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Advancement in wound healing drug delivery strategies for diabetic foot ulcer

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Abstract
A problem that affects the majority of patients with type 2 diabetes mellitus is diabetic foot ulcers. It is typically brought on by inadequate foot care, peripheral vascular disease, neuropathy, or poor glycemic control. Globally, patients, healthcare providers, and the healthcare system face significant clinical challenges when it comes to the effective management of chronic wounds. This study covers the pathogenesis of diabetic foot ulcers (DFU), important considerations when choosing a dressing, and the polymeric modalities that are currently being used to help DFU patients heal. The article discusses the development of dry powder formulations for diabetic foot ulcers and associated production methods.

Keywords: Diabetic foot ulcer (DFU), Diabetic mellitus (DM), hyperbaric oxygen therapy (HBO), fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF)

Introduction

Diabetic Foot Ulcer

Diabetic foot ulcer are the most common complication in type 2 DM patient which is not well controlled. It is usually the result of poor glycemic control, underlying neuropathy, peripheral vascular disease or poor foot care. It is also one of the common causes for osteomyelitis of the foot and amputation of lower extremities. The ulcer are usually in the area of foot which encounters repetitive trauma and pressure sensation. Staphylococcus is the most common infective organism. Local debridement and appropriate foot wear and foot care are vitally important in the early treatment of foot lesion [1].

Types of Diabetic Foot Ulcer

1. Neuropathic diabetic foot ulcer.
2. Ischemic diabetic foot ulcer.
3. Neuro-ischemic diabetic foot ulcer.

Neuropathic diabetic foot ulcer

Neuropathic diabetic foot ulcer occur when a patient with the poor neurological function of the peripheral nervous system has pressure points that cause ulceration through the epidermal and dermal tissue layer.

Ischemic diabetic foot ulcer

Ischemic diabetic foot ulcer occur where there is peripheral artery disease present without the involvement of diabetic peripheral neuropathic.

Neuro – ischemic diabetic foot ulcer

It occurs in people who have both peripheral neuropathy and ischemia resulting from peripheral artery disease. Neuroischemic ulcers are often seen on the margin of the foot.

Risk Factors

- Increase with age.
- Duration of diabetics.
- Neuropathy.
- Trauma.
- Peripheral vascular disease.

- Abnormal foot pressures.
- Hyperglycaemia [1, 2]

Pathophysiology of Diabetic Foot Ulcer

Normal wound healing is a complex process that involves the simultaneous actuation of soluble mediators, blood cells, extracellular matrix (ECM) and parenchymal cells. This process can be divided into several phases: homeostasis/coagulation, inflammation, proliferation (granulation tissue formation), re-epithelialization.

After tissue injury, a fibrin plug is formed in order to re-establish homeostasis, and aggregated platelets secrete several growth factors and cytokines and monocyte chemoattractant protein 1(MCP-1) that recruit neutrophils and monocytes to the wound site. The angiogenic factors, such as fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) induce angiogenesis by stimulating the production of basic fibroblast and of vascular endothelial growth factors by macrophages and endothelial cells. These promote the wound healing process [3, 4].

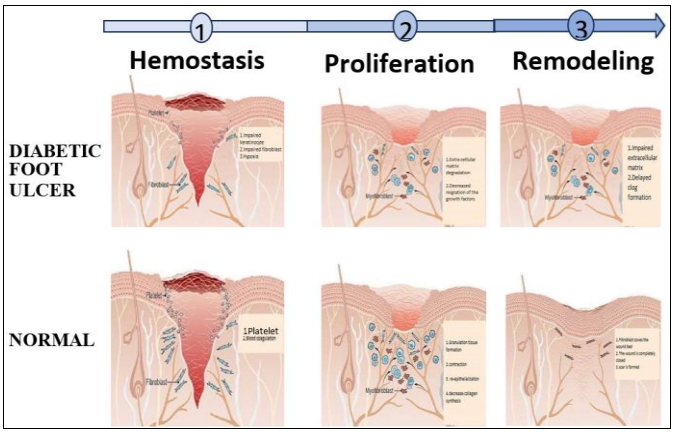

Fig 1: Mechanism of Action

Treatment and Management

The DFU treatment include debridement of the wound, management of the infection, revascularisation procedures when indicator and offloading of the ulcer. Other methods have also being suggested to be beneficial as add on therapies such as hyperbarric oxygen therapy, use of advanced wound care product, and negative pressure wound therapy.

1) Debridement
2) Offloading
3) Dressing

1. Debridement

Debridement should be carried out in all chronic wounds to remove surface debris and necrotic tissues. It improves healing by promoting the production of granulation tissue and can be achieved surgically, enzymatically, biologically and through autolysis.

Surgical debridement are effective in removing hyperkeratosis and dead tissue. Enzymatic debridement is indicated for ischemic ulcer. Recent report suggest that biological debridement method is also effective in the elimination of drug resistant pathogen such as methicillin resistant staphylococcus Aureus from wound surface.

Autolytic debridement involves the use of dressings that create a moist wound environment so that host defence mechanism can clear devitalized tissue using the body's enzymes. Autolysis is enhanced by the use of proper dressings, such as hydrocolloids, hydrogel and film. Autolysis is highly selective, avoiding damage to the surrounding skin.

2. Offloading

Off-loading of the ulcer area is extremely important for the healing of plantar ulcers. In addition, any existing foot deformities may increase the possibility of ulceration, especially in the presence of diabetic peripheral neuropathy and inadequate off-loading.

Therapeutic shoes, custom insoles, and the use of felted foam are alternative methods to off-load wounds located on the forefoot, and can reduce pressure at the site of ulceration by 4–50%.

3. Dressings

Ulcers heal more quickly and are often less complicated by infection when in a moist environment. The ideal dressing should be free from contaminants and able to remove excess exudates and toxic components, maintain a moist environment at the wound-dressing interface, be impermeable to microorganisms, allow gaseous exchange, and, finally, should be easily removed and cost-effective [5].

Other Therapies

1. Hyperbaric oxygen

It is the one of the adjunct therapy which is used from decade to treat complex DFU, in chronic wound affected tissue become hypoxic, hence oxygen plays a big role in chronic wound healing. In HBOT patient is kept in a chamber with 100% breathing oxygen and increase atmospheric pressure greater than sea level for better clinical outcome.

2. Glycemic control

Most foot ulcer have their origin in inadequate control of blood sugar, which results in development of lower limb neuropathy. There is no excellent evidence that improved control of diabetes can markedly reduce the incidence of neuropathy.

3. Tissue engineering

Despite adequate blood flow and good wound care, some neuropathic DFU fail to heal. Impairment of the normal cellular functions involving growth factors and fibroblasts necessary for wound healing has been postulated to account for the failure to close theses wounds.

4. Fibroblast growth factor

It is a family of cell signalling proteins, which can mediate various processes such as angiogenesis, wound healing, metabolic regulation through its specific receptors [5].

Advancement of drug delivery in diabetic foot ulcer treatment

Diabetic wounds are heterogeneous, so the treatment and outcome depend very much on precise strategies. Many therapeutics have been applied in diabetic non-healing wounds, such as hyperbaric oxygen therapy and smart wound dressings. All the treatment that only reduce the complications and cannot be completely cure. Therefore, the discovery of new therapeutic methods for diabetic wound healing is urgently required. Thus its also will be cost effect to the patients.

A drug delivery system that delivers therapeutic molecules in a sustained release manner could be a promising method of

improving diabetic wound healing. These advanced systems can control drug release over a long time period, maintain drug concentration and release drugs in a target site. Nevertheless, conventional drug delivery systems are not always designed optimally for various drugs and inadequate to protect drugs from probable degradation, which causes the waste of a large number of drugs. There are various emerging therapies that are different from the standard care for DFUs, whose main objective is to accelerate ulcer healing. Some examples of these treatments are adjuvant growth factors, inflammatory modulators, plant extracts, blood products, biologic therapy, wound negative pressure, hyperbaric oxygen therapy, and skin substitutes. However, these therapies are companion therapies and do not replace standard care for diabetic foot problems. Some emerging therapies are explored below in more detail: Nanotechnology, control of infection using antibiotics, cell engineering, localised drug delivery, microcarriers.

1) Nanotechnology

Current developments of nanotechnology benefit the design and fabrication of drug delivery systems for diabetic wound healing. Various nanostructures, such as liposomes, nanoparticles, nanofibers and nano hydrogels, these nano drug delivery systems are being studied to provide better drug performances and achieve maximum drug encapsulation efficiency. Various carriers exhibit anti- inflammatory action, ROS scavenging, reduction of local blood sugar levels and senescence cell clearance, their application in diabetic wound treatment are receiving increasing attention [6].

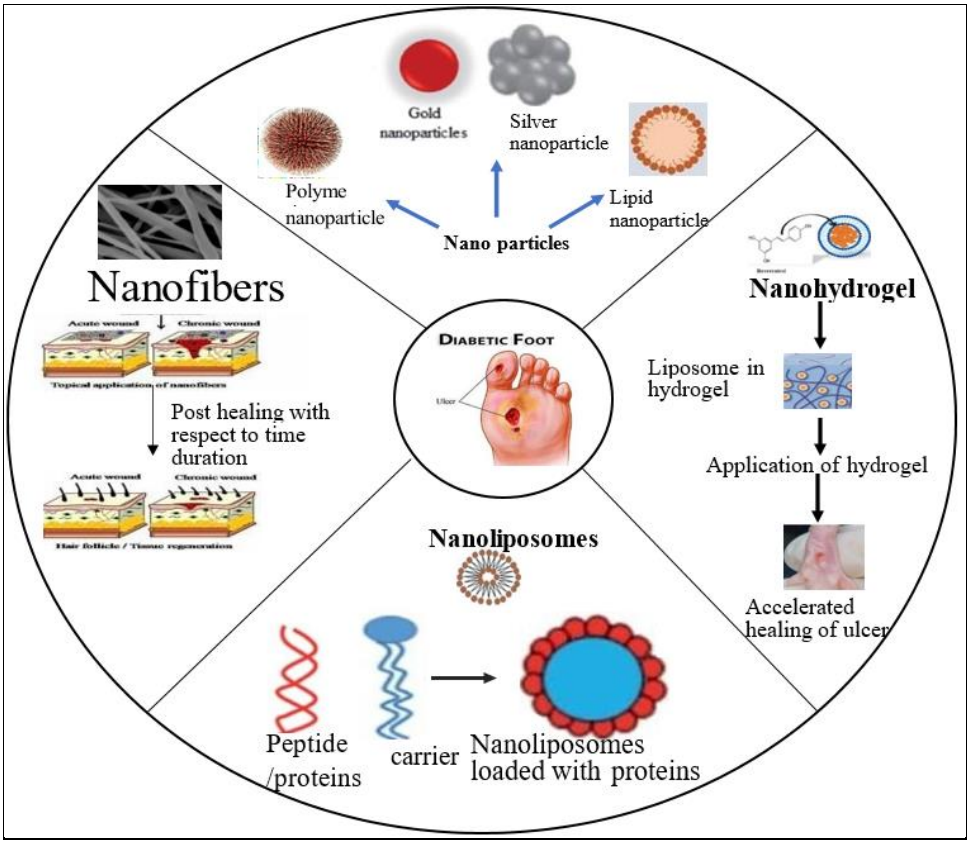

Fig 2: Nanoparticle Delivery of Therapeutic Drugs for Diabetic Wound Healing

2) Anitibiotic Therapies

Systemic antibiotic therapy is indicated when signs of localized, advancing, or systemic infections are present. The route of administration and type of antimicrobial agent to be used are determined by the results of a microbiological culture, the severity of the clinical signs, the body structures involved, and the immunocompetence of the patient. DFIs can present a complication known as skin and skin structure infections. Antimicrobial therapy, along with surgical treatment or debridement, is essential for treating any chronic deep infections in the bone. Topical antimicrobials are not a preferred treatment for chronic wounds due to their lack of contribution to moisture balance maintenance and autolytic debridement, as well as the potential for the development of contact dermatitis. When used, topical antimicrobials are selected based on their low toxicity to the host tissue. To decrease the ulceration antibiotics have a crucial role in maintaining that infection.

3) Cell Engineering

There are different biologics used as therapies for the treatment of DFUs, which comprise several proteins and growth factors. Growth factors, such as the growth factor derived from platelets-BB (PDGF-BB), fibroblast growth factor β (FGFb), epidermal growth factor (EGF), VEGF, and granulocyte colony-stimulating factor (G-CSF), among others, are used to accelerate the healing of wounds. There is currently insufficient data regarding their efficacy, and they are not widely available. Some of these factors are combined with different extracts and molecules to yield a synergy of activity. PDGF-BB is the most widely studied growth factor in wound healing and is currently approved for clinical use in recombinant DNA technology. EGF was also used in several clinical studies in advanced DFUs, and its administration showed promising results in the formation of granulation tissue and the prevention of amputation in patients.

1. Stem Cells
2. Fibroblast Cultures
3. Grafting (Bioengineering)

4) Localized Drug Delivery System

❖ Insulin

The use of topical insulin recently became of greater interest as a healing agent in DFUs. Different presentations of insulin, such as insulin-based sprays, creams, and dressings, showed great success in treating the chronic ulcers of patients with diabetes mellitus, as well as in animal studies.

❖ **Hydrogels**

The composition material of hydrogel dressings includes insoluble copolymers capable of binding water molecules. The water in the matrix can be donated to wounds and, conversely, the matrix is capable of absorbing wound exudates, thereby maintaining an optimal level of moisture in the wound. Some evidence suggests that hydrogel dressings are more effective in healing DFUs than other dressings.

❖ **Alginate Dressings**

Alginate products (calcium alginate, calcium sodium alginate, or alginic acid) are derived from seaweed. These products act similarly to hydrogels by absorbing wound exudates and maintaining a moist wound environment. Previous reviews and meta-analyses showed no significant difference with basic contact dressings or silver hydrocolloid dressings.

❖ **Hydrocolloids**

The composition of this type of dressing involves hydrophilic carboxy components and hydrophobic methylcellulose bound to a polyurethane film. These components promote autolytic debridement; they are also self-adherent and long-wearing.

❖ **Foam Adhesive**

This type of adhesive is composed of absorbent polyurethane with different pore sizes and can serve as a vehicle for silver and ibuprofen onto the wound. However, foam adhesives have the disadvantage of inducing macerations in the surrounding skin.

❖ **Hydrofibers**

Hydrofibers are composed of carboxymethylcellulose sheets. Some advantages are their highly absorptive capacity and ease of removal. However, a secondary dressing is needed.

❖ **Powders**

Dry powder spray exhibited successful exudate management, providing good medium to high level exudate absorption, infection control, inflammation and pain reduction during dressing changes for diabetic patients [7].

Powders

- Pharmaceutical powders are solid dosage forms of medicament which are meant for internal and external use
- It consist of a mixture of finely divided drug and /or chemicals in dry form.
- Powders are available in crystalline or amorphous form.

Advantages of Powders

1) Powders are usually more stable than liquids because chemical reactions take place more rapidly in atmospheric conditions when the drug is in liquid dosage form than powder.
2) Incompatibility is less in case of powders than liquids
3) Faster onset of action, smaller particle size of powders produce more rapid dissolution in the body fluids than other solid dosage forms of medicament.
4) The rapid dissolution increases the blood concentration in a shorter time, there by the action is produced in a lesser time.
5) Powders are more easy to carry than liquids.
6) They are more economical when compared to other dosage forms because for extemporaneous preparation, they do not require any special technique or machinery.
7) Children and old persons who cannot swallow solid dosage forms can easily ingest powders which can be dispersed in water or any other liquid and may be administered through feeding tube to the patients who are fed by tubes.

Classification of Powders

1) Bulk powders for external use.
2) Bulk powders for internal use.
3) Special powders.

1. Bulk Powders for External Use.

- They are usually non potent substances.
- These powders are supplied in cardboard glass or plastic containers, which are designed for the specific method of application.
- Example.

a) Dusting powders
b) Dentifrices
c) Insufflation

2. Bulk Powders for Internal Use

- Powders are dispensed in bulk, when accuracy of dosage form is not important
- They are supplied in wide-mouthed containers that permits easy removal of a spoonful of power [8].

Powders in Wound Healing

Powder formulations can be used for systemic and local applications. Powder formulations can tackle the challenges of liquid formulations including, limited contact with the tissue, physicochemical stability issues, microbial contamination and growth, insolubility of active pharmaceutical ingredients (APIs) in water, and the use of toxic co-solvents and surfactants.

The advantage of powders over other forms such as hydrogels or films is that particulate systems can provide immediate access of body to the components due to their higher surface area. Even for treating deep or irregular-shaped wounds, powders can be easily used and removed by washing.

The powder could be applied and distributed throughout the wound using a small scoop and because the moisture present in the wound environment was enough to start the powder rehydration process, this offered an additional advantage as a means of absorbing the wound exudate [9].

Review of Literature

1. Tassiapoulas A *et al*., (2001) suggest primary foot care in diabetic foot ulcer patients. Foot ulceration is the most common complication in diabetic patient.Early care should be given to them to prevent the complications. Fortunately, better control of blood sugar levels, early recognition of complications of peripheral neuropathy and ischemia, and using a multidisciplinary approach to therapy when an ulcer develops can dramatically reduce this problem [2].
2. Afsaneh Alavi *et al.,* (2012) said that additional treatment

along with given treatment in diabetic foot ulcer patient can increase the benefit to prevent the ulceration [3].

3. Liane I.F. Moura *et al.*, (2005) described the components of assessment and treatment that can help ensure successful and rapid healing of foot ulcers in diabetic patients. These approaches should be used whenever feasible to reduce the high morbidity and risk of serious complications resulting from foot ulcers [4].
4. Rajpurohit Sanjay, Suthar Narayan, Choudhary ManuPriya *et al.*, (2017) explained about the in-process checks by QA gives assurance that the product conforms to its specification and ensure that the quality of product is built up within the product.monitoring processes for a finished product, manufacturing of an Active Pharmaceutical Ingredients is the first step to ensuring quality in pharmaceutical manufacturing [11].
5. Rakesh Singh Asiwal *et al.*, (2016) focused on detailed information of effluent treatment process [10].
6. Muhammad Saleem *et al.*, (2007) involves the physiochemical study for the treatment of pharmaceutical waste water [12].
7. Mehta R.M *et al.*, (2003) this book indicate the basis of pharmaceutical study and detailed information about different dosage forms [8].

Conclusion

Diabetic foot ulcer are the most common complication in type 2 DM patient. It is usually the result of poor glycemic control, underlying neuropathy, peripheral vascular disease or poor foot care. Effective management of chronic wounds presents major clinical burdens to the patients, healthcare providers and the healthcare system around the globe. This review discusses the pathophysiology of DFU, factors that need to be focussed while selecting a suitable dressing, and the polymeric modalities currently available to achieve healing in DFU patients. However in most instances, the treatment of DFUs impose a substantial challenge to the conventional wound dressings and demand the development of novel and advanced wound healing modalities.

Advanced wound dressing products can help alter the wound environment to optimize healing conditions. Powders are most preferable forms. Hence the advantage of powders over other forms such as hydrogels or films is that particulate systems can provide immediate access of body to the components due to their higher surface area. Powders are simple to manufacture. The article explains the GMP details on the powder manufacturing facility. The main processes in the production of powder include milling, sifting, mixing, and filling. Even said, more research must be done to fully understand how the powders work in treating diabetic foot ulcers.

Discussion

There are numerous benefits to using powder medication rather than another formulation when treating diabetic foot ulcers. Firstly, they have a great penetrating power because they are the tiniest solid particles. Powders have many distinguishing qualities that make them useful in DFU. A case study has been demonstrated wherein powders appear to be more advantageous than other formulation in the treatment of DFU.

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