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Review Article

Nanotechnological Advances in Cutaneous Medicine

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Wound healing is an area of unmet clinical need. Current treatments include occlusive dressings, hydrogels, and antimicrobials to control infection. However with the growing number of antibiotic-resistant bacteria and the increase in population age and clinical obesity, it is becoming proportionally harder to treat wounds with the drugs that have worked in the past. There is an urgent requirement for efficient mechanism-based treatments and more efficacious drug delivery systems. The potential of using nanoparticles as a drug delivery system has been identified and investigated. Nanoparticles have the ability to protect and carry drugs to specific targets in the body, enabling slower degradation, enhancing drug penetration, improving treatment efficacy with lower systemic absorption, and reducing unwanted side effects. Here we discuss the advantages and limitations of nanotechnology for the treatment of wounds and other cutaneous disorders.

1. Introduction

The skin is the largest organ in the body and is the first line of defence against invading pathogens. The primary function of the skin is to act as a protective barrier against the environment as any large insult or loss of skin integrity can lead to disability or death [1, 2]. Adult cutaneous wound healing is a complicated process involving a cascade of events and interactions between numerous cells and cell mediators [3, 4]. This process aims to restore the complete skin barrier function quickly, often at the expense of correct anatomical repair [5]. There are several dressings and devices currently available on the medical wound care market impregnated with a range of compounds which aim to optimise the wound healing environment, providing faster, more efficient wound healing [6]. There are, however, many limitations with using these dressings in clinical practice including poor skin penetration, low stability, and localised side effects. Consequently, there is a need for the development of novel and more efficient drug-delivery systems [7]. The advent of nanotechnologies has the potential to fulfil this and the design and implementation of target-selective, time-controlled drug delivery systems for cutaneous healing and regenerative medicine now exists [8, 9].

While naturally occurring nanoporous minerals have been used on an industrial scale as effective catalysts for decades, today there are a number of different substances used for the production of nanoporous materials including carbon, silicon, silicates, ceramics, metals, various polymers, metallic minerals, and compounds of organic materials [10]. The use of micro- and nanotechnology is becoming more frequent in biomedical science, both in the development of diagnostics and in clinical therapies. Development of novel therapies in cutaneous healing has been greatly facilitated by the discovery of novel nanomaterials including nanoparticles, nanotubes, nanoengineered scaffolds, and nanoscale surface modifications [11]. The use of this technology has the potential to increase drug efficacy and decrease adverse effects by delivering specific quantities of drugs to specific target sites over a determined period of time. Nanomaterials are currently being investigated for their applications in cutaneous wound healing and their potential uses include molecule delivery, nanofibres for tissue scaffolds and surface modification for implantable materials [12]. Nanotherapy is manipulation of matter, at an atomic or molecular scale, used for delivery of therapeutic agents to tissues in vivo [13]. The main examples of nanotherapy being developed for use in cutaneous medicine include solid lipid nanoparticles, which are

nanoparticles made of lipids and lipids blends, and nanostructured lipid carriers, a second generation of smarter drug carrier systems made up of physiological, biodegradable, and biocompatible lipid materials and surfactants. These are both currently accepted as applicable routes for the delivery of drugs in vivo [14, 15]. The aim of this paper is to review the potential of nanomaterials for the improvement of cutaneous healing, while comparing current clinical therapies to developing ones and assessing the strengths and limitations of both.

2. Transcutaneous Delivery of Nanoparticles

Penetration of nanoparticles through intact skin is a controversial topic and has been a major focus of research in both the pharmaceutical and cosmetic industry examining the transcutaneous delivery of both nonbiodegradable and biodegradable nanomaterials [16]. Titanium dioxide (TiO2) and zinc oxide (ZnO) are two of the most widely characterized nonbiodegradable nanoparticles studied in this regard due to their wide use in both sunscreens and cosmetics. There are, however, conflicting studies reporting on the epidermal penetration of titanium dioxide and its accumulation in several majors organs. This has raised safety and toxicity concerns due to oxidative stress induced by deposited nanoparticles after prolonged dermal exposure [13, 17]. In recent years, however, developments in nanotechnology have highlighted the potential use of biodegradable nanoparticles including liposomes, niosomes, nanosized emulsions, and solid lipid nanoparticles as the carrier systems for drug delivery through the protective stratum corneum [18]. Solid lipid nanoparticles (SLN) are a new generation of nanoparticulate active-substance vehicles with advantages of controlled release, low irritation, and protection of active compounds [19]. Their small particle size ensures close contact with the stratum corneum and improved penetration of the encapsulated agent through the skin layers [20]. The complete biodegradation of lipid nanoparticles and their biocompatible chemical nature has highlighted lipid nanoparticles as "nanosafe carriers" for topical drug delivery with studies examining their use for delivery of glucocorticoids (prednicarbate, betamethasone, and prednisolone) and nonsteroidal anti-inflammatory drugs (indomethacin, celecoxib, ketoprofen, ketorolac, flurbiprofen) for potential treatment of acne, skin mycoses, atopic dermatitis, and psoriasis [21].

The efficacy of topically applied drugs used in clinical dermatology is determined by their mechanism of action and their ability to pass through the protective skin barrier. Drug permeation through the skin occurs via the passive diffusion of drugs through the transepidermal or transappendageal route [13]. In contrast, transcutaneous delivery of nanoparticles is dependent on a number of factors including desquamation rate of stratum corneum, permeation pathway, and the size of nanoparticles [22]. The majority of studies to date suggest that nanoparticles only permeate the superficial layers of the skin in vivo and remain in the stratum corneum, while only a few studies suggest full epidermal penetration and dermal absorption. It is generally accepted that nanoparticles do not diffuse across the basement membrane and their deposition in the skin occurs through follicular penetration (Figure 1(a)) [18]. In the context of clinical dermatology, controlled drug delivery and release via the hair follicles using nanoparticles offer an exciting opportunity for therapy development as hair follicles are surrounded by capillaries and antigen presenting cells, are associated with the sebaceous glands, and are the host of stem cells in the bulge region of the hair follicle [23]. Consequently delivery of drugs, proteins, or antibodies to the epidermis through follicular penetration offers novel avenues of therapy development for number of dermatological conditions where patients still have intact skin eg eczema, psoriasis, mycoses and atopic dermatitis (further discussed in Section 4 and Table 1).

One area of current research focus is the potential use of nanoparticles for noninvasive transcutaneous immunisation. Compared to microparticles which cannot penetrate the skin to the extent that would allow the application of the required dose of antigen nanoparticles, delivery through the follicular pathway has been shown to penetrate deeper into the hair follicle than molecules in solution, help stabilize the protein based antigens, and can improve and modulate immune response [40]. This particular route of drug/vaccine delivery is particularly important for immunocompromised patients including the elderly, patients with poor wound healing, and young children [41]. Studies by Mittal et al. demonstrate an effective needle-free application of vaccines across the skin by delivery of polymeric nanoparticles using ovalbumin antigen and a double emulsion nanotechnology method using pharmaceutically biocompatible and biodegradable polymers poly(lactide-co-glycolide) (PLGA) or chitosan-coated PLGA (Chit-PLGA) demonstrating increased protection from cleavage and functional biological activity of the antigen [41]. In addition, epidermal permeation of nanoparticles has also been reported following mechanical stress including the use of harsh vehicles or skin damage following needle puncture or wounding [13].

Transcutaneous delivery of nanoparticles and dermal absorption of drugs, proteins, or antibodies to patients suffering from chronic inflamed wounds or nonhealing ulcers are not hindered by the protective skin barrier as those patients have large open wounds. For patients with open wounds, treatments can be delivered using nanotechnology by incorporating drug carrying nanoparticles into dressings or hydrogels allowing controlled sustained release of nanoparticles to the dermis (Figure 1(b)). Preliminary in vitro and in vivo studies have shown that both solid lipid nanoparticle and nanostructured lipid carrier hydrogels can be used to successfully deliver flurbiprofen to skin with sustainable and controlled drug delivery over 24 hrs with functional anti-inflammatory effects on the tissue [30]. Current research developments are focused on designing biodegradable dressings and dermal scaffolds incorporating nanoparticle delivery systems for the controlled release of drugs, proteins, and antibodies to open wounds in vivo.

The use of antibody based therapy for treatment of cutaneous diseases has been demonstrated previously with Infliximab (trade name Remicade), a monoclonal antibody against tumour necrosis factor alpha (TNF-α) used to treat

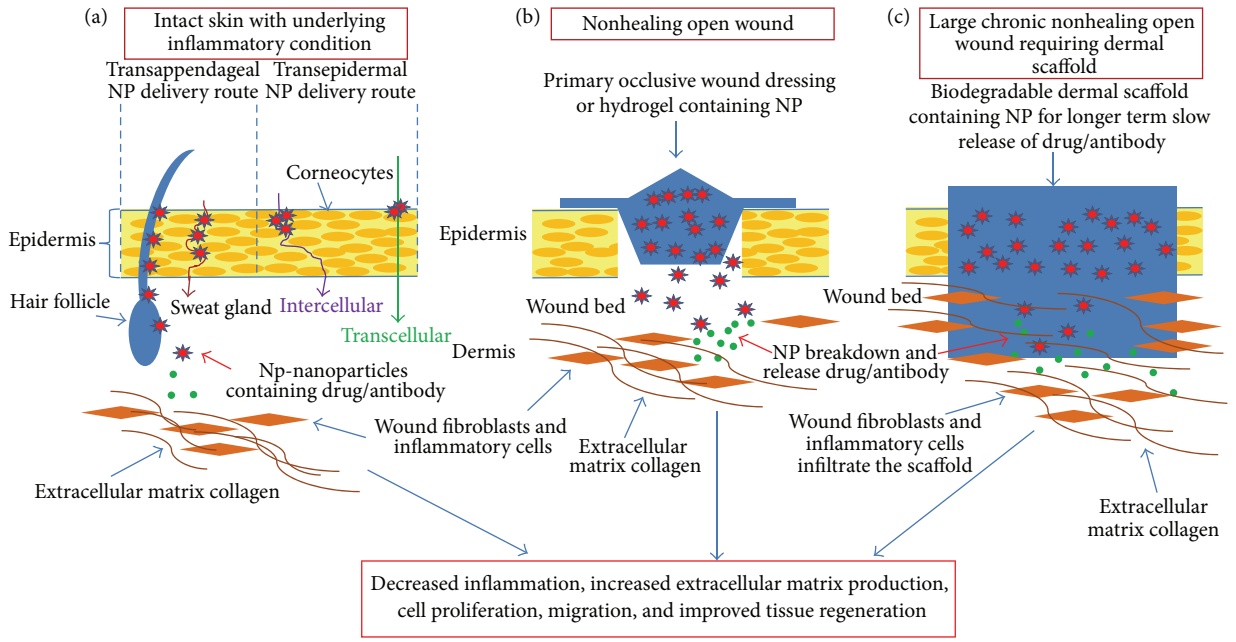

Figure 1: Nanoparticle technology for transcutaneous delivery of drug agents to intact or wounded skin leading to improved wound outcomes. (a) Transepithelial delivery of nanoparticles is limited by the poor penetration through the protective stratum corneum. Transappendageal nanoparticle delivery through hair follicle offers potential for treatment of conditions where skin is intact. ((b)-(c)) Incorporation of drug carrying nanoparticles into dressings and scaffolds allows controlled sustained release of biologically active agents into open wounds intradermally hence resulting in improved healing and reduced scarring.

Table 1: The use of nanoparticle technology for delivery of drugs transcutaneously targeting the most common cutaneous pathologies.

Nanoparticle type	Drug	Skin type	Study	Delivery type and penetration	Targeted cutaneous disease pathology	Literature studies
Solid lipid nanoparticle	Glucocorticoids, corticosteroids	Human	In vitro and in vivo	Transepidermal delivery, no penetration to the dermis	Inflammatory skin diseases, dermatitis, rheumatic disease	Sivaramakrishnan et al., 2004 [24]; Jensen et al., 2010 [25]; Zhang and Smith, 2011 [26]; Schlupp et al., 2011 [27]; Puglia et al., 2006 [28]
Solid lipid nanoparticle	Nonsteroidal anti-inflammatory drugs	Human	In vitro and in vivo	Delivery via NP enriched hydrogels with sustained continued drug release to the dermis	Musculoskeletal disorders	Jain et al., 2005 [29]; Bhaskar et al., 2009 [30]
Solid lipid nanoparticle	Antiandrogens, retinoids	Human	In vitro and in vivo	Transappendageal NP delivery to hair follicle and upper papillary dermis	Skin acne	Munster et al., 2005 [31]; Štecová et al., 2007 [32]; Castro et al., 2007 [33]
Solid lipid nanoparticle	Antifungal agents	Human	Ex vivo and in vivo	Topical gel delivery of NP with penetration to upper papillary dermis	Skin mycoses	Bhalekar et al., 2009 [34]; Sanna et al., 2007 [35]
Solid lipid nanoparticle	Retinoids, furocoumarins	Mouse and human	In vivo	Topical gel delivery to the epidermis	Psoriasis	Fang et al., 2008 [19]; Agrawal et al., 2010 [15]; Lin et al., 2010 [36]
Solid lipid nanoparticle	Tacrolimus	Porcine	In vitro and in vivo	Topical gel delivery with dermal penetration	Atopic dermatitis	Pople and Singh, 2010 [37]
Nanostructured lipid carriers	Antihypersensitive drugs and anaesthetics	Mouse and human	In vitro and in vivo	Topical gel delivery to the epidermis	Hair loss treatment and pain relief after surgery	Silva et al., 2009 [38]; Puglia et al., 2011 [39]

autoimmune diseases including psoriasis [42]. While the use of nanotechnology for the delivery of antibodies to wounds using scaffolds in vivo is yet to be demonstrated, nanotechnology has been used in numerous studies exploring the delivery of antibodies to tissue in vivo using experimental animals models of breast [43] and colon [44] cancer and osteoarthritis [45]. In addition, recent studies using nanomedicine to deliver therapeutic antibody in the experimental model of myeloma have shown that a combination therapy of anti-ABCG2mAb and paclitaxel loaded iron oxide magnetic nanoparticles has a significant effect on reduction of tumour growth in vivo compared to paclitaxel, iron oxide nanoparticles, or anti-ABCG2mAb treatment alone hence demonstrating the synergetic effect of combinational therapy in nanomedicine [46].

3. Nanotechnology and Cutaneous Infection

With the evolution of new antibiotic resistant strains of bacteria, wound infection rates are increasing and more aggressive wound management is required [47]. Infection in wounds, particularly in chronic, nonhealing, and burn wounds is a leading cause of morbidity and mortality. Good clinical practice involves using systemic and topical antimicrobial prophylaxis to reduce the microbial load in the wound as infected wounds have slower healing outcomes [48]. One of the current strategies for combating these infections is the use of noble metals as antimicrobial agents. The leader in this field is silver which has been used for its antimicrobial properties for centuries [49]. Silver based compounds are highly toxic to microorganisms showing strong effects on 16 bacterial species including *E. coli* [50]. It is now regularly used as an antimicrobial prophylaxis treatment for burns, open wounds, and chronic ulcers [51]. Silver in its metallic state is inert but upon reaction with wound fluid and moisture from skin it becomes ionized and highly reactive [52]. It binds to tissue proteins, blocks bacterial respiratory enzyme pathways, and causes structural changes of the bacterial cell wall and nuclear membrane hence leading to cell death [53–55]. Nanosilver particles are commonly used in many forms in the treatment of wounds. Silver nitrate is a common antimicrobial used in the treatment of chronic wounds; however, it can be irritating to tissues and also causes semipermanent staining of tissues and surfaces to which it contacts [56]. Silver sulfadiazine (SSD) was introduced as a topical chronic and burn wound treatment in the 1960s to overcome the shortcomings of silver nitrate, but both are limited due to a short therapeutic window, silver inactivation by wound fluid, and the formation of a pseudoeschar [57]. Using new nanotechnology to create sustained release of silver nanoparticles increases the therapeutic window of each dressing. One of these nanosilver impregnated dressings is Acticoat, which is an absorbent rayon-polyester core sandwiched between two layers of silver-coated, high-density polyethylene [57]. The outer layer works to provide antimicrobial effects whilst the inner core maintains a moist wound environment [58].

The use of silver dressings for the management of burns and chronic wounds is now a globally accepted therapy, with Acticoat leading the way for the worldwide management of burns. The efficacy of Acticoat and silver sulfadiazine against several strains of bacteria including MRSA showed 100% clearance for both dressings by the end of the study. Acticoat; however, showed a significantly higher clearance at days 6 and 12 [59]. The effectiveness of Acticoat to chlorhexidine acetate and fusidic acid also showed no significant difference in effectiveness against resistant bacteria, however Acticoat was suggested as the best choice of treatment due to its sustained release properties [60].

New advances in polymer technology are allowing many dressings, previously used only to provide an optimal healing environment, to be impregnated with silver nanoparticles to add to their effectiveness. Bacterial cellulose hydrogels produced by *Acetobacter xylinum* have long been used to provide an effective, moist healing environment but without any antimicrobial activity, and the risk of infection was high. Impregnation of these dressings with silver nanoparticles by immersion in silver nitrate has significantly improved the efficiency of these hydrogels [61]. Although the powerful antimicrobial effects of silver compounds are well documented, there is evidence to suggest that it may have a negative effect on wound healing. Studies have shown that silver compounds can delay wound healing by extending the inflammation phase [62]. They have also been shown to be highly toxic to keratinocytes and fibroblasts [51]. A large oral intake of silver causes a condition known as "argyria" which is characterised by silver granule deposition into the skin leading to a permanent blue/gray discoloration [63]. In patients affected by argyria, silver granules can be found in all organs of the body and recent case studies have suggested that argyria can be an effect of topical delivery of silver in dressings such as Acticoat [64–66]. Treatment of burn wounds with Acticoat has caused raised liver enzymes and argyria like symptoms in some patients [67]. This has resulted in changes in clinical guidelines with current recommendation of using these dressings for shorter period of time and intermittently hence highlighting the need for improved design of dressings with antibacterial activity and functional wound promoting ability.

4. Dermatological Advances

Skin diseases are one of the most widespread complaints with over 80% of the population suffering from a condition at some point in their lives [68]. Although some are merely a cosmetic issue, others are more serious, causing pain, severe scarring, and morbidity. Due to the lower risk of systemic side effects and the ability to apply directly to the problem area, topical treatments of skin disease are preferred [69]. Current treatments are effective but many carry severe side effects so there remains a need for more advanced technology and nanotechnology is fast becoming a leader in this field.

Acne is a common skin disease with a high rate of prevalence in adolescents. It is characterised by increased sebum production, ductal cornification, bacterial colonization of the pilosebaceous ducts, and inflammation [70]. Acne can be severe and often results in permanent scarring and disfigurement. The most common treatment for mild to moderate

acne is the use of oral retinoids. This is a highly effective treatment option; however, it does cause a high incidence of side effects including sensitivity to sunlight, irritation, and erythema, resulting in low patient compliance. The encapsulation of retinoids into solid lipid nanoparticles (SLN) for use as a topical treatment has increased drug penetration, improved efficacy, and reduced side effects [61]. The current treatment for moderate to severe and prolonged acne involves the use of oral antiandrogens, such as combined cyproterone acetate/ethinyl estradiol to reduce sebum secretion and acne lesions. However, these drugs have severe side effects including feminisation of the male fetus in females, and use in males can lead to loss of libido, gynecomastia, and loss of bone mineral density [71]. To avoid these systemic effects and to reduce the side effects, research has led to the discovery of liposomes and solid lipid nanoparticles (SLN) loaded with steroidal and antisteroidal antiandrogens (drospirenone and cyproterone). The use of these nanoparticles increases drug penetration fourfold, increases the efficacy, and reduces the side effects when compared to oral drug options [72].

Psoriasis is a chronic skin inflammatory disorder that drastically impairs quality of life. The most common forms of treatment currently are topical; however, with limited information on their mechanism of action and evidence of accumulation in adipose tissue [73], their use in clinical practice is limited. The advent of new lipid nanoparticle drug delivery systems has the possibility to improve the efficacy and safety of these topical compounds [68]. One of the most common treatments for mild psoriasis is topical application of Tretinoin, a metabolite of vitamin A. Although effective against psoriasis, this treatment has severe side effects including erythema, burning, and increased sensitivity to light [74]. To overcome this, tretinoin has been incorporated into SLN, which not only improved permeation and efficacy, but also significantly decreased the incidence of erythema and sun sensitivity [75]. More severe psoriasis can be treated with Acitretin, an oral retinoid which although effective also has severe side effects including alopecia, skin peeling, and cheilitis [76]. Once incorporated into SLN, a higher deposit of Acitretin at the plaque site as well as significantly improved therapeutic response and a significant reduction in local side effects has been observed [68]. In addition, a recent clinical trial using Acitretin delivered via nanostructured lipid carriers demonstrated significantly improved clinical effects on patients with psoriasis [15].

Fungal skin infections are one of the most widespread diseases known to man with topical therapy the preferred method of treatment due to high patient compliance, self-administration, and low risk of systemic side effects [77]. Current treatments although effective are relatively slow-acting and so SLN are being investigated to improve efficacy. There are several antifungal agents used for the treatment of human mycoses which are currently undergoing investigation of their efficacy when incorporated with SLN including miconazole nitrate [78], clotrimazole [79], ketoconazole [80] and econazole nitrate [35].

The results from these studies show that when the drugs were incorporated into an SLN there was an increased rate and level of skin penetration, higher efficacy, and less local side effects. Selected examples of current research developments using nanoparticle technologies for the delivery of drugs transcutaneously are presented in Table 1.

5. Development of Nanoengineered Dermal Scaffolds for Improved Healing and Reduced Scar Formation

The impact of scarring, both mentally and physically, immensely affects a large number of patients and their families which is often witnessed following burn injuries to large area of the body. Currently, there is a lack of effective scaffold treatments available for treatments of nonhealing wounds, with no approved scaffold treatments that have been shown to reduce scar formation during wound healing [81]. In the case of major burns where injury damages the deep dermis and no sources of cells for regeneration remain, there is a requirement to provide a dermal scaffold to fill in the deep wound [82]. Current commercial products address some of the immediate demands of wound care including protective covering or lost epidermal/dermal material; however, these are far from optimal, often addressing only one aspect of injury. Current scaffolds are made from xenobiotic animal derived materials and have short shelf life, nontrivial application, and high production costs [81, 83]. While there is a wide range of biologic and polymeric materials currently available on the market their efficacy is far from optimal highlighting the need for the development of next generation scaffolds which actively promote healing, and decrease scarring [81].

In the past five years there has been a significant increase in the in vivo use of both synthetic and natural biodegradable polymers and materials. Through the process of electrospinning, nanofibres can be processed to create nanofibrous scaffolds with open and interconnected porosity. Poly-(ε-caprolactone) (PCL)/gelatin nanofibrous scaffolds have been shown to have improved biocompatibility and improved mechanical, physical, and chemical properties, allowing improved wound healing and dermal reconstitution [82]. In addition, nanofibrous scaffolds facilitate the impregnation of allogeneic keratinocytes, xenogenic fibroblasts, and antibacterial agents for improved wound healing and decreased infection rates [14, 84, 85].

The use of nanotechnology now provides a novel platform for the design of functionalized, treatment specific scaffolds which, in addition to providing a matrix for cell proliferation and differentiation, can also carry drug containing nanoparticles. Enzymes, present in the wound environment, can dynamically degrade the nanoparticles allowing the optimal dose of biologically active drug to be released intradermally over a sustained period. This may promote rapid cellular migration under the dressing and onto and into the scaffold, resulting in regenerative wound healing and reduced scar formation (Figure 1(c)). While the use of nanotechnology for drug delivery using dermal scaffold is still being developed, further research in nanomedicine offers hope for improved treatment options in cutaneous medicine.

6. Conclusion

Nanotechnology presents an exciting new opportunity for the development of a safer and more efficient drug strategy for many dermatological conditions. While there are a number of examples of nanoparticle cosmetic products currently on the market, commercially available nanoparticle products for drug delivery through healthy or wounded skin are still under development [21, 22]. With the advent of new nano-based drug delivery systems which can be specifically formulated to target specific cells and fit a desired release profile and penetration depth, the face of medical research is truly evolving. There is, however, much research still to be performed to understand the chronic effects and to continue to improve patient tolerance and drug efficacy in vivo.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Jessica E. Jackson and Zlatko Kopecki contributed equally to this paper.

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