Scope of Nano Delivery for Atopic Dermatitis

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Abstract

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disorder characterised by intense itching and recurrent eczematous lesions. It affects not only children but also the adults with prevalence rates varying from 1-20% in different regions of the world. Although the pathogenesis of the disorder is not completely understood, it appears to result from the complex interplay between defects in skin barrier function, environmental and infectious agents, and immune abnormalities. Further, the role of reactive oxygen species (ROS) though has been studied in AD and other skin diseases to some extent, but its importance in atopic dermatitis has rarely been investigated. The current therapies for AD involve the use of topical corticosteroids (first-line) and/or topical calcineurin inhibitors (TCIs), first-generation antihistamines and phototherapy to manage the sleep disturbances and skin infections. Inspite of current therapies, AD is associated with potential and undesirable adverse effects. Nanotechnology based therapeutics are being explored by researchers to alleviate the symptoms of AD and have potential applications in topical and systemic therapy. However, still additional innovative research is needed to address the cost-effectiveness and long-term safety of these nanoparticles. This short review discusses the scope of nanotechnology with special emphasis on the reports on lipidic and polymeric nanoparticles of the last half decade for the treatment of atopic dermatitis.

Keywords: Atopic dermatitis; Nano delivery; Inflammation; Lipidic nanoparticles; Pathogenesis

Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disorder characterised by intense itching and recurrent eczematous lesions. It affects not only children but also the adults with prevalence rates varying from 1-20% in different regions of the world [1]. Although the pathogenesis of the disorder is not completely understood, it appears to result from the complex interplay between defects in skin barrier function, environmental and infectious agents, and immune abnormalities. Further, the role of reactive oxygen species (ROS) though has been studied in AD and other skin diseases to some extent, but its importance in atopic dermatitis has rarely been investigated. The current therapies for AD involve the use of topical corticosteroids (first-line) and/or topical calcineurin inhibitors (TCIs), first-generation antihistamines and phototherapy to manage the sleep disturbances and skin infections. Inspite of current therapies, AD is associated with potential and undesirable adverse effects [2,3]. Nanotechnology based therapeutics are being explored by researchers to alleviate the symptoms of AD and have potential applications in topical and systemic therapy. However, still additional innovative research is needed to address the cost-effectiveness and long-term safety of these nanoparticles.

Nanotechnology has become a rapidly growing field with potential applications in health and drug therapy. The efficacy of topically applied drugs used in clinical dermatology is generally observed by their mechanism of action and their ability to pass through the protective skin barrier. Topical drug delivery for attaining local and systemic effects has been very well explored for the delivery of nanoparticles (NPs) [4]. Topical treatment of skin diseases is immensely attractive, due to reduction in the achievable systemic drug concentrations and thus also systemic side effects as compared to the parenteral or oral drug administration. Furthermore, drug application to the skin surface avoids the first passage metabolism of the drug through liver after intestinal absorption, thus help preventing the major fluctuations of plasma levels typical for repeated administration of rapidly eliminated drugs [5].

The skin provides a natural physical barrier against particle penetration, but there are opportunities to deliver therapeutic NPs, especially in diseased skin and to the openings of hair follicles. Whilst nanoparticle drug delivery has been touted as an enabling technology, its potential in treating local skin and systemic diseases has yet to be realized [6-9].

Lipid nanoparticles present a superior drug delivery mode due to the avoidance of organic solvent during their production. Apart from, imparting a high entrapment efficiency and capability to hold both the lipophilic and hydrophilic drug they provide easy scalable solutions and stability to the developed formulations. Latter is another concern which adds to challenges during the production of nanoparticles. Solid lipid nanoparticles (SLNs) possess a great potential for encapsulating a range of anti-microbial, anti-inflammatory and antioxidant molecules [10-14].

Sequential studies on tacrolimus loaded nanoparticles (T-LNs) have been reported by Pople and Singh. In their first report, tacrolimus the drug-of-choice for AD which inhibits T-cell activation resulting in suppression of inflammation was loaded into lipid-nanoparticles and characterized suitably. *In vitro* studies revealed much higher drug release, skin penetration and enhanced skin accumulation as compared to reference Protopic*. *In vitro* and *in vivo* occlusion studies demonstrated similar occlusiveness for T-LNs and reference however; T-LNs showed significantly higher drug levels penetrating into deeper skin layers where dendritic cells responsible for immunopathogenesis of AD mainly reside. *In-vivo* skin retention demonstrated 3.36, 30.81 and 28.68-times higher stratum corneum, epidermal and dermal levels respectively compared to reference. Further, confocal laser scanning microscopy (CLSM) confirmed targeting to deeper skin layers and Draize test showed no skin irritation with primary irritation indices (PII) 0.00. Thus, T-LNs displayed superior performance, effective skin targeting and improved safety as compared to reference [15].

Pople and Singh (2011) studied the development of tacrolimus-loaded modified nano lipid carrier (T-MNLC) by using high pressure homogenization technique with an aim to enhance the drug solubility in carrier lipid matrix using lipophilic solubilizer for topical delivery. T-MNLC displayed sufficient stability attributed to reduce total lipid concentration in carrier. Thus, the study highlighted the usefulness of novel T-MNLC using lipophilic solubilizers to increase the encapsulation efficiency of colloidal lipid carriers with an advantage of improved performance in terms of stability and skin localization [16].

More to the above, Pople and Singh (2013) investigated the skin hydration properties, site-specific delivery, therapeutic effectiveness, and safety of modified nanolipid carrier. The improved targeting ameliorated therapeutic efficacy against AD-like skin lesions in BALB/c mice. In addition, T-MNLC treated group showed no evident toxicity demonstrating significantly improved safety. Thus, these studies strongly demonstrate that the novel T-MNLC formulation would be more appealing and beneficial to the patient with better compliance to treat large skin areas of AD requiring long-term treatment [17].

Furthermore, Fang et al. [18] proposed an innovative topical ointment containing betamethasone dipropionate loaded nanostructured lipid carrier (BD-NLC) for the treatment of AD. *In vitro* drug release test indicated a better skin retention with w/o ointment loaded with BD-NLC. The self made topical ointment also showed desirable drug retention in skin tissue of living mice with an absence of any signs of skin irritation in rabbits. This study emphasized the development of BD-NLC as a therapeutic owing to improved skin retention and reduction in skin irritation and the adverse effects induced by systemic absorption [18].

Maia et al.[19] developed solid lipid nanoparticles of a topical glucocorticoid prednicarbate (PC), to improve targeting to the viable epidermis. PC penetration into human skin was increased by 30.0% as compared to PC cream possibly due to the small particle size and close interaction of SLNs with the stratum corneum. The penetration study of prednicarbate solid lipid nanoparticles (PC-SLNs) showed that the biotransformation of PC did not change by SLNs-incorporation. Authors reported a 3-fold increase in PC permeation post incorporation into SLNs [19].

Nanoparticles based on synthetic polymers were also evaluated for their potential in enhancing the efficacy of hydrocortisone acetate. Rosado et al. [20] proposed the hydrocortisone acetate (HCA)-loaded poly (ε-caprolactone (PCL) nanoparticles (NPs) by using solvent displacement method to achieve a prolonged release of drug and reduction of side effects. It was confirmed that the developed formulation indicated minimum side effects and increased its therapeutic efficacy [20].

Katas et al. [21] studied the chitosan nanoparticles (CS NPs) as a percutaneous drug delivery system for hydrocortisone (HC), prepared by ionic gelation method. Despite low permeation of HC from CS NPs in aqueous cream, this formulation was considered to be a good candidate as a sustained release drug delivery system for HC. These findings therefore suggested that HC-loaded CS NPs could be used as a promising delivery system for anti-inflammatory moieties which could improve drug efficacy and reduce related side effects [21].

Another microemulsion cream formulation of tacrolimus against ointment in hapten-induced murine model of dermatitis was developed which enhanced the penetration through skin. The enhanced penetration was assigned to possibility of dose reduction. The developed cream in this investigation has been found to be deposited significantly in the targeted site and has also shown significant reduction in cytokine expression [22].

Alam et al. [22] developed the clobetasol propionate (CP) topical o/w nanoemulsion by aqueous phase titration method. It was found that the CP loaded nanoemulsion significantly increased their anti-inflammatory activity and nucleoside triphosphate diphosphohydrolases activity in lymphocytes. Absence of irritation in *In vivo* irritation studies inspite of high amount of surfactant proved the safety of developed nanoemulsion for human use [23].

Keck et al. [24] developed the physically and chemically stable positively charged prednicarbate nanoemulsion as a carrier system for the treatment of AD. In context of dermal delivery, the uses of positively charged carriers are beneficial, owing to the positive charge which promotes an intensive adsorption to the negatively charged skin. This increases the retention time and thus the bioavailability [24].

Songkro et al. [25] formulated the micro emulsions and nanoemulsions as delivery vehicles for plaunoi extract (*Croton stellatopilosus*) containing plaunotol as a chemical constituent. Latter has shown to possess antimicrobial activity for treatment of dermatitis. A 2% w/w plaunoi-loaded formulations exhibited somewhat improved antibacterial activity for *Staphylococcus aureus (S. aureus), Staphylococcus epidermidis (S. epidermidis)* when compared with the blank formulations. The skin irritation was not observed in all treated rabbits for the plaunoi loaded nanoemulsion (NE-P). Both plaunoi loaded micro emulsions (ME1-P) and ME2-P showed slight erythema. These results suggest a potential use of nanoemulsions for topical delivery of plaunoi extract [25].

Very recently, Muller et al. [26] demonstrated the cyclosporine A (CyA) amorphous nanoparticles suspension using wet bead milling method and studied the physical/chemical long term stability. The improvement in skin penetration-amorphous cyclosporin micronized vs. nanonized-was studied using tape stripping in the pig ear skin test and explained the superiority in penetration. Based on amorphous CyA nanoparticles, dermal formulations for improved dermal CyA delivery seem to be feasible [26].

Furthermore, Azuma et al. (2016) evaluated the effect of chitin nanofibril (CNF) application via skin swabs on an experimental AD model. CNF also showed the anti-inflammatory effects via suppression of the activation of nuclear factor-kappa B, cyclooxygenase-2, and inducible nitric oxide synthase. It may be concluded that CNF is a potential functional biomaterial for suppression of AD [27].

Batheja et al. [28] have investigated the potential of tyrosine derived nanospheres containing diclofenac sodium as effective carriers for the topical delivery of lipophilic molecules. Tyrosine-derived nanospheres as either aqueous dispersion or gel formulation are biocompatible for topical delivery systems since they did not induce any short-term cytotoxicity or morphological changes in stratum corneum. Hence, gel formulation of tyrosine-derived nanospheres offers a promising, adjustable platform for the safe and effective topical delivery of lipophilic therapeutics as required for treatment of dermatological conditions [28].

Kang et al. [29] developed the topical preparations of taxifolin glycoside (TXG). The TXG-loaded Pep1-elastic liposomes formulation was prepared by conjugating Pep-1 peptides to drug-containing EL via the thiolmaleimide reaction and examined for their efficacy and skin permeation. Moreover, the formulation normalized multiple immunological parameters including IL-4, IgE, and IFN-γ in NC/Nga mice, with serum levels approaching those of healthy mice. It may be concluded that TXG-loaded Pep1-EL preparations may provide a potential therapeutic tool for the treatment of AD, and should be further investigated [29].

We wish to notify here, that this short review, details the nanotechnology research for AD taken by researcher in the last five years with special emphasis on lipidic and polymeric nanoparticles.

Based on the above research findings, it can be affirmed that nanotechnology tailored product holds immense potential for the treatment and cure of AD.

Also, the clinical translation may occur often with nanotechnology based product, especially for topical applications, once the US-FDA gives a realistic nod to the draft guidelines. Latter have been regarded as one of the milestone to result in commercialization of nanopitched product.

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