Bulletin of Faculty of Pharmacy, Cairo University xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Bulletin of Faculty of Pharmacy, Cairo University

journal homepage: www.sciencedirect.com

Review Paper

Exploring preclinical and clinical effectiveness of nanoformulations in the treatment of atopic dermatitis: Safety aspects and patent reviews ☆

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ARTICLE INFO

Article history:
Received 18 October 2016
Received in revised form 26 November 2016
Accepted 14 December 2016
Available online xxxx

Keywords:
Nano-formulations
Topical delivery
Atopic dermatitis
Inflammation
Corticosteroids
Clinical status
Pre-clinical aspects

ABSTRACT

Atopic dermatitis (AD) is the most prevalent chronic disease that affects the skin and is featured by inflammation of the skin. Treatment of AD is entirely focused on to limit the itching, skin repairing as well as reducing the inflammation whenever required. A number of therapeutic agents are available for the treatment of AD. However, topical delivery to the skin has been a consistent challenge for researchers, because of the barrier nature of skin. The present review explores the novel nano-sized formulations of various actives researched for AD therapy via topical route. Feasibility of various nano-carrier systems such as elastic vesicles, nanoemulsions, lipid nanoparticles, polymeric micelles and dendritic nanoparticles has been elaborated. The write up traces the pre-clinical and clinical aspects of the nano-formulations. Nano-formulations are found to be an emerging modality for the treatment of AD as they offer targeted delivery, better penetration, enhanced therapeutic efficacy and decreased systemic side effects.

Contents

Abbreviations: AD, atopic dermatitis; AdCbl, adenosylcobalamin; CLSM, confocal laser scanning microscopy; sNLC, silver based nanolipidic carrier; CsA, cyclosporine A; CpG, cytosine phosphate-guanine; EE, entrapment efficiency; GNPs, gelatin nanoparticles; IFN, interferon; IL, interleukin; IgE, immunoglobulin E; IgG, immunoglobulin G; LFA-1, lymphocyte function-associated antigen-1; mPEG, methoxypoly(ethylene glycol); mRNA, messenger ribonucleic acid; NEs, nanoemulsions; NLC, nanostructure lipid carriers; NPs, nanoparticles; NTPDase, nucleoside triphosphate diphosphohydrolases; HC, hydrocortisone; PBMCs, peripheral blood mononuclear cells; PLGA, poly(lactic-co-glycolic acid); PCL, poly(ε-caprolactone); ROS, reactive oxygen species; SNPs, silica nanoparticles; siRNA, short interfering RNA; SLNs, solid lipid nanoparticles; Th, helper T cells; TSLP, thymic stromal lymphopoietin; TCIs, topical calcineurin inhibitors; UVB, ultraviolet B.

Peer review under responsibility of Faculty of Pharmacy, Cairo University.

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http://dx.doi.org/10.1016/j.bfopcu.2016.12.003
1110-0931/

Please cite this article in press as: N. Akhtar et al., Exploring preclinical and clinical effectiveness of nanoformulations in the treatment of atopic dermatitis: Safety aspects and patent reviews, Bulletin Facult Pharmacy Cairo Univ (2016), http://dx.doi.org/10.1016/j.bfopcu.2016.12.003

1. Introduction

Atopic dermatitis (AD) or might be termed as atopic eczema is reported to be the most prevalent disease of skin affecting predominantly children [1]. It is a chronic disease featured by highly pruritic inflammation of skin [2]. Several studies have also suggested that AD is related with the cutaneous indication of a systemic disorder that might results into other atopic problems. New apprehensions into AD suggested constructional skin deformity as well as immune dysregulation to be responsible in defining the pathophysiology. Thus, optimum treatment of AD necessitates a dual methodology that targeted in providing the protection of skin as well as healing it [3]. Disease management requires application of emollient frequently to the skin to provide soothing and moisturizing effect, followed by topical medicines and physician visit regularly [4]. For the treatment of AD, conventional treatment comprising use of creams/ointments have also been available that showed limited accessibility into the deeper skin [5]. Thus, there is a need of development of such formulations that reaches deep into the epidermis to treat the disease, provide more effective results than systemic adverse effects. Keeping in mind this objective, several researchers across the globe have worked out to design various formulations that overcome the limitation of conventional products. Nanoformulations, among these formulations are considered to be optimum carriers for topical delivery of therapeutic actives deep into the epidermis [6]. Thus, in this article an attempt has been made to overview the literature from last ten years related to the development of nanoparticles (NPs) for the treatment of AD, focusing on the clinical, preclinical and safety aspects with recent advancements in NPs.

2. Atopic dermatitis: Pathophysiology and diagnosis

The pathological process of AD is still unknown; however, the disorder thought to occurs due to the complex interaction between skin barrier functional abnormality, immune deformity, infective and environmental effects. Malfunctioning of skin might appear to be due to the mutation of filaggrin gene. Deficiency of ceramides and antimicrobial peptides is also observed in AD skin [7]. These abnormalities in functioning of skin barrier lead to transepidermal water loss and enhance the penetration of microbes (most commonly *Staphylococcus aureus*) and allergens into the skin. Defects in innate immune response also resulted in enhanced bacterial and viral infections [1,3].

No specific tests are yet available to diagnose AD. However, the diagnosis is based on specific criterion by taking into consideration the medical history of the patient and clinical indications [8]. As devised by Williams et al., AD diagnosis depicted the sign of an itchy skin along with the presence of three/more minor criteria. Scalp, face, trunk, neck, and extensor (outer) surfaces of the extremities are influenced where as the diaper area is usually spared, in case of infants. Children generally involve the region of the flexural surfaces of the extremities, neck, wrists, and ankles. Disregarding the age factor, the itching usually continues to occur during day time and get worsens during night, leading to loss of sleep and substantial impairments in the quality of life [9,10]. Thus, appropriate treatment is required to overcome all these problems related with AD.

3. Treatment strategies

AD treatment strategies focused on controlling itching, repairing skin and reducing the inflammation whenever required. Therefore, the successful management and treatment facilitates the use of multi-targeted strategy that requires caregiver and patient education. Along with this, skin care, anti-inflammatory therapy with topical calcineurin inhibitors (TCIs), corticosteroids and cure of skin infections are also recommended. Use of systemic corticosteroids might also be employed in case of severity [3,11–14]. A simplified treatment strategy of AD is described in Fig. 1. The availability of the treatment with conventional products (like cream, ointment, lotion etc. as available in market listed in Table 1) showed several issues because of adverse effects specifically in long-term therapy.

Current investigation focused on the treatment strategies to optimize the potency of formulation while reducing the adverse effects. Numerous research attempts have been done to improvise the safety of treatment, including special vehicles (patch, liposome, nanoparticle, etc.), combined therapy and newly synthesized drugs

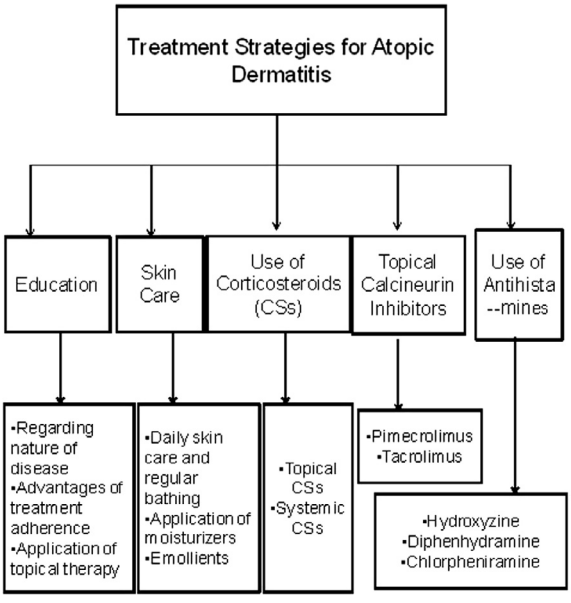

Fig. 1. Treatment strategies in atopic dermatitis.

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