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Material engineering for atopic dermatitis treatment

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ABSTRACT

Atopic dermatitis (AD) is a chronic inflammatory skin disease with a prevalence of 30% for children and to 17% for adults. There is observed an increasing trend of occurring AD over time in the world. Many factors contribute to the development of the disease, such as environmental, genetic and psychological factors. The proper AD treatment should be complexed and consists of skin care with emollients and pharmacological treatment. Most of the topical corticosteroids and other drugs have unpleasant side effects, therefore, developing new therapies is very useful. To minimize side effects with a simultaneous reduction in the duration, a NPs (nanoparticles) therapy application is highly proposed. On the other hand, hydrogels and their shielding properties with high hydrating level and drug delivery capability are also widely studied. Some works report on the combination of these two solutions with promising results. Material engineering for biomedical applications is a dynamically growing field which offers new drug delivery systems (DDS). In this paper, based on the literature we discuss the new methods of AD treatment using hydrogels and nanotechnology.

Key words: atopic dermatitis, drug delivery system, nanoparticles, hydrogels

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Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin disease initiated by the abnormal immune response, microbiome, genetic and/or environmental factors [1]. This disease mainly appears in childhood but it can also starts in later life [2]. Although prevalence in Poland not exceeding 4% [3], studies suggest that in the world there is an increasing trend of occurring AD over time, especially in children at the age between 6 and 7 or between 13 and 14, depends on the country [4]. Among all cases in the world, the rate for children is 30% and 17% for adults [2].

Pathophysiology

AD is characterized by dry skin, erythema, eczematous inflammation and persistent pruritus which together have a negative impact on the quality of life [2]. Pathogenesis of AD is heterogeneous because both genetic and environmental factors are involved in the development of the disease [4].

Filaggrin (FLG) is an epidermal protein that provides the integrity of the skin barrier and promotes corneocytes formation. As a result of the physiological intracellular transformations of the filaggrin, its metabolites (urocanic acid and pyrrolidone-5-carboxylic acid) form components of the natural moisturizing factor [5]. FLG loss of function variants is the most common genetic mutations associated with AD, which the consequence is the reduction or lack the filaggrin protein [6]. Furthermore, the single-nucleotide polymorphism (SNP) of the genes for IL-4, IL-13 and their receptors play a crucial role in the immune dysfunctions and the development of AD [1]. IL-4 and IL-13 are pro-inflammatory cytokines mediated by T-helper 2 cells (Th2) which contribute to the skin barrier integrity changes. Increased levels of IL-4 and IL-13 inhibit the expression of epidermal proteins like filaggrin, involucrin and loricrin and play a role in the regulation of epidermal homeostasis. In addition, these cytokines increase the chances of infection by the destabilization of tight junctions and interfere with intercellular transport. Not only Th2 but also Th22 cells secrete pro-inflammatory cytokines, such as IL-22 and INF- γ , which affect the lichenification (Rodrigues and Torres, 2019).

On the other hand, many environmental and emotional factors strengthen symptoms of AD. Study shows that the low humidity reduces the expression of filaggrin through unknown mechanism [8]. Also, a positive linear association between AD prevalence and mean and minimum monthly ultraviolet radiation exhibition were investigated [9]. Increased sensitivity to dust, air pollution and food allergens are mainly observed in adult patients with AD. Exacerbated the symptoms of AD are also observed after exposure on fragrance (e.g. balsam of Peru), hard water and metals including nickel and cobalt [10, 11]. Some emotional experiences such as stress or deprivation improve symptoms or even give rise to the disease [12]. Jaworek et al. suggest that there are relations between comorbidity of the AD and depression or anxiety. Moreover, the AD's symptoms of patients who suffer from depression and smoke are more persistent, than patients who do not smoke [3, 13].

Non-Pharmacological and Pharmacological Treatments

Treatment should contribute by proper skin care to rehydrate, improve skin barrier and repair. Cosmeceuticals for supporting AD treatment contain emollients which fulfil all these functions. Regular use of emollients in the first six months of life prevent the occurrence of AD in children at high risk of the illness [14]. Corticosteroids have anti-inflammatory effects but the treatment should last no longer than two weeks because of strong side effects of the therapy [15]. During systemic therapy the most oral used corticosteroid is prednisolone but the therapy of AD also consists of immunosuppressant treatments include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate and dupilumab [16, 17]. The last mentioned is a human monoclonal antibody which inhibits IL-4 and IL-13. Because of low toxicity profile dupilumab is recommended for patients who cannot use any other therapy [18]. However, therapy needs to be supplemented by vitamins D and E and some patients need psychotherapy to relieve symptoms of AD [15, 18].

Phototherapy is an additional anti-inflammatory treatment allowed only for patients without any medical contraindications, such as hypertension, heart disease and diabetes [19]. This therapy is also a challenge for children treatment because of the inconvenience associated with the eyewear [20]. The ultraviolet radiations used in phototherapy are ultraviolet A (UVA) and ultraviolet B (UVB) which modulate some immune pathways, mainly for Th2, Th22 and Th1 cells and cytokines secreted by these cells. The disadvantage of this method is the acceleration of skin ageing and skin cancer [19, 20]. Narrow-band UVB also significantly

reduces the infection caused mainly by *Staphylococcus aureus* [21]. Unfortunately, recurrent skin infections are very common among patients with AD. The occurrence of *S. aureus* is the most prevalent infection co-occurring with AD. Infections are caused by the reduction of the skin barrier and bacterial virulence factors secreted by *S. aureus* [22]. Also, there was investigated that the *S. aureus* colonization may be one of the irritating factors and causes a persistent itching [23]. Sometimes, antibiotic therapy is required [24].

Nanotechnology

Term „nanotechnology” is a name of technique and method of synthesis materials and particles in nano-scale [25]. It was presented for the first time in 1959 by Richard P. Feynman in his lecture „There's Plenty of Room at the Bottom”. Nanoparticles (NPs) are materials with dimension from 1 to 100 nm [24]. Depending on the size, chemical and physical characteristics, NPs are divided into several categories [26]. The classifications of NPs has been presented in Table 1.

The biggest advantage of NPs using for medical applications is the reduction of the side effects of treatment due to the targeting delivery of the drug. Two types of DDSs (drug delivery system) can be distinguished: active and passive targeting. Passive targeting uses the mechanism of enhanced permeability and retention, where NPs penetrate blood vessels and accumulate in diseased cells. Active targeting involves chemical modifications of NPs' surface e.g. by specific ligand for tumor cells which may provide more accurate diagnosis and/or delivery of the substance. Both mechanisms allow to introduce less drug to the organism and reduce the side effects of therapy [32]. Also, it is possible to encapsulate low solubility drugs or even two drugs for multidrug therapy or bypass limited skin permeability [24].

Nanotechnology for AD treatment

Most solutions using NPs for AD treatment were prepared for topical use. Lipid NPs such as liposomes show high capability with skin components and also polymeric NPs made from polylactic-co-glycolic acid (PLGA), polylactic acid (PLA) and chitosan. It shows promising results because of biocompatibility, biodegradability and non-toxic properties [24, 33].

Hydrocortisone and hydroxytyrosol loaded chitosan nanoparticles obtained by ionic gelation method formulated as a topical cream showed no toxicity, no local-irritation and high tolerance even during 28 days of *in vivo* treatment. Hydrocortisone and hydroxytyrosol

Table 1. Classification of NPs including dimensionality and materials

Classification including dimensionality			
Dimensionality (D)		Examples	References
0D		quantum dots, solar cells, single-electron transistors, lasers	[27]
1D		nanowires, nanorods, nanotubes, nanobelts, nanoribbons	
2D		nanoplates, nanosheets, nanowalls, nanodisks	
3D		nanoballs, nanocoils, nanopillars, nanoflowers	
Classification including material			
	Material	Examples	References
Inorganic	Metal	nanorods, spherical NPs, 0D hollow nanoporous NPs,	[26, 31]
	Ceramic	nanoshells, nano-scaffold	[30]
Organic	Carbon-based NPs	fullerenes, carbon nanotubes	[26]
	Polymeric	microspheres, micelles	[28]
	Lipid-based	micelles, reverse micelles, liposomes	[29]

are glucocorticoids, while chitosan is a natural anti-microbial and anti-oxidant compound with wound-healing properties. It is approved by FDA (Food Drug Administration) due to its biocompatibility, biodegradability and low toxicity [33].

To improve the penetration ability of tacrolimus, Zhuo et al. [34] encapsulated it into polymeric NPs and coated it all with hyaluronic acid. NPs were obtained by high-pressure homogenization–solvent evaporation method. In result, they received controlled released drug system. Coat made of hyaluronic acid may provide limited water diffusion into polymeric NPs and in effect slows rapid drug release to 8 hours. Obtained *in vivo* test on AD mice group and control group have shown greater control over AD-like skin lesions. Moreover, the histological examination has shown less infiltration of inflammatory cells and increasing skin integrity in the treated group.

Chitosan-NPs coated with hyaluronic acid have been also proposed to delivery betamethasone valerate. NPs were prepared by high-pressure homogenization–evaporation method and obtained spherical shape particles with smooth surfaces. The optimal drug release was obtained in pH = 5.5 what mimics the microenvironment of the inflammation process during AD. Moreover, NPs with betamethasone valerate efficiently retained into the epidermis and the dermis [35].

To improve solubility and anti-pollutant activity of 7,3',4' — Trihydroxyisoflavone (734THI), Huang et al. prepared polyvinylpyrrolidone (PVP) NPs loaded with potential drug — 734THI [36]. This substance shows antioxidant, skin whitening and anti-AD properties that have a promising application in dermatology and cosmetology. NPs did not show HaCaT cell line cytotoxicity. Moreover, 734THI loaded into NPs has higher anti-inflammatory activity, compared with raw substance.

Another tacrolimus-loaded thermosensitive solid lipid NPs were obtained by a solvent emulsification-diffusion technique. The shell of the particles was coated by different types of surfactants. It was confirmed that the drug release depends on the melting point of the surfactant. In addition, this NPs are able to penetrate a deeper layer of the skin and release the drug at 37°C [37].

NPs for veterinary application were prepared by two-step desolvation method. Cytosine-phosphate-guanine oligodeoxynucleotides were encapsulated into gelatin NPs as a immunomodulatory factor which increases secretion of IL-10 and decreases IL-4 level in atopic dogs. This study, as the only one in this paper, assumes subcutaneous injections of the potential drug [38].

Despite the side effects of silver NPs, their potential use in dermatology is still being tested. Kang et al. compared the immune response of mast cells to the use of 5 nm and 100 nm silver NPs. Results suggest that 5 nm silver NPs indicate mast cells degranulation and generate oxidative stress via an increase level of Ca²⁺. Moreover, histological examination of mice skin treated 5 nm silver NPs have shown an increased number of mast cells. Strong immune response was not observed for 100 nm silver NPs [39].

Levocetirizine is an antihistaminic drug and H₁ blocker used in the treatment of chronic idiopathic urticaria, hay fever and seasonal allergic rhinitis. It was shown that levocetirizine is able to reduce IL-13 and IL-4 level and increase IL-10 level which has a promising potential treatment for AD. Another novel proposition are flexible vesicles loaded with levocetirizine for topical use characterized by no pathological changes in histological studies and ability to penetrate the skin barrier [40].

Hydrogels

In general, hydrogels are three-dimensional polymeric matrices with hydrophilic and adsorption properties but without possibilities to dissolving. The classification is complexed and depends on the origin, properties, nature of polymeric side groups and response to the stimuli [41]. Hydrogels were fully defined for the first time by Wichterle and Lim in 1960. The definition included biocompatibility and high water affinity [42]. After that time, hydrogels were intensively studied and the process of developing the hydrogels formulations was divided into three stages. Nowadays hydrogels being designed as supramolecular compositions with excellent biocompatibility, ability to respond to specific stimuli (pH, temperature) and elicit specific response [41].

Hydrogels for AD treatment

Hydrogels are attractive vehicles for the transdermal drug delivery but the biggest limitation is the ability to deliver only hydrophobic drugs. Many studies use compositions of micelles and hydrogels to obtain DDS (drug delivery system) complex despite the hydrophobic or hydrophilic drug nature [41].

Alginate hydrogels with cynaroside as an anti-inflammatory and anti-allergic natural substance were tested as a potential DDS for AD. The results show a reduction in the number of T cells in histological examination. Moreover, alginate hydrogels with cynaroside are characterized by high bioadhesion and viscosity properties [43].

Another proposition with natural drug substance is hydrogel with *Rhus verniciflua* extract (RVE). RVE is widely known by its anti-microbial, anti-inflammatory, anti-allergic and AD-protective properties. Authors obtained pullulan-RVE film for topical application which limits the mast cells migration in AD lesions. Total amount of extract was released from this system by 6 hours, but the effect of pullulan without drug substance have not been investigated [44].

To reduce the pruritus associated with AD, Kircik made desonide hydrogel. Desonide is a topical corticosteroid used for various skin conditions. Hydrogel treatment for 3–7 days significantly improved skin condition and potentially quality of patients' life [45].

Thermosensitive transdermal hydrogel made of poloxamer is a dual-functional moisturizing and medicinal DDS. Liquid formula has been transformed into gel almost immediately after the temperature rises to 37°C. *In vitro* cytotoxicity analysis have shown high safety and biocompatibility of use [46].

As mentioned earlier, some systems contain NPs and hydrogel to ensure penetration of the hydrophilic substances. Augustin et al. elaborated a pilot study of liposomal polyvinylpyrrolidone-iodine hydrogel. This system were well tolerated by most patients even with sensitive skin conditions. In addition, it may be a potential treatment method for a inflammatory skin diseases associated with bacterial colonization [47].

Utilizing anti-inflammatory potential of prostaglandin PGJ₂, hydrogel vehicles were made and compared with tacrolimus treatment and no treatment rats group. Both, tacrolimus and PGJ₂ hydrogels reduced the IgE level in serum and decreased mast cells infiltration. There were no significant differences between PGJ₂ and tacrolimus groups. These findings suggest that PGJ₂ hydrogels may be a potential topical treatment for AD [48].

Summary and conclusions

AD is a serious skin ailment correlated with environmental factors and mental condition. The AD treatment is a complexed and long-lasting process causing many side effects and bad quality of life. Moreover, most of them may not be effective. New DDSs provide multidrug cure with simultaneous high moisture level and relieved feeling. In addition, novel materials for the medical application do not require much duration of treatment compared with the traditional medical approach. NPs are great vehicles for drugs which require deep skin penetration but on the other hand, hydrogels also provide a high level of hydration and wound healing. The examples cited in this paper require further research but the *in vitro* and *in vivo* results are promising and shed new light on pharmacology.

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