Chapter: 1

Introduction

1 Introduction

Human skin is one of the largest and heaviest organ of our body, it serve as protective barrier to guard bones, muscle and vital organs, and maintain vital functions. Human skin is made up of three different layers, epidermis, dermis and hypodermis [1]. In case of injury, it can open body organ to the foreign pathogens and make us more vulnerable to illness. These injuries can be classified into different types based on skin layer it affect. The abrasion are skin injuries that affect the superficial layer of skin and results from the blunt trauma or friction with rough surfaces. Avulsions are severe wounds that affect the epidermis and dermis and require immediate medical attention. The burn injuries are caused by the different heat source i.e. chemicals, electricity, or radiation. Laceration are skin injury resulted from the tearing skin layer and exposing bones and fatty tissue.

Every injury create a unique skin response i.e. erythema, ulcers, macules, papules, erosion, vesicles/bullae etc. and healing pattern could be complex. Generally wound healing involve sequential process majorly involving four phases, namely, hemostasis, inflammation, proliferation, and remodelling [2]. Hemostasis is the first phase that starts with vascular constriction, platelet aggregation, degranulation, and fibrin clot formation. During this, clot and surrounding wound tissue release pro-inflammatory cytokines and growth factors. Thereafter, the inflammatory cells (neutrophils, macrophages, lymphocytes etc.) migrate at wound site and initiate an inflammatory response [2]. Macrophages in the early-stage release cytokines (which promotes inflammatory response) and clear apoptotic cells. Then, macrophages stimulate keratinocytes, fibroblast and angiogenesis to promote the tissue regeneration [3]. T- Lymphocytes can also migrate at wound site in the late proliferative phase associated with scar formation [4]. After that, epithelial cells proliferate and migrate at wound area to support the collagen formation, growth of capillary and granulation tissue

[2]. At the end, remodelling of extracellular matrix occurs which help break the collagen and make it similar to normal tissue.

The normal wound healing could be affected by different diseases and diabetic mellitus is one them. Diabetes mellitus significantly affect skin regeneration after wound damage [5]. High blood glucose levels impair the function of white blood cells, which are central to the immune system. When white blood cells are unable to function correctly, the body is unable to fight bacteria and close wounds [6]. Diabetes might also affect wound healing by reducing the production of growth and healing hormones. Diabetes can decrease the production and repair of new blood vessels (increase oxidative stress), weaken the skin barrier, and reduce collagen productions [7].

Diabetic wounds are difficult to treat with conventional dressing materials due to long term complications associated with diabetes. The open wound exposed to external surrounding are ideal place for bacterial or yeast colonization, mainly *Candida* and *E.coli* and can lead to impaired healing, trauma, patient discomfort, high treatment cost, and even organ loss or death [8] [9–11]. Fungal infections at wound site mainly by candida species has highest incidence rate [12–16]. About 80% diabetic wounds are reported to get infected with predominant microbial species i.e. *E.coli*, *S.aureus*, *C.albicans, C.tropicalis, C. parapsilosis* [9,15]. About 23-27% of diabetic patient with diabetic wounds observed to get infected by *C. albicans, C. tropicalis* fungal strains [17]. The fungi infection can also form biofilm around wound, further worsening the condition, resulting drug resistance and thus worsen the condition and delay the healing [11,18,19]. Further, lack of optimum microenvironment for proliferation of fibroblasts and stem cells may hinder wound healing.

Generally, conventional dressings and products like topical creams or ointments are proposed for such infections [18]. However, they are found inefficient at harsh environmental conditions of infected diabetic wounds [20]. Recently various formulations like hydrogels, films, sponges, nanofiber and foams have been proposed for application at wounds [21]. However, nanofibrous scaffolds have extra edge over conventional dressing materials due to numerous advantages i.e. interconnected nano-dimensional structure of nanofiber mimic extracellular matrix of tissue and facilitate efficient exchange of water, oxygen and nutrient. Nanofiber also facilitate wound healing by absorbing exudate from wound site, protection of wound site by microbial invasion, and providing simultaneous release of multiple drugs for therapeutic benefits [22].

Nanofibers based dressing materials can be fabricated using various polymers, mainly synthetic, natural or blend of both [23–29]. The composite nanofibers fabricated using blend of synthetic and natural polymers can provide nanofibers with optimum biodegradation, mechanical strength, cell adhesion, wettability and drug release. The natural polymers offer biocompatibility, biodegradability, and bio-adhesiveness, however lack mechanical strength. Therefore, synthetic polymers can be incorporated to provide sufficient mechanical strength to the nanofibrous scaffolds and provide controlled release kinetics. Composite nanofibers consisting of blend of synthetic and natural polymer can provide the dressing material with desired characteristics like strength, hydrophilicity, biodegradability, biocompatibility, non-immunogenicity and controlled drug kinetics.

Poly (Ɛ-caprolactone) (PCL) is a semi crystalline and hydrophobic polymer with significant applications in drug delivery [30]. PCL is biodegradable synthetic polymer with high mechanical strength but suffers from the disadvantage of from poor cell adhesion and low wettability that limits its use in wound dressing and drug delivery [31]. While, Gelatin is a natural polymer obtained from the partial hydrolysis of animal bones. It's hydrophilic, biodegradable, biocompatible, and provides inherent bioadhesive properties as it contains integrin-binding sites responsible for cell adhesion and cell differentiation [32]. However, gelatin is highly hydrophilic and has low mechanical strength. Therefore, gelatin and PCL can be used to give composite nanofiber with optimum biodegradation, mechanical strength, cell adhesion, wettability and drug release. Similarly, Polyvinyl alcohol (PVA) owing to its good biocompatibility and hydrophilic properties, making it highly effective in absorbing exudate and maintaining moist environment [33]. However, the strength of PVA is low due to high aqueous solubility, and thus can be incorporated with chitosan. Chitosan is a natural biopolymer with inherent characteristics like biodegradability, biocompatibility, good water absorption capacity, non-immunogenicity, remarkable mechanical strength, and antibacterial and antifungal activity [34–37]. So, use of PVA/CH composite nanofiber would provide the optimum characteristic to nanofiber scaffold for wound healing.

In addition, both composite nanofibers can be easily loaded with one or two drugs. Luliconazole is an azole drug widely reported for potent activity against wide range of candida species. Currently, numerous marketed gels and creams are present, which provide clinical antifungal benefits in clinical settings. But development of these gels/ creams carry complexity due to limited water solubility leads to poor drug release window and repetitive application over wound for clinical benefits.

For this nanoformulation approaches were tested to prepared NP and NF of luliconazole to improve the drug release window and better antifungal activity. Further, the use of luliconazole alone could limit formulation efficacy in wound healing application. And simultaneous loading of the antioxidant agents with into the nanofiber patch would potentiate the healing

Silver nanoparticles (AgNPs) and naringenin (NAR) are excellent candidates due to their well-known antioxidant and wound healing properties. AgNPs exhibit strong antioxidant activity, which plays a crucial role in reducing oxidative stress within the wound environment. This is particularly important in chronic wounds, where excessive reactive oxygen species (ROS) can impair the healing process. By neutralizing ROS, AgNPs create a more favourable environment for tissue repair. Moreover, their ability to promote cell proliferation and collagen deposition and reduce inflammation enhances the overall wound-healing response [38,39].

Similarly, naringenin, a natural flavonoid, possesses potent antioxidant activity that helps counteract oxidative stress in wounds. It has been shown to enhance fibroblast migration and collagen synthesis, which are critical for tissue regeneration. Naringenin also exhibits anti-inflammatory effects, reducing cytokine levels that contribute to prolonged inflammation in chronic wounds [40,41]. These properties support not only infection control but also active wound healing. So, by integrating AgNPs or NAR into the LZ-loaded nanofiber system, the therapeutic approach could be expanded beyond simple infection control. This combination leverages the antioxidant and wound healing capabilities of AgNPs and NAR, addressing complex issues, more effective healing of chronic wounds such as DFUs [42].