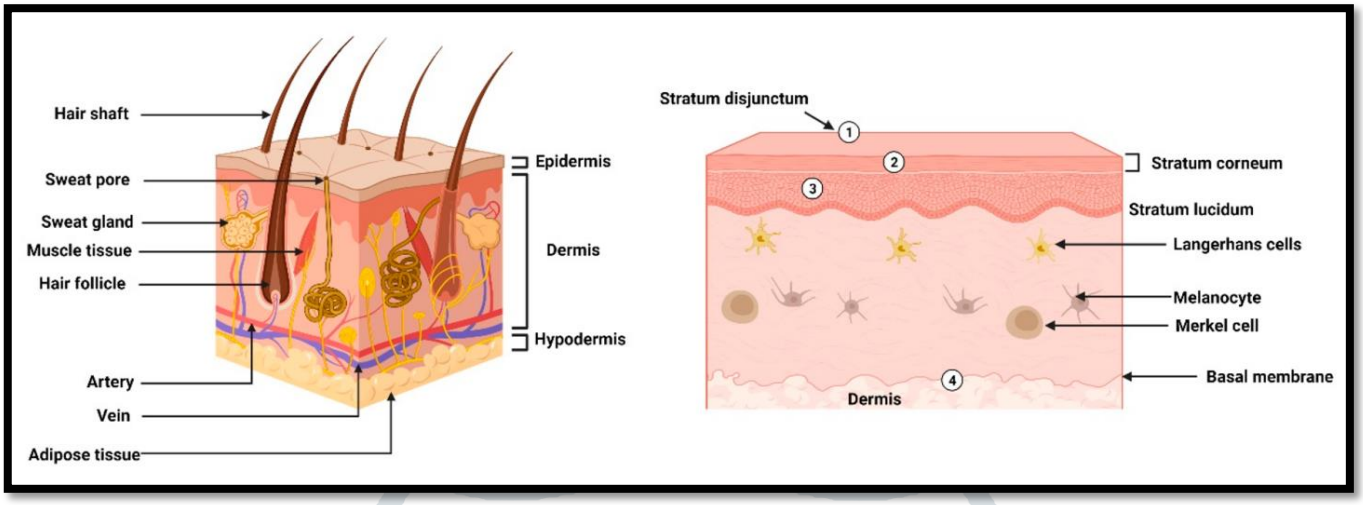

Figure 1. Morphology and physical barriers in the epidermis layers of skin.

The basement membrane, between the epidermis and dermis, regulates cell migration, adhesion, and differentiation. Topical drug delivery offers advantages over systemic drugs, bypassing issues like gastrointestinal pH changes and hepatic metabolism, improving drug bioavailability, especially for drugs with short half-lives and controlled release [14].

However, limitations exist, such as the challenge of penetrating the skin's barriers for particles larger than 500 Da. Only drugs capable of skin penetration and reaching target sites are selected for topical delivery, considering factors like drug properties, vehicle characteristics, dosing, and skin health. This approach enhances efficacy while ensuring patient compliance and meeting consumer preferences and needs [15].

III. Treatment Approaches For Various Disorder Using Topical Drug Delivery

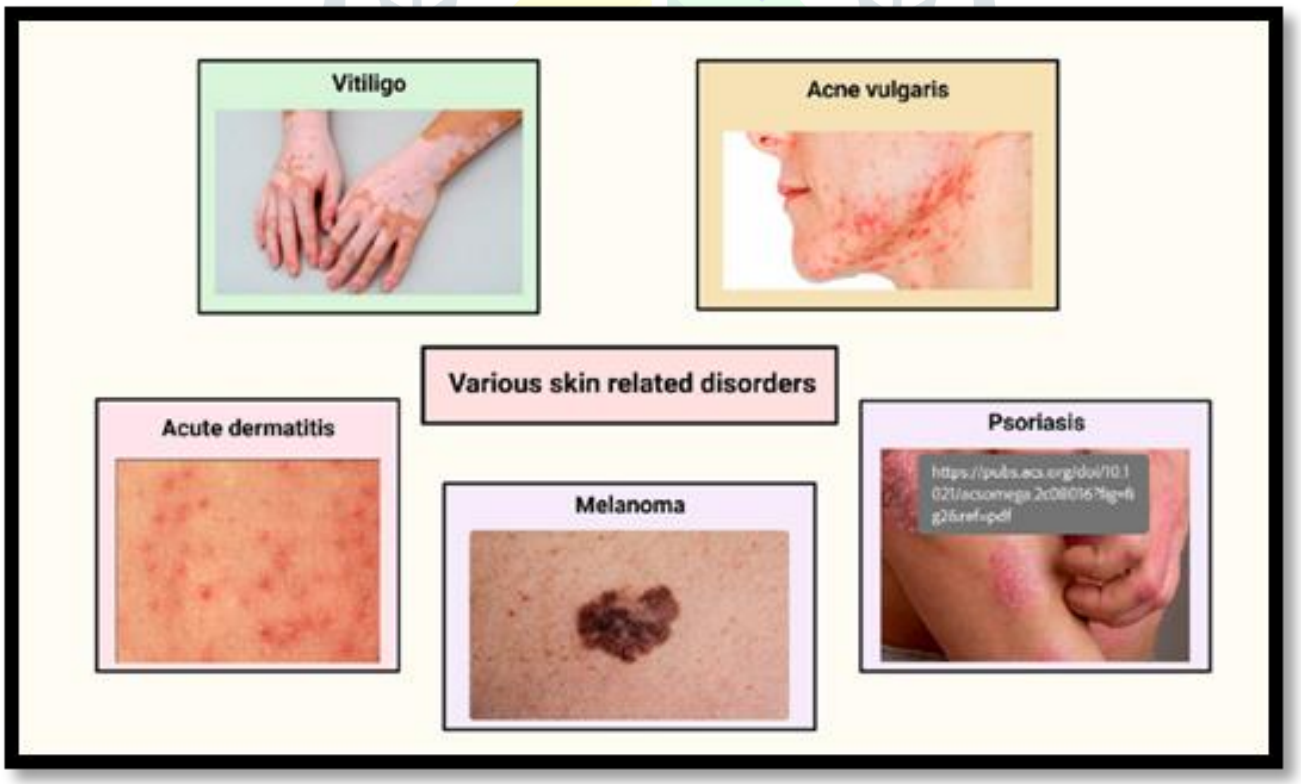

Figure 2. Treatment of skin disorders using topical therapy.

The skin controls the entry and exit of many chemicals, preventing moisture loss and controlling body temperature to preserve balance as homeostasis within the body. Topical medication delivery systems obviously depend on the drug being able to transmit into the skin’s barrier and reach its intended delivery site [16].

A. Acne

Acne is a skin condition characterized by chronic inflammation of the sebaceous glands, typically affecting the back and face areas. Factors contributing to acne development include colonization by propionibacterium acnes, elevated androgen levels, release of proinflammatory cytokines, and abnormal sebaceous gland keratinization [17].

A study explored a novel treatment approach involving the co-delivery of azelaic acid and tea tree oil using ethosomes, delivered through a solvent injection technique. Additionally, Carbopol was incorporated to create a hydrogel of the drug-loaded ethosome, which was compared to existing market products. Results showed improved drug permeation and retention across dermal layers in a rat model, with a favorable safety profile [18]. Moreover, ethosomes loaded with hexylaminolevulinate (HAL) exhibited promising potential for photodynamic therapy against acne, demonstrating significant inhibition of biofilm formation compared to plain HAL solution, suggesting a potential application in acne management [19].

B. Cellulitis

Cellulite is a skin condition characterized by an uneven texture, presenting as dimples and lumps resembling an "orange peel," "cottage cheese," or "mattress." It predominantly affects about 85% of post-pubertal females over 20 years old, commonly appearing on the pelvic region, lower limbs, and abdomen [20].

Diagnosis typically involves a physical examination, with digital photography being a primary method for assessing severity. This technique utilizes standardized images captured under specific lighting and camera settings. Ultrasound is also utilized to evaluate tissue firmness and visualize oedematous components [21].

Skincare formulations often contain caffeine, aminophylline, theophylline, and theobromine, which inhibit the phosphodiesterase enzyme to increase cAMP levels. This activation promotes lipolysis, reducing the appearance of cellulite. Caffeine, sourced from botanical extracts like Coffee Arabica and Camellia sinensis, is considered safer than aminophylline and theophylline [22].

C. Atopic Dermatitis

Atopic dermatitis (AD), characterized by chronic inflammation and symptoms like swelling, oozing, itching, and redness, is currently under investigation for treatment using topically applied Cephalosporin A (CSA) nanocapsules (NCs). These NCs have shown enhanced drug penetration into various layers of porcine ear skin, leading to improved skin barrier integrity, reduced systemic inflammation markers, and decreased skin inflammation. In comparison to existing topical treatments for AD, this novel CSA-NCs formulation demonstrates promising efficacy [23].

Additionally, three vesicular formulations loaded with cyanocobalamin were prepared using ethosomes, liposomes, and transferosomes via a film-hydration technique. These lipid vesicles exhibited superior permeation efficiency across skin layers and scavenging activity against nitric oxide, particularly relevant for pathological conditions like AD and psoriasis. The study suggests lipid vesicles as a potential carrier system for topical cyanocobalamin application in treating psoriasis and AD [24].

D. Psoriasis

Psoriasis, characterized by chronic inflammation and hyperproliferative epidermis responses, presents challenges in treatment due to immature keratinocyte development and hyperactivation [24].

Recent studies explore novel formulations like ethosomal and liposomal gels loaded with anthralin for improved efficacy and safety in psoriasis patients. Ethosomal gels showed superior permeation in ex vivo tests on rat abdominal tissue, with minimized side effects clinically [25].

Apremilast-loaded solid lipid nanoparticles (SLNs) in topical hydrogel formulations demonstrated enhanced skin permeation, extended drug release, and reduced systemic absorption, promising improved therapeutic outcomes in psoriasis. Additionally, hydrogels containing clobetasol propionate-embedded nanosponges exhibited controlled drug release and effective psoriasis treatment without adverse effects in animal models [26].

IV. Conclusion

In conclusion, topical drug delivery systems offer significant potential for treating various skin disorders by overcoming the barriers of skin permeation. Innovative formulations, such as ethosomes and nanocapsules, demonstrate enhanced efficacy and safety profiles, promising improved therapeutic outcomes. Further research and development in this field hold promise for advancing dermatological care.

V. REFERENCES

[1] P. Kamble, B. Sadarani, A. Majumdar, and S. Bhullar, "Nanofiber based drug delivery systems for skin: A promising therapeutic approach," *Journal of Drug Delivery Science and Technology*, vol. 41. Editions de Sante, pp. 124–133, Oct. 01, 2017. doi: 10.1016/j.jddst.2017.07.003.

[2] D. Seth, K. Cheldize, D. Brown, and E. E. Freeman, "Global Burden of Skin Disease: Inequities and Innovations," *Current Dermatology Reports*, vol. 6, no. 3. Current Medicine Group LLC 1, pp. 204–210, Sep. 01, 2017. doi: 10.1007/s13671-017-0192-7.

[3] M. Schäfer-Korting, W. Mehnert, and H. C. Korting, "Lipid nanoparticles for improved topical application of drugs for skin diseases," *Advanced Drug Delivery Reviews*, vol. 59, no. 6. pp. 427–443, Jul. 10, 2007. doi: 10.1016/j.addr.2007.04.006.

[4] C. Flohr and R. Hay, "Putting the burden of skin diseases on the global map," *British Journal of Dermatology*, vol. 184, no. 2. Blackwell Publishing Ltd, pp. 189–190, Feb. 01, 2021. doi: 10.1111/bjd.19704.

[5] C. Gorzelanny, C. Mess, S. W. Schneider, V. Huck, and J. M. Brandner, "Skin barriers in dermal drug delivery: Which barriers have to be overcome and how can we measure them?," *Pharmaceutics*, vol. 12, no. 7. MDPI AG, pp. 1–31, Jul. 01, 2020. doi: 10.3390/pharmaceutics12070684.

[6] J. Van Zuylen, "The microscopes of Antoni van Leeuwenhoek," 1981.

[7] N. Raina, R. Rani, V. K. Thakur, and M. Gupta, "New Insights in Topical Drug Delivery for Skin Disorders: From a Nanotechnological Perspective," *ACS Omega*, vol. 8, no. 22. American Chemical Society, pp. 19145–19167, Jun. 06, 2023. doi: 10.1021/acsomega.2c08016.

[8] A. M. Kligman and E. Christophers, "Preparation of Isolated Sheets of Human Stratum Corneum." [Online]. Available: http://archderm.jamanetwork.com/

[9] M. S. Roberts *et al.*, "Topical drug delivery: History, percutaneous absorption, and product development," *Advanced Drug Delivery Reviews*, vol. 177. Elsevier B.V., Oct. 01, 2021. doi: 10.1016/j.addr.2021.113929.

[10] I. Brody, "THE ULTRASTRUCTURE OF THE HORNY LAYER IN NORMAL AND PSORIATIC EPIDERMIS AS REVEALED BY ELECTRON."

[11] T. Richter *et al.*, "Dead but Highly Dynamic – The Stratum corneum Is Divided into Three Hydration Zones," *Skin Pharmacol Physiol*, vol. 17, no. 5, pp. 246–257, 2004, doi: 10.1159/000080218.

[12] V. Patel, O. P. Sharma, and T. Mehta, "Nanocrystal: a novel approach to overcome skin barriers for improved topical drug delivery," *Expert Opin Drug Deliv*, vol. 15, no. 4, pp. 351–368, Apr. 2018, doi: 10.1080/17425247.2018.1444025.

[13] R. R. Warner, M. C. Myers, and D. A. Taylor, "Electron Probe Analysis of Human Skin: Determination of the Water Concentration Profile," *Journal of Investigative Dermatology*, vol. 90, no. 2, pp. 218–224, Feb. 1988, doi: 10.1111/1523-1747.ep12462252.

[14] J. A. S. Quaresma, "Organization of the Skin Immune System and Compartmentalized Immune Responses in Infectious Diseases," *Clin Microbiol Rev*, vol. 32, no. 4, Sep. 2019, doi: 10.1128/CMR.00034-18.

[15] P. Munde, S. Khandekar, A. Dive, and A. Sharma, "Pathophysiology of merkel cell," *Journal of Oral and Maxillofacial Pathology*, vol. 17, no. 3, p. 408, 2013, doi: 10.4103/0973-029X.125208.

[16] B. W. Barry, "D rug delivery routes in skin: a novel approach," 2002. [Online]. Available: www.elsevier.com/locate/drugdeliv

[17] W. Poomanee, W. Chaiyana, M. Mueller, H. Viernstein, W. Khunkitti, and P. Leelapornpisid, "In-vitro investigation of anti-acne properties of Mangifera indica L. kernel extract and its mechanism of action against Propionibacterium acnes," *Anaerobe*, vol. 52, pp. 64–74, Aug. 2018, doi: 10.1016/j.anaerobe.2018.05.004.

[18] A. Bisht *et al.*, "Azelaic acid and Melaleuca alternifolia essential oil co-loaded vesicular carrier for combinational therapy of acne," *Ther Deliv*, vol. 13, no. 1, pp. 13–29, Jan. 2022, doi: 10.4155/tde-2021-0059.

[19] T. Wang, L. Wu, Y. Wang, J. Song, F. Zhang, and X. Zhu, "Hexyl-aminolevulinate ethosome–mediated photodynamic therapy against acne: in vitro and in vivo analyses," *Drug Deliv Transl Res*, vol. 12, no. 1, pp. 325–332, Jan. 2022, doi: 10.1007/s13346-021-00942-5.

[20] A. V. Rawlings, "Cellulite and its treatment," *Int J Cosmet Sci*, vol. 28, no. 3, pp. 175–190, Jun. 2006, doi: 10.1111/j.1467-2494.2006.00318.x.

[21] A. M. Rossi and B. E. Katz, "A Modern Approach to the Treatment of Cellulite," *Dermatol Clin*, vol. 32, no. 1, pp. 51–59, Jan. 2014, doi: 10.1016/j.det.2013.09.005.

[22] A. Herman and A. P. Herman, "Caffeine's Mechanisms of Action and Its Cosmetic Use," *Skin Pharmacol Physiol*, vol. 26, no. 1, pp. 8–14, 2013, doi: 10.1159/000343174.

[23] A. Badihi *et al.*, "Topical nano-encapsulated cyclosporine formulation for atopic dermatitis treatment: Topical cyclosporine NCs for AD," *Nanomedicine*, vol. 24, Feb. 2020, doi: 10.1016/j.nano.2019.102140.

[24] S. Marepally *et al.*, "Topical administration of dual siRNAs using fusogenic lipid nanoparticles for treating psoriatic-like plaques," *Nanomedicine*, vol. 9, no. 14, pp. 2157–2174, Oct. 2014, doi: 10.2217/NNM.13.202.

[25] D. Fathalla, E. M. K. Youssef, and G. M. Soliman, "Liposomal and ethosomal gels for the topical delivery of anthralin: Preparation, comparative evaluation and clinical assessment in psoriatic patients," *Pharmaceutics*, vol. 12, no. 5, May 2020, doi: 10.3390/pharmaceutics12050446.

[26] S. Kumar, M. Prasad, and R. Rao, "Topical delivery of clobetasol propionate loaded nanosponge hydrogel for effective treatment of psoriasis: Formulation, physicochemical characterization, antipsoriatic potential and biochemical estimation," *Materials Science and Engineering C*, vol. 119, Feb. 2021, doi: 10.1016/j.msec.2020.111605.