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Review article

# Expanding arsenal against diabetic wounds using nanomedicines and nanomaterials: Success so far and bottlenecks

Ankit Awasthi [a], Sukriti Vishwas [a], Monica Gulati [a,b], Leander Corrie [a], Jaskiran Kaur [a], Rubiya Khursheed [a], Aftab Alam [c], Faris F.Aba Alkhayl [d,e], Farhan Riyazuddin Khan [f], Sivagurunathan Nagarethinam [g], Rajan Kumar [a], Arya K.R. [a], Bimlesh Kumar [a], Dinesh Kumar Chellappan [h], Gaurav Gupta [i,j,k], Kamal Dua [b,l], Sachin Kumar Singh [a,b,*]

[a] School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, 144411, India
[b] Faculty of Health, Australian Research Centre in Complementary and Integrative Medicine, University of Technology Sydney, Ultimo, NSW, 2007, Australia
[c] Department of Pharmacognosy, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al Kharj, 11942, Saudi Arabia
[d] Department of Pharmaceutical Chemistry and Pharmacognosy, College of Dentistry and Pharmacy, Buraydah Colleges, Buraydah, Saudi Arabia
[e] Department of Medical Laboratories, College of Applied Medical Sciences, Qassim University, Buraydah, Saudi Arabia
[f] College of Applied Medical Sciences, AlQuwayiyah, Shaqra University, Riyadh, Saudi Arabia
[g] Faculty of Medical Science and Research, Sai Nath University, Ranchi, Jharkhand, India
[h] Department of Life Sciences, School of Pharmacy, International Medical University, Bukit Jalil, 57000, Kuala Lumpur, Malaysia
[i] School of Pharmacy, Suresh Gyan Vihar University, Mahal Road, Jagatpura, Jaipur, India
[j] Department of Pharmacology, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India
[k] Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun, India
[l] Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Ultimo, NSW, 2007, Australia

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ABSTRACT

Diabetic wound (DW) is disease that occurs as a secondary complication of diabetes. The use of current therapies being employed to treat DW is associated with a number of limitations. However, the advancement in novel drug delivery system (NDDS) and nanomaterials in recent years has provided new options in the field of tissue rejuvenation. This review discusses the pathogenesis of DW, role of GFs and nucleic acids in DW healing, conventional treatments and need for NDDS. Various NDDS and nanomaterials reported for the treatment of DWs include liposomes, niosomes, transfersomes, exosomes, nanoemulsion, nano hydrogel, SLNs, NLCs, metallic NPs, polymeric NPs, dendrimers, wafers, hydrogel nanotubes, scaffolds, nanofibers and nanocomposites. Delving deeper, the clinical trials of NDDS based formulations and patents on treatment strategies of DW are also enlisted. The article has shown the potential of the aforementioned NDDS in treating DW, however, their clinical translation is hindered by certain issues such as their physicomechanical and storage instability, toxicity, poor drug loading and yield, poor site specificity and expensive manufacturing procedures. It is important to work on these bottlenecks to achieve better in vivo performance of formulation. This can be possible by the joint efforts of formulation scientists, biomaterial engineers, clinicians as well as regulatory officials. They have to understand the key areas that require more attention and that should be addressed for their better clinical translation.

## 1. Introduction

Diabetes mellitus (DM) is a multifactorial endocrine disorder characterized by glucose intolerance and hyperglycaemia. Lack of insulin or its inefficient action or both lead to development of DM [1]. Globally, DM is reported to be afflicting more than 422 million individuals [2]. With progress in time, DM leads to various complications such as diabetic nephropathy, diabetic retinopathy and diabetic wounds (DWs) [3]. Global prevalence of these complications is reported as; DWs 42.2% [4], diabetic nephropathy 21.8% [5], diabetic retinopathy 3·4–12·3% while the rest includes other complications related to the cardiovascular system and neurological complications [6]. DW generally manifests as an open sore wound that can occur in any part of the body but it is most common in the foot and is known as a diabetic foot ulcer (DFU). Among

* Corresponding author. School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, 144411, Punjab, India.
*E-mail address:* singhsachin23@gmail.com (S.K. Singh).

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the DWs occurring in various parts of the body, the global prevalence of DFU is 85% while the rest 15% manifest in the form of gangrene. The major attributing factors for DW/DFU are neuropathy, hypoxia, impeded angiogenesis and cellular damage due to release of reactive oxygen species (ROS) [7,8]. These, in turn, lead to vasculopathy, immunopathy and neuropathy that result in delayed wound healing sequences of defensive/inflammatory, proliferative and maturation phase. This delay in the healing process increases the chance of infection, which eventually may lead to amputation. Global percentage of amputation due to DW/DFU is reported to be 7–20% [9,10]. As the prevalence rate of DW/DFU is increasing rapidly, it is important to explore various treatment strategies for the condition. In this review, we critically discuss the pathophysiology of DW. A comprehensive overview of various treatment strategies currently in use against DW and their limitations is also provided. Finally, we highlight the potential of novel drug delivery systems in increasing the therapeutic activity of existing treatment options for combating DWs.

## 2. Pathogenesis of diabetic wound and diabetic foot ulcer

During hyperglycemia, the levels of *miRNA-146a* and *miR-132* decrease while those of *miR-155* increase. Suppression of *miRNA-146a* upregulates the proinflammatory mediators such as interleukin-1 receptor (IL-1R) associated kinase (IRAK1) and tumour necrosis factor (TNF) receptor-associated factor 6 (TRAF6). These extend the inflammatory phase and impede the wound healing process [11]. Reduction in the level of *miR-132* expression also delays the wound healing process by increasing the levels of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), nucleotide-binding oligomerization domain (NOD)-like receptor, toll-like receptors (TLR) and TNF signaling pathway. Increase in the levels of these proteins prolongs the inflammatory phase by releasing various inflammatory mediators from macrophages, monocytes and delays the wound healing process. Furthermore, *miR-132* also targets the heparin-binding EGF-like growth factor (Hb-EGF) and facilitates the transition from the inflammatory phase to the proliferative phase [12]. On the other hand, overexpression of miR-155 leads to an increase in myeloperoxidase (MPO)-positive cells and decrease in angiogenic markers indicative of ECM build-ups such as TGF-β1, collagen 1 and alpha-smooth muscle actin (α-SMA) [13]. It was found that an increase in the levels of *miR-191* and *miR-200b* is positively associated with higher levels of inflammation-associated markers such as C-reactive protein (CRP) which result in reduced tube formation capacity, migration, and zona occludens-1 expression in human dermal endothelial cells and impede wound healing process [14]. Increase in the levels of *miR-26a* also influences the DW healing process by targeting *SMAD-1* gene [Mothers Against Decapentaplegic Homolog1 (Drosophila)] and impairs wound edge angiogenesis and granulation tissue thickness. The other nucleic acids implicated in DW healing are *miR-15b, miR-200 and miR-205–5p*. Increase in levels of these nucleic acids results in the deactivation of vascular endothelial growth factor (VEGF) pathways and impairs the wound healing process [15]. Overall, all these factors lead to the formation of DW.

Hyperglycemia is known to result in idiopathic complications viz. neuropathy, immunopathy, and vasculopathy. Neuropathy affects autonomic nerves, motor nerves, and sensory nerves. In motor neuropathy, weakness and wasting of intrinsic foot muscles take place that finally leads to ulceration. In sensory neuropathy, there is a loss of pain leading to unnoticed trauma, which, in turn, may lead to ulcer formation. In autonomic neuropathy, sweating is decreased resulting in dry and brittle skin. This leads to secondary infections and finally causes ulceration. Vasculopathy is a general term used to describe any disease affecting blood vessels. It is categorized into two types i.e., macroangiopathy and microangiopathy. Macroangiopathy occurs due to the deposition of blood clots and fats in the blood vessels. Obstruction in the blood flow leads to tissue necrosis and finally, ulceration takes place. In case of microangiopathy, more glycoproteins are formed on the surface of the basement membrane due to which vessel walls grow abnormally thicker and weaker leading to disruption of vessels. It causes leakage of blood and proteins and also slows down the flow of blood to different parts of the body. This is another cause of ulcer formation. In immunopathy, polymorpho-nuclear leukocyte migration, phagocytosis, chemotaxis and intracellular killing rate get decreased. Decreased chemotaxis of growth factors (GFs) and cytokines, coupled with an excess of metalloproteinases, impedes normal wound healing by creating a prolonged inflammatory state (Fig. 1a and b) [16,17].

## 3. Treatment strategies against the diabetic wound

Various molecules that have been successfully employed for the treatment of diabetic wounds are described below:

### 3.1. Growth factors (GFs)

On the onset of DW, platelets start moving towards the wound site to control the loss of blood and release matrix metalloproteinases (MMPs) as well as platelet-derived growth factor (PDGF). These help in the chemotaxis of macrophages and neutrophils towards the site of injury. Neutrophils help in the infiltration of the wound and secrete MMP-8, MMP-9, and fibronectin. In the next step, monocytes migrate towards the wound site and bind to the fibronectin. This results in macrophage differentiation, which secretes other GFs such as VEGF, transforming growth factor beta-1 (TGF-β-1), PDGF and fibroblast growth factor-1 (FGF-1). Release of TGF-β-1 stimulates the production of collagen as well as extracellular matrix (ECM) components that include fibronectin and hyaluronic acid. ECM provides tensile strength to the injured skin and aids in migration of keratinocytes towards the wound site. This helps in the healing of the wound [18,19].

Also, the inflammation and hypoxic environment in the DW cause activation of Angiotensin II (Ang II) which, in turn, results in the release of ROS, MMP-9 and MMP-2. All these, in turn, lead to cleavage of laminin-5. The resulting fragment binds to EGF receptors to promote fibroblast migration. The released FGF from macrophages binds to the FGF receptors of endothelial cells and heparan sulfate proteoglycan (HSP), resulting in the migration of keratinocytes. This promotes epithelization at the site of injury. Collagen binds to discoidin domain receptors (DDR) and integrin on fibroblasts, which stimulate the production of MMP-2, ECM remodelling, cell differentiation, and migration of fibroblasts [20,21]. This leads to healing of a wound.

### 3.2. Nucleic acid

A number of nucleic acids have shown remarkable potential in the field of tissue rejuvenation due to their effects on the biological behaviours of cells. They have been reported to exert their action on parameters like -inflammation, proliferation, migration and oxidation resistance [22]. *Tetrahedral framework nucleic acids* (*tfNAs*) which are DNA nanomaterial which synthesized from single-stranded deoxyribose nucleic acid (DNA) molecules are known to possess good stability, water solubility and biocompatibility [23]. These, *tFNAs* help in DW healing by activating Akt/Nrf2/HO-1 signaling pathway, increase nuclear factor erythroid 2-related factor 2 (Nrf2) levels and heme oxygenase-1 (HO-1) levels. Upregulation of these pathways results in angiogenesis, collagen deposition, oxidation resistance, neovascularization, epithelization and collagen alignment which, in turn, accelerates the DW healing [24]. Ganglioside-monosialic acid 3 (GM3) *siRNA* based spherical nucleic acids help in DW healing by GM3 synthase lockdown. It is pertinent to add here that GM3 inhibits cell growth and the function of GF receptors. They also increase the phosphorylation of IGF-1 receptor and epidermal growth factor and allow migration of keratinocytes at the site of injury [25]. TNF-α is a mediator of inflammation and its low blood levels promote normal wound healing. It is responsible for the migration and proliferation of fibroblasts and wound remodelling when present in a

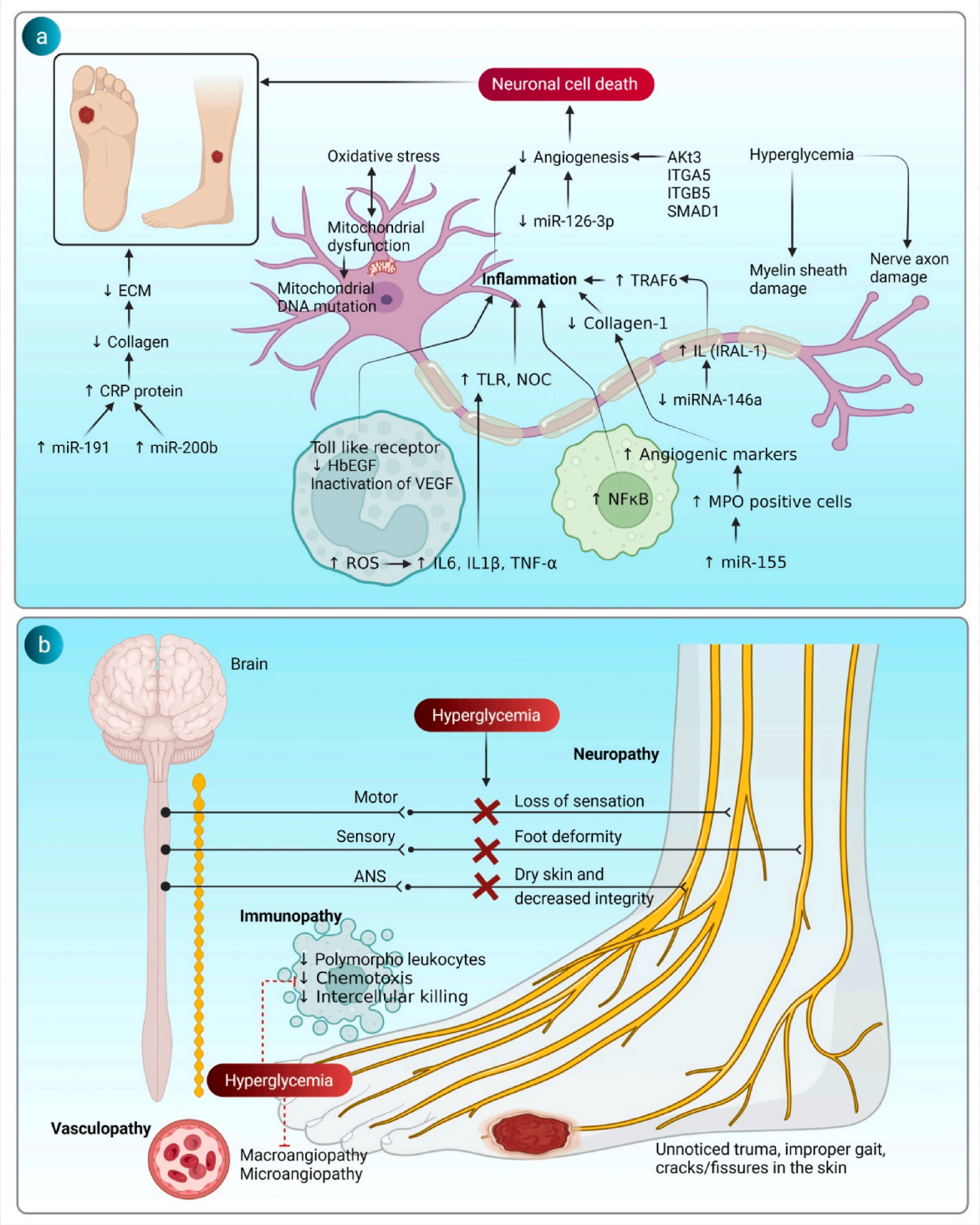


**Fig. 1.** Pathogenesis of a. DW; b. DFU.

small concentration. While the body is afflicted with DW, the levels of TNF-α get increased, which impedes wound healing by increasing cell apoptosis, matrix degradation and oxidative stress. TNF-α *siRNA* targets the TNF-α and lowers its level and promotes DW healing [26,27]. In DWs, levels of ROS are higher than normal, which results in oxidative stress. Due to oxidative stress, modification of Kelch-like ECH-associated protein 1 (Keap 1) takes place at some regions and prevents degradation of Nrf2. As a result of this, Nrf2 enters the nucleus and dissociates from the repressor site of Keap 1. Then Nrf2 binds to the antioxidant response element (ARE) in the promotor region and interrupts genes and enzymes that are responsible for proteasome integrity, oxidation resistance, cellular protection and protein stability. Keap 1 *siRNA* lowers the levels of Keap 1, promotes degradation of NrF2 and decreases the cellular oxidative stress which helps in wound healing [28]. In DWs, there is also an activation of nuclear factor-kappa B, which results in the over-production of pro-inflammatory cytokines such as interleukin IL-6, and IL-8 which impede the wound healing process by prolonging the inflammatory phase [29]. The *miR-146a* acts as a molecular brake in the inflammatory response. It inhibits nuclear factor kappa B by suppressing TNF receptor-associated kinase 6 (TRAF6) and interleukin-I

receptor-associated kinase 1 (IRAK 1) and downregulates over-production of pro-inflammatory cytokines such as IL-6 and IL-8 and thus, promotes DW healing [30].

During normal conditions, the GFs and nucleic acids are available in our body to heal the wounds through the aforementioned mechanisms (Fig. 2.). However, during diabetes, these get decreased to levels that are insufficient to mediate wound healing. This causes a delay in wound healing [20,21]. To increase their levels, various GFs and nucleic acids may be administered externally. Some of the GFs that are widely used to treat DW include PDGF, TGF-β, recombinant human platelet-derived growth factor (rhPDGF) and placenta growth factor (PlGF) [30–34]. Nucleic acids used so far to treat DW are *small interfering ribonucleic acid (siRNA)*, *tFNAs*, *long non-coding RNA (lncRNA)*, *sphingosine phosphate*, and *HoxD3 plasmid DNA* [35–37]. A list of commonly used GFs and nucleic acids in DWs is given in Table 1 [36,37].

### 3.3. Synthetic drugs

Hyperglycemia is the one of the most important factors that contribute towards the susceptibility of DW patients for bacterial infections. Impairment of the T lymphocyte response, neutrophil function and humoral immunity is the starting point of this phenomenon. This results in reduction of inflammatory cytokines and polymorphonuclear leukocytes, which promote invasion of bacteria at the site of injury [38]. The most common bacteria found in DW patients are *Pseudomonas aeruginosa*, *Escherichia coli, Staphylococcus aureus* and *Proteus mirabilis* [39]. To contain the invasion of microorganisms at the DWs site, antibiotics are used [40]. Commonly used antibiotics used for this purpose include vancomycin, ceftazidime, piperacillin/tazobactam, amoxicillin-clavulanate, clindamycin, ampicillin-sulbactam and ciprofloxacin [41]. Diabetic patients with clean ulcers but showing positive ulcer swabs are recommended for an early antibiotic treatment. As DW is susceptible to repeat infection and untreated infection can lead to amputation, this cycle needs be broken only with antibiotics [42]. Antibiotics do not heal the wound but decrease the microbial load on DW by different mechanisms which are discussed in the subsequent sections.

Vancomycin exerts its antibacterial effect by acting on the bacterial cell wall and inhibiting the peptidoglycan polymerization. This inhibition leads to leakage in the bacterial cell wall and causes bacterial cell death [43]. In one of the studies, Davani et al., revealed that vancomycin nanofibers when used against DW microorganisms (Methicillin resistant *Staphylococcus aureus* (MRSA), *S. aureus*, *Escherichia coli* and *P. aeruginosa*. They exhibited antimicrobial action against *S. aureus* and MRSA with zone of inhibition of 2.9 and 2.5 cm and gram-negative bacteria species of *E. coli* and *P. aeruginosa* with zone of inhibition of 1.9 and 2.8 cm, respectively [44]. It is available in the market under the name Vancocin (ViroPharma). It is used in parenteral and oral form to treat DW. Its recommended dose to treat DW is 10–15 mg/kg (up to 1g) in divided doses [45]. Ceftazidime shows its antibacterial activity against penicillin-binding protein-3 (PBP-3), which results in filamentation and cell lysis of *P. aeruginosa* and *E. coli*. It also helps in the inhibition of PBP-1α and PBP 1β that induces cell elongation [46,47]. It is available in the market under the name of Fortaz (GlaxoSmithKline) and administered parenterally to treat DW. Its dose to treat DW is 500

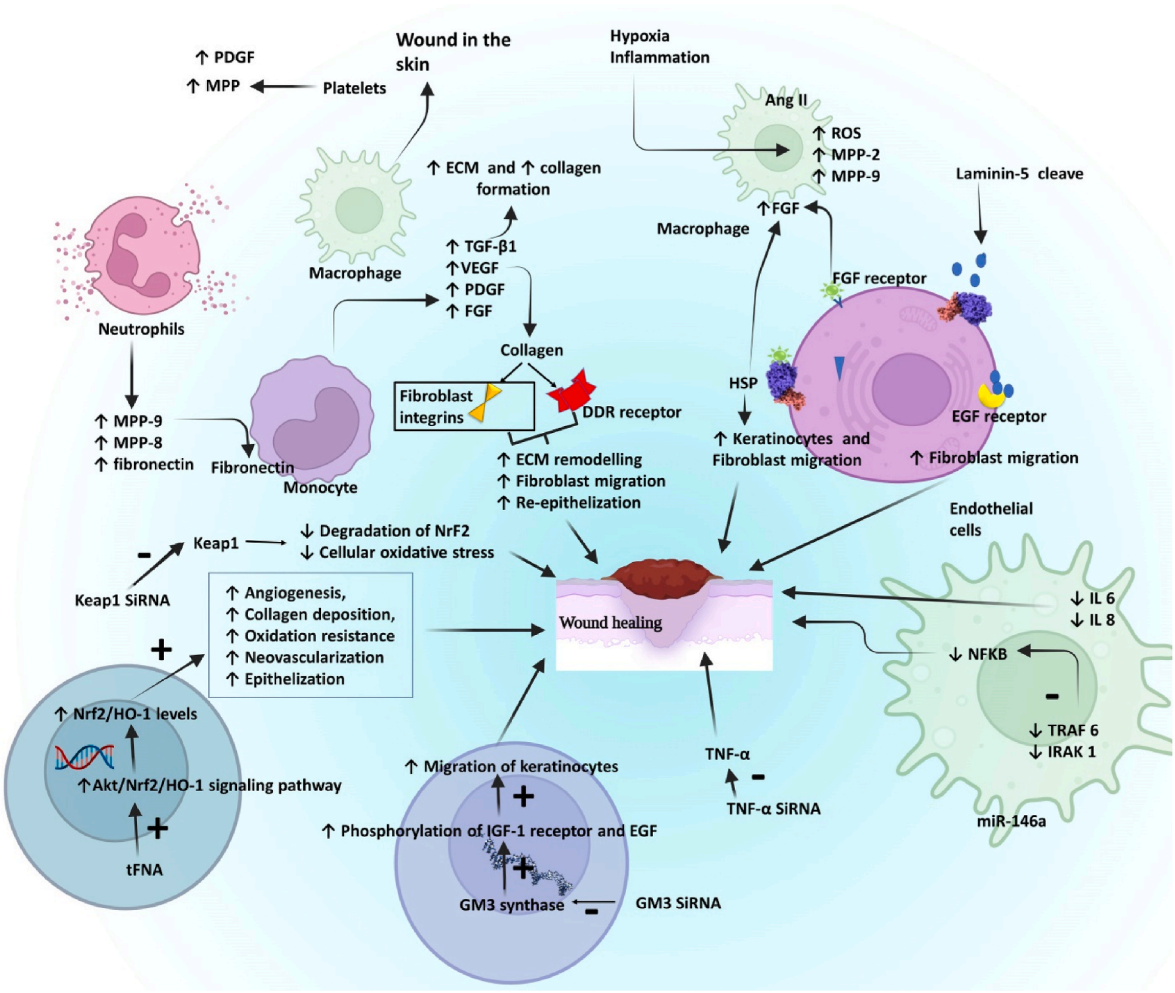


**Fig. 2.** Role of growth factors and nucleic acids in diabetic wound healing.

**Table 1**
Various treatments available for diabetic wounds.

| Sr. No. | Therapeutics | Formulation | Animal model used | Key findings | References |
|---|---|---|---|---|---|
| GFs | | | | | |
| 1. | TGF-β and Insulin-like Growth Factor-I | Gel | STZ induced male SD rats | 50% greater wound tensile strength as compared to collagen vehicle alone | [30] |
| 2. | Human epidermal growth factor | Cream | – | 2.25 folds increase in wound healing as compared to control groups | [31] |
| 3. | Placenta growth factor | – | STZ induced C57Bl/6 male mice | 1.68-folds increase in granulation tissue area as compared to saline-treated groups | [34] |
| 4. | Recombinant human platelet-derived growth factor | Gel | Male Wistar diabetic rats | 1.14-folds increase in re-epithelization as compared to vehicle-treated groups | [33] |
| 5. | PDGF | Gel | STZ induced male Wistar rats | 1.41-folds increase in cell proliferation as compared to a vehicle control group | [32] |
| Nucleic acids | | | | | |
| 1. | *HoxD3 plasmid DNA* | Methylcellulose pellets | Genetically diabetic db/db mice | ↑collagen deposition and angiogenesis | [37] |
| 2. | Sphingosine phosphate | Injection | db/db diabetic mouse | 3.75-folds increase in angiogenesis as compared to control groups | [36] |
| 3. | *lncRNA* | – | ICR male Swiss mice | Activate hypoxia-inducible factor-1a signaling pathway and increased fibroblast migration and collagen deposition at the site of injury | [35] |
| 4. | tFNAs | – | Alloxan induced male Wistar diabetic rats | 2.19-folds increase in epidermal thickness as compared to a diabetic control group | [22] |
| Synthetic drugs | | | | | |
| 1. | Acidified nitrite | Cream | Lepr db diabetic mice | 1.11-folds increase in wound closure as compared to control groups | [83] |
| 2. | Azelnidipine | Solution | Diabetic rats | ↑ collagen fibers, fibroblast density and angiogenesis as compared to control groups | [59] |
| 3. | Simvastatin | Ointment | db/db diabetic mice | 1.28-folds increase in wound contraction as compared to control groups | [84] |
| 4. | Tocopherol | Cream | STZ induced male SD rats | 1.26-folds increase in wound contraction as compared to placebo cream treated groups | [85] |
| 5. | Hydrogen sulfide | Ointment | STZ induced male SD rats | 1.22-folds increase in wound contraction as compared to untreated diabetic control groups | [86] |
| 6. | Propranolol | Cream | Female diabetic mice | 4-folds decrease in wound area as compared to control groups | [87] |
| 7. | Naltrexone | Cream | STZ induced male SD rats | 1.93-folds increase in percentage VEGF + vessels as compared to Regranex treated groups | [88] |
| 8. | Grotto cream + Fucidin cream | Cream | STZ induced male Wistar rats | 1.07-folds increase in epithelization as compared to grotto cream treated groups | [89] |
| **Herbal drugs** | | | | | |
| 1. | Panchavalkala | Cream | – | ↑ antimicrobial and anti-inflammatory action | [90] |
| 2. | Acheflan | Cream | STZ induced SD diabetic rats | ↑ angiogenesis, collagen deposition and hydroxyproline content. Exhibited 1.10-folds increase in hydroxyproline content as compared to control groups | [91] |
| 3. | Aloe vera | Ointment | STZ induced male Wistar rats | 1.14-folds increase in wound closure as compared to marketed formulation | [92] |
| 4. | *Hypericum perforatum* | Gel | STZ induced Female Wistar rats | ↑collagen deposition, antibacterial activity, antioxidant activity and re-epithelization | [93] |
| 5. | *Chrozophora tinctoria* | Leaves extract | STZ induced Albino Wistar rats | 1.34-folds increase in collagen content as compared to control groups | [94] |
| 6. | *Rosa Damascena* Mill | Lotion | Diabetic rats | 1.11-folds increase in wound closure as compared to control groups | [95] |
| 7. | *Euphorbia hirta* linn | Ointment | Alloxan induced female Swiss albino diabetic rats | 1.7-folds increase in wound contraction as compared to control groups | [96] |
| 8. | Curcumin | Cream | Inbred diabetic male C57BL/6 mice | ↑ neoangiogenesis and exhibited about 1.56-folds increase in angiogenesis as compared to placebo-treated groups | [97] |
| Stem cells | | | | | |
| 1. | Bone marrow-derived MSC | Gel | db/db diabetic mice | ↑ cytokines production and stimulation of endogeneous resident cells | [98] |
| 2. | Autologous Keratinocytes and fibroblasts | Cell suspensions | STZ induced female diabetic pigs | 1.6-folds increase in epithelization rate as compared to normal saline-treated groups | [99] |
| 3. | ADMSC | Intra-dermally | STZ induced male SD rats | 1.04-folds increase in collagen fibers | [100] |
| 4. | Embryonic stem cells | Injection | STZ induced male SD rats | 3.3-folds decrease in wound size as compared to control group | [101] |
| 5. | Human Wharton's jelly stem cells | Jelly | SCID mice | 1.18-folds increase in wound closure as compared to control groups | [102] |
| 6. | Allogenous skin fibroblasts | Cell suspensions | Alloxan induced diabetic sheep | 1.16-folds increase in wound contraction as compared to control group | [103] |

**Abbreviations** ADMSC; Adipose derives mesenchymal stem cells, *lncRNA*; *long noncoding RNA* TGF-β; Transforming growth factor-beta, *tFNAs*; Tetrahedral framework nucleic acids.

mg to 1 g by intravenous (i.v) or intramuscular (i.m) route every 8 h [48]. Piperacillin, acts on bacterial cell wall and binds to specific PBPs. It also inhibits the third and last stage of bacterial cell wall synthesis. Cell lysis is then mediated by bacterial cell wall autolytic enzymes such as autolysins [49]. Anneke et al., conducted a clinical trial on use of piperacillin/tazobactam treatment in 25 DW patients with *P. aeurogonisa, E. coli* and *S. aureus* load at the site of injury. The piperacillin/tazobactam treatment showed antibacterial action against these microorganisms with an average zone of inhibition of 18 mm and 22 patients showed no sign of bacterial load at the wound site. It is available in the market under the name of Tazocin® and Zosyn® and is administered both orally as well as i.v. A combination of piperacillin 4g and tazobactam 0.5g is i.v. administered 3 times a day to treat DW [50, 51]. Amoxicillin exerts its antimicrobial effect by acting on bacterial cell

wall and results in bacterial lysis. It is used in superficial and neuroischemic ulcers to combat staphylococcal and streptococcal infections [52]. It is available in the market under the name Augmentin® and is given through oral route. Its dose to treat DW is 500–875 mg every 8–12 h peroral [42]. Clindamycin binds to the 50s ribosomal subunit, which results in inhibition of protein synthesis. It is given in the oral form to treat DW. It is available in the market under the name Cleocin®. Its oral dose to treat DW is 300 mg Q6H [53]. Ampicillin sulbactam binds reversibly to the 30s ribosomal subunit which results in the inhibition of protein synthesis and shows a bacteriostatic effect. It is given either orally i.v. It is available in the market under the name Unasyn®. Its dose to treat DW is 3g every 6 h through iv route [52]. Ciprofloxacin acts on bacterial DNA-gyrase and DNA topoisomerase, and as a result of this, replication of DNA does not take place. It is given orally as well as in i.v. form. It is available in the market under the name Cipro®. Its dose to treat DW is 750 mg BD (oral) [54]. Doxycycline binds reversibly to the 30s ribosomal subunit which results in the inhibition of protein synthesis and shows a bacteriostatic effect. It penetrates the cell wall of bacteria and binds to PBPs and results in bacterial cell death. The bactericidal effects result in inhibition of cellular growth and division as well as loss of cell wall integrity, eventually causing cell wall lysis [52]. It is available in the market under the name WELL-DOX 100. Its dose to treat DW is 100 mg BD (oral) [54]. . However, overuse of antibiotics has negative effects for the patient and may promote the problem of antibiotic resistance. In diabetic foot infections antibiotics are to treat infection, not to heal wounds [55,56].

In recent years, some of the existing drugs have been repurposed for treating DW owing to some of their mechanisms of action that are involved in treating the disease. These drugs include HMG CoA reductase inhibitors e.g. mevastatin, simvastatin [57] and atorvastatin [58], biguanides e.g. metformin and calcium channel blockers (CCBs) e.g. azelnidipine [59]. HMG CoA-reductase inhibitors such as meyastatin, simvastatin and atorvastatin help in inhibition of cholesterol synthesis. This leads to the inhibition of farnesyl pyrophosphate (FPP) and cortisol which, in turn, causes increase in epithelization and migration of keratinocytes at the site of injury. Furthermore, statins also exhibit anti-inflammatory, antioxidant and antibacterial actions and promote wound healing process. The biguanides such as metformin help in wound healing by showing inhibition of mTOR and NOD-like receptor protein 3 (NLRP3) which further activate the AMPK pathway. This leads to increase in the polarization of macrophages towards the phenotype M2 and accelerate wound healing process [60]. In addition, (CCBs) such as, azelnidipine help in wound healing by showing antioxidant action as well as enhancing endothelial NO synthase (eNOS)-catalyzed NO production which improves vascular endothelial function. Furthermore, CCBs also decrease the expression of nicotinamide-adenine-dinucleotide phosphate (NADPH) oxidase responsible for production of superoxide ($O_2^{-1}$) [59]. These drugs are administered in the form of tablets, capsules, gels, ointments and solutions to treat DWs. Advantages of these conventional drugs include a quick onset of action, well-known safety and clinical profiles, cost-effectiveness and clinical applicability. A list of some synthetic drugs that have been explored to treat DW are presented in Table 1.

### 3.4. Herbal drugs

Many herbal drugs possess anti-inflammatory as well as antioxidant potential. These can quench the free radicals and reduce oxidative stress. Inflammation and oxidative stress are the root causes of DWs. These can be explored for their potential in the treatment of the DWs owing to their anti-inflammatory and antioxidant potential [61]. Some of the plants in their crude form or in the form of extracts are already reported for their use in DWs since ancient times. These include *Trigonella foenum-graecum*, *Vitis vinifera*, *Rubus fruticosus*, *Prosopis farcta*, *Cinnamomum zeylanicum*, *Ferula assafoetida*, *Melilotus officinalis, Hypericum perforatum* [62], *Cordia verbenacea* [63], *Aloe vera* [64], *Chrozophora tinctoria* [65], *Rosa damascena* Mill [66] and *Euphorbia hirta* linn [67], *Radix rehmanniae* [68], *Carica papaya* [69], *Punica granatum* [70], *Curcuma longa* [71], *Allium cepa* L. [72], *Phoenix dactylifera* [73], *Vitis vinifera* [74], *Citrus aurantium* L [75], *Martynia annua* [76] and *Annona squamosa* [77]. The isolated phytoconstituents that are extensively used to treat DW include flavonoids such as curcumin [78], quercetin [79], hesperidin [80] and luteolin [76], glycosides such as aloenin [81], naringin [74] and carbohydrates such as beta-glucan [82]. A list of herbal drugs that have been utilized to treat DW is given in Table 1.

## 4. Need for novel drug delivery systems and their mechanism of drug release

Various treatment strategies mentioned in the previous sections of the manuscript to treat DWs exhibit certain limitations related to their delivery. For example, GFs get degraded by the enzyme protease present at the wound site upon topical application at the wound. Large molecular size, short half-life and toxicity at higher systemic doses showed that the conventional treatment of GFs in their free form is not suitable to deliver them successfully at the wound site. Similarly, nucleic acids such as *siRNA*, upon topical application at the wound get degraded by the enzyme nuclease present at the wound site. Also, as *siRNA*s are negatively charged, they do not penetrate the negatively charged cells due to electrostatic constraints. Herbal drugs given through the conventional route also possess some inherent challenges similar to those discussed in above sections for synthetic drugs such as poor stability, solubility, permeability as well as target specificity. To overcome these limitations, various research endeavours have been made for encapsulating/complexing these both natural as well as synthetic drugs used for wound healing, using novel drug delivery system to deliver them through topical route. Advantages of using NDDS include closer interactions with the biological target, increased penetration at the wound site and sustained delivery of encapsulated drugs [104,105]. Some of the NDDS extensively explored to treat DW include polymeric nanoparticles, inorganic nanoparticles [106], nanohydrogels [107], liposomes [108], nanoemulsions [109], lyophilized wafers [110], solid lipid nanocarriers (SLNs) [111] and nanostructured lipid carriers (NLCs) [112]. Another significant advantage of non-invasive topical delivery of these NDDS is the increase in patient compliance due to convenience. They can enhance the permeability of drug across the skin via transcellular, paracellular and endocytosis, provide target specificity and release the drug at the wound site. In transcellular route drug directly passage from the lipid layers whereas, in paracellular route drug reaches at the target site by passing through the tight junctions present in the skin. In endocytosis drug reaches the wound site by entering through the pores present on skin. However, these nanocarriers show short retention time at wound site, leading to limited success of the aforementioned nanocarriers in treating DW [107–112].

To achieve sustained release and better localization at the site, these NDDS have generally been prepared by incorporation into nanomaterials such as nanofibers [113], scaffolds [114] and nanocomposites [115]. These nanomaterials are versatile in nature, possess controlled size and tunable physicochemical properties. They also offer a larger surface area to volume ratio to allow cell adhesion of the drug for the desired time period [116]. The various nanocarriers and nanomaterials used to treat DW and their mechanism of drug release at the wound site are shown in Fig. 3.

Despite having many advantages of NDDS and nanomaterials they are associated with some limitations which are given in Table 2.

### 4.1. Vesicular drug delivery systems (VDDS)

VDDS are defined as highly ordered assemblies comprising of concentric lipid bilayers with encapsulation of active moieties in their lipid or aqueous layer (95). They are generally formed by self-assembling of the amphiphilic building blocks on coming in contact

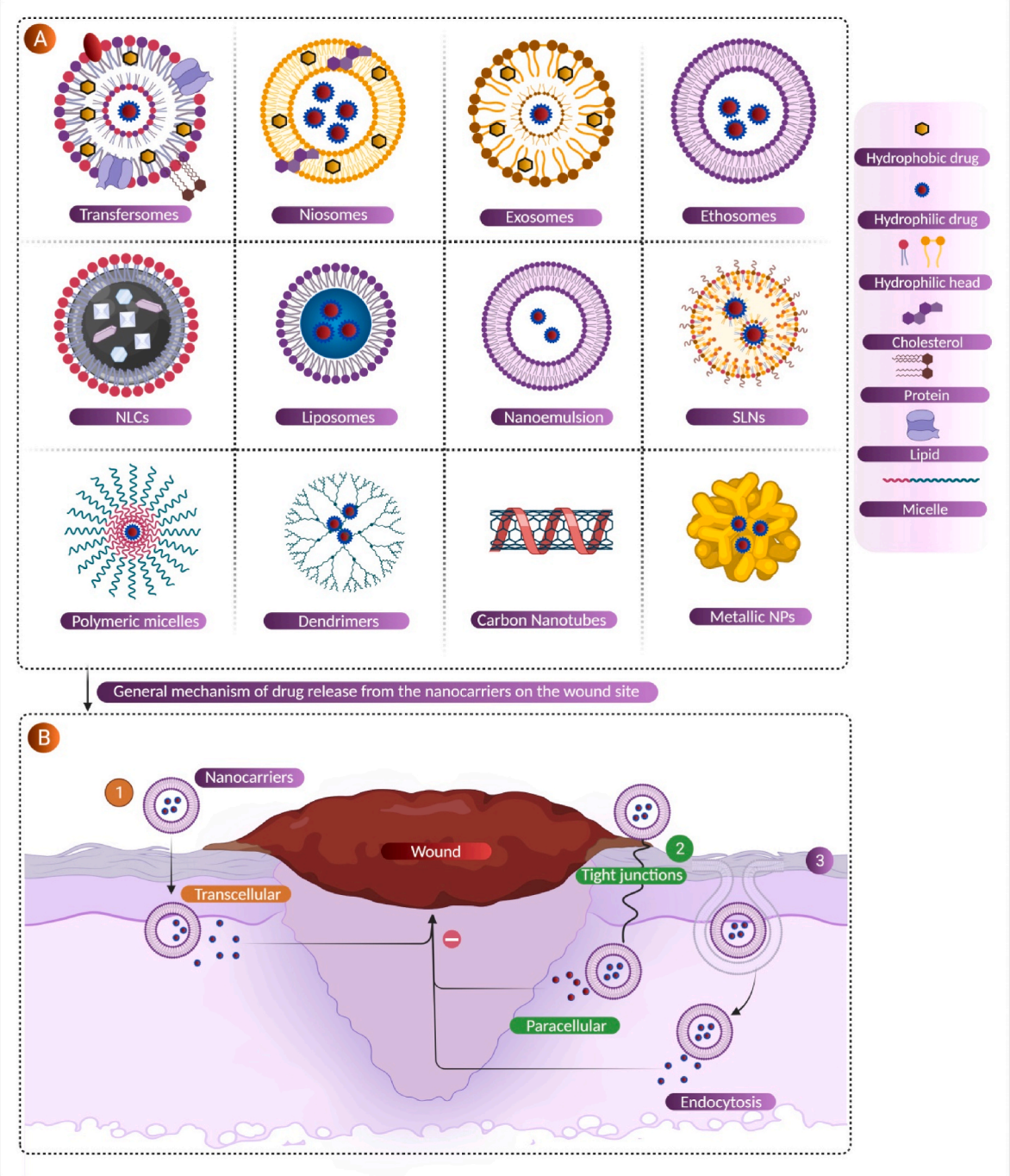


**Fig. 3.** Figure depicting (A) Various nanocarriers used for treating DW and (B) Mechanism of drug release from nanocarriers.

with an aqueous medium [117]. The VDDS reported so far to treat DW include liposomes, exosomes, niosomes and transfersomes. These are discussed below:

Liposomes are spherical vesicles composed of one or more partially substituted phospholipid bilayers along with cholesterol (CHL). They consist of hydrophilic aqueous core and hydrophobic phospholipid bilayer due to which they can encapsulate both hydrophilic and lipophilic drugs. This composition of liposomes facilitates their use in encapsulating a range of drug payloads, due to which their application in drug delivery systems is increasing rapidly. In addition to this, liposomes have gained importance as potential drug delivery systems owing to their stable lipid bilayer membrane, minimized enzymatic degradation, biocompatibility and cell-specific targeting [118,119]. These have been also explored as carriers to treat DW by surface functionalization of therapeutic moieties such as collagen mimetic peptide (CMP) (97) and RGPK (peptide) (100). In one of the research works Olekson et al., have investigated the effect of stromal-derived factor-1 (SDF-1) liposomes against DW in streptozocin (STZ) induced BKS.Cg-Dock7m1/1Lepr (db)/J genetically modified diabetic mice. In this study, the percentage wound closure of SDF-1 liposomes was evaluated and results were compared with free SDF-1. The results revealed that the SDF-1 liposomes treated group showed 15% more wound contraction within 21 days as compared to free SDF-1. SDF-1 liposome treated group demonstrated an increase in diameter of $CD31^{+}$ luminal structure as well as resident cell proliferation [120]. Similarly, Choi et al. investigated the effect of cationic elastic liposomes (CELs)-low molecular weight protamine

**Table 2**
Advantages and disadvantages of NDDS and nanomaterials.

| Delivery system | Advantages | Limitations | References |
|---|---|---|---|
| Liposomes | • Increased the therapeutic index and efficacy of the drug entrapped<br>• Increased the drug stability by entrapping in its core<br>• Non-toxic, biodegradable and flexible to tailor<br>• Helpful in reducing toxicity of therapeutics<br>• Target specific drug delivery | • It consists of phospholipids which undergo hydrolysis and oxidation<br>• The cost of production is high<br>• The issue of fusion and leakage of encapsulated drug/molecule | [108] |
| Nanoemulsion | • Nanoemulsion is a best alternate for vesicles and liposomes<br>• It is helpful in improving bioavailability of drugs<br>• Non-irritant and non- toxic<br>• It improves physical stability of drugs<br>• It increases solubility of lipophilic drugs<br>• It is used in formulating many formulations like foams, spray and creams<br>• Its small droplet size provide more surface area for drug absorption | • Require high amount of surfactants and co-surfactants<br>• Associated with surfactant induced toxicity risk<br>• Stability related concerns pertaining to change in temperature and pH of the system | [109] |
| Nanohydrogels | • Targeted drug delivery<br>• Controlled release of bioactive substances<br>• High drug encapsulation capacity<br>• Less toxicity<br>• Size tunable property<br>• Ease of preparation | • High cost<br>• Difficult to handle<br>• Low mechanical strength | [107] |
| Solid lipid nanocarriers (SLNs) | • Provide targeted and controlled release property<br>• Capacity of carrying both hydrophilic and lipophilic drugs in its core<br>• Bio-compatible and bio-degredable in nature<br>• . Cost effective or economic | • .Poor drug loading capacity<br>• The dispersions consist of high water content (70–90%)<br>• Due to polymeric transitions, explusion of drug takes place during storage | [111] |
| Nano lipid carriers (NLCs) | • The ability to enhance storage stability<br>• Increases the solubility of drugs in their lipid matrix<br>• . Improved permeability and bioavailability<br>• Impart higher adhesive property by reducing water loss from skin<br>• Tissue targeted delivery | • Chances of skin irritation specially when fatty acids used in formulating NLCs | [112] |
| Scaffolds | • Good biocompatibility and biodegradability<br>• Good bioresorption<br>• Overcome the limitation of hydrophobicity of several therapeutics<br>• Helps in tissue regeneration<br>• Non- toxic in nature | • Difficult to process while preparing<br>• Highly brittle<br>• Hard to maintain stability for a longer period of time | [114] |

Various NDDS explored for treatment of DWs are described below.

(LMWP)-GFs-hyaluronic acid (HA) against DW in STZ induced female C57/BL6 diabetic mice in which they found that on 11th day, CELs-LMPW-GFs-HA treated groups exhibited 2.84-folds and 2.4-folds decrease in wound area in comparison to diabetic control and HA treated groups. In addition, CELs-GFs-HA treated groups exhibited about 1.2-folds increase in re-epithelization thickness as compared to vehicle (CELs) treated groups indicating the DW healing potential of formulation [108]. In another study, Rabbani et al., studied the effect of Keap1 *siRNA* liposomes against DW in male Lepr db/db diabetic mice where they observed significant enhancement in wound healing potential (1.47-folds) as compared to siNS treated group [121]. In another study, Chhibber et al. reported the effect of bacteriophage entrapped liposomes (LCP) against DW in an alloxan-induced BALB/c diabetic mice model where they found six days faster wound healing rate in comparison to free cocktail phage (FCP) treated groups due to enhanced collagen deposition and re-epithelization at the site of injury indicating the wound healing potential of the formulation [122]. In one of the study, effect of collagen mimetic peptide (CMP)-vancomycin (Van) loaded liposomes-based co-gel was reported against methicillin-resistant *S. aureus* (MRSA) wounds in BALB/c mice model in which they found 7-folds faster antibacterial activity as compared to CMP-Van-Lipo treatments alone [123]. Similarly, in a study on the effect of cinnamon extract liposomes against DW in alloxan-induced monohydrate induced albino rats, the topical administration of cinnamon extract liposomes exhibited about 1.10-folds and 1.11-folds decrease in wound diameter as compared to chitosan and imipenem treated groups respectively [124]. In another study, Bhattacharyya et al., studied the effect of co-administration of RGDK (small peptide)-lipopeptide-1 and recombinant human platelet-derived growth factor-B (rhPDGF-B) lipoplex against DW in STZ induced SD diabetic rats. The results revealed that RGDK lipopeptide-1 and rhPDGF lipoplex co-administration accelerated DW healing within 10 days by 1.8-folds and 2.3-folds as compared to RGDK lipopeptide-1 alone and RGDK lipopeptide-2 co-administered with rhPDGF lipoplex, respectively The accelerated wound healing was attributed to enhanced keratinization, epithelization, angiogenesis and fibrocollagenation activity of RGDK lipopeptide-1 co-administered with rhPDGF lipoplex at the site of injury [125].

To overcome the problem of poor elasticity associated with liposomes which leads to their poor permeation, a newer class of VDDS i.e., “transferosomes” has been introduced with slight modifications in their chemical composition. Transfersomes are defined as highly deformable and elastic vesicular structures comprising of phospholipids, surface and edge activators, alcohol and buffering agents [126]. Edge activators are bilayer softening component in which amphiphilic drug is incorporated in order to increase lipid bilayer flexibility and permeability. These include Span 65, Tween 80, Tween 60 and sodium deoxycholate. They are known to alter the interfacial tension within the system. Penetration ability of transfersomes makes them an ideal carrier for target specificity at the local region of the DW. However, the major drawback of this VDDS is their low stability due to predisposition towards oxidative degredation and their high cost [127]. The study on transfersomes based delivery system for DW is very limited. Only one study is available on transfersomes for the treatment of DW which is discussed below.

Gizawy et al., studied the effect of deferoxamine (DFO) transfersomes based gel against DW in STZ induced adult male Wistar

diabetic rats where they found 1.36- folds and 3.09-folds increase in VEGF levels as compared to DFO solution and plain Na-CMC gel respectively. Furthermore, DFO transfersomes based gel showed 1.42-folds and 2.08-folds decrease in TGF-β levels as compared to that of DFO solution and plain Na-CMC gel respectively. The collagen study revealed that DFO transfersomes based gel showed 1.5-folds and 1.9-folds increase in collagen deposition as compared to that of DFO solution and plain Na-CMC gel respectively [128].

Niosomes are modified form of liposomes consisting of non-ionic surfactants such as polyoxyethylene fatty acid esters and CHL. Niosomes may be unilamellar or multilamellar depending upon the preparation technique. Presence of non-ionic surfactant in niosomes helps in the alteration of the structural arrangements of stratum corneum (SC) leading to enhanced permeation across the membrane. The better chemical stability and deeper permeability of these nanocarriers have led to their use in the treatment of DW which is discussed below.

El-Ridy et al., studied the effect of metformin loaded niosomes against DW in STZ induced adult male Wistar rat diabetic model. Topical application of metformin niosomes accelerated DW healing within 2 weeks by stimulating serum TGF-β-1, collagen deposition and antidiabetic action at the site of injury as compared to that on treatment with oral metformin. In addition to above observation, reduction in blood glucose level of rats treated with metformin niosomes and oral metformin were also observed [129].

Exosomes are endosomal derived nanovesicles that help in the intercellular transportation of materials. Therapeutics such as proteins, nucleic acids and drugs can be incorporated into these nanovesicles and can be targeted to the specific site [130]. Exosomes are associated with various advantages such as amenability to gene and drug delivery, convenient storage and stability in the body. Furthermore, exosomes help in the proliferation, migration and angiogenesis process in the wound environment [131]. Looking at these benefits, a number of drugs in the form of exosomes have been used for the treatment of DW are discussed below.

In one of the study, Yu et al., explored the effect of atorvastatin (ATV) pretreated MSC exosomes against DW in STZ induced male SD rats in which they found 1.31-folds and 1.66-folds increase in blood vessels area as compared to control and exosomes alone treated group respectively. In addition, ATV pretreated MSC exosomes exhibited about 1.06-folds and 1.12-folds increase in percentage wound closure within 14 days as compared to control and exosome alone treated group respectively [132]. In another study, co-administration of *Curcuma zedoaria* polysaccharide (ZWP) and platelet-rich plasma exosomes (PRP-Exos) assembled chitosan/silk hydrogel sponge (ZWP-PRP-Exos sponge) was studied on DW in STZ induced female SD diabetic rats in which they found that on 15th day, ZWP/PRP-Exos sponge treated groups demonstrated 1.02-folds, 1.34-folds and 2.05-folds increase in wound closure rate as compared to diabetic control, diabetic group/100 μg PRP-Exos and diabetic/ZWP treated groups respectively [133]. Similarly, Qijun et al., explored the effect of *miR-21-5p* exosomes against DW healing in STZ induced male SD rats for a period of 15 days. *miR-21-5p* exosomes accelerated DW healing by showing a 1.9-folds increase in re-epithelization as compared to diabetic control groups [134]. In another study, effect of long noncoding RNA (*lncRNA*)-H19 exosomes were tested against DW in STZ induced male C57BL/6J mice revealed that the *lncRNA H19* exosomes accelerated DW healing within 13 days by showing decreased apoptosis and inflammation of fibroblasts by inhibiting phosphatase and tensin homolog (PTEN) protein. Additionally, *lncRNA* H19 exosomes exhibited about 1.33-folds increase in wound closure as compared to negative control groups [135]. In one of the study, effect of *miRNA-221-3p* exosomes were evaluated against DW in STZ induced male C57BL/6 mice in which they 1.6-fold increase in wound contraction as compared to diabetic control groups indicating wound healing potential of the formulation [136].

The VDDS used so far to treat DW healing are summarized in Table 3.

### 4.2. Nanoemulsion

Nanoemulsion (NE) is a thermodynamically stable isotropic mixture of oil, emulsifier, and water. The oil phase used in NE is generally made up of free fatty acids, monoacylglycerol, diacylglycerol, and triacylglycerol [151], while the aqueous phase consists of co-solvents and polar solvents [152]. The most commonly used stabilizers are emulsifiers (surfactants) which help in reducing the interfacial tension between the two immiscible liquids (oil and water) and provide stability to NE [153]. The surfactants used in NE may be non-ionic and ionic. Non-ionic surfactants oppose the aggregation of droplets by showing hydration, steric hindrances, and thermal fluctuation interactions. In contrast, ionic surfactants prevent agglomeration by electrostatic repulsion [154]. Some of the recent studies in which NE are used to treat DW healing are discussed in subsequent sections.

In one of the study, Kaur et al., reported the effect of sea buckthorn (*Hippophae rhamnoides* L.) seed oil NE gel against DW in STZ induced male Wistar diabetic rat model in which they found 1.49-folds increase in hydroxyproline content as compared to sea buckthorn oil indicated the wound healing potential of the formulation [155]. In another study, effect of astaxanthin and alpha-tocopherol conjugated κ-carrageenan NE (AS-TP@KCNE) was studied against DW in STZ induced adult ICR (Institute of cancer research) female mice diabetic model, it was found that on the 15th day the percentage of wound contraction of prepared formulation was found to be 1.3-folds higher than that of diabetic control group respectively [156]. Similarly, Jee et al., studied the effect of LMWP-GFs/quercetin/oxygen-perfluorooctyl bromide- NE-GEL (LMWP-GFs/QCN/OXY-PFOB-NE-GEL) against DW in STZ induced female C57BL/6 diabetic mice model in which they found 1.42-folds, 1.13-folds and 1.08-folds increase in wound contraction as compared to QCN-NE-GEL, LMWP-GFs-GEL and OXY-PFOB-NE-GEL respectively [157]. In one of study, the effect of topical application of boronophenylalanine (BFA)-Zn-containing NE was studied against DW in STZ induced male SD diabetic rat model where they observed significant enhancement in DW healing potential by 2-folds, 1.3-folds and 1.1-folds as compared to placebo NE, Zn NE and diabetic control groups respectively [158]. Similarly, Chua et al., studied the effect of palm glyceryl monocaprylate (GMCY) NE against *S. aureus* infected wounds in a male adult SD rat model. Topical application of GMCY NE exhibited DW healing within 14 days by promoting antibacterial action against *E. coli* and *S. aureus*. On the 14th day, the percentage of wound closure was found to be 80% and 75% for GMCY NE and placebo NE respectively [159]. In another study, the effect of sesame oil NE (SONE) containing levofloxacin (SONEL) was reported against DW in STZ induced male albino Wistar rat diabetic model where they exhibited 2-folds, 2.3-folds, 1.97-folds, 1.06-folds and 2.57-folds increase in blood vessels and 2.33-folds, 4.44-folds, 2-folds and 5.1-folds decrease in inflammatory cells as compared to SONE, SSD, D-NC and non-diabetic control group (ND-NC) respectively [160].

### 4.3. Nanohydrogels

Nanohydrogels are combinations of nanoparticulate system and hydrogels. They can be prepared by using polymers and crosslinking agents. Common polymers used in the preparation of nanohydrogels are N-vinyl-2-pyrrolidone (NVP), methoxy ethoxy ethyl acid (AA), ethylene glycol (EG), polyethylene glycol methacrylate (PEGMA), polyethylene glycol dimethacrylate, N-(2-hydroxypropyl) methacrylamide (HPMA), ethylene glycol dimethacrylate (EGDMA), hydroxy ethoxy ethyl-methacrylate (HEEMA), hydroxyethyl methacrylate (HEMA), hydroxydiethoxyethylmethacrylate (HDEEMA) [161,162]. Commonly used crosslinking agents in the preparation of nanohydrogels include $N_0$-Methylene-bis-acrylamide (N, $N_0$-MBAAm) (BIS), epichlorohydrin (ECH) and divinyl sulfone (DVS) etc [163,164]. Some of the recent studies in which nanohydrogels are used to treat DW healing are discussed in subsequent sections.

**Table 3**
List of various vesicular drug delivery systems used so for to treat diabetic wounds.

| Sr. No. | VDDS | Therapeutic moiety | Method of Preparation | Animal model | Research highlights | Reference |
|---|---|---|---|---|---|---|
| 1. | Liposome | Haaemoglobin | Ultracentrifugation followed by precipitation | dB/dB mice | • ↑ 4.7-folds wound contraction at $7^{h}$ day<br>• ↓ cell apoptosis and inflammatory cascade and matrix metalloproteinase-9 (MMP-9)<br>• ↑ granulation formation | [137] |
| 2. | Liposome | α-gal | Thin lipid film hydration | Diabetic mice | • ↑ 3.03-folds wound contraction within 12 days<br>• ↑ vascularization, epithelization and granulation tissue deposition | [138] |
| 3. | Exosome | Human umbilical cord blood-derived EPCs | Ultracentrifugation | SD rats | • ↑ 1.6-folds wound contraction within 14 days<br>• ↑ collagen deposition, re-epithelialization and less scar formation | [139] |
| 4. | Exosome | Menstrual blood-derived MSCs | Ultracentrifugation | Male C57BL/6 mice | • ↑ 1.82-folds wound contraction within 12 days<br>• ↑ migration of epithelial cells | [140] |
| 5. | Exosome | Macrophage-derived Exosomes | Ultracentrifugation | SD rats | • ↑ 1.17-folds wound contraction within 14 days<br>↑ reepithelization, collagen deposition and angiogenesis | [141] |
| 6. | Exosome | Oxidative hyaluronic acid | Differential centrifugation | Diabetic mice | • ↑ 1.37-folds wound contraction within 14 days<br>• • ↑ reepithelization, collagen deposition, antimicrobial action and Angiogenesis | [142] |
| 7. | Exosome | Polyurethane + Calcium peroxide | Ultrafiltration | Diabetic rats | • ↑ 1.06-folds wound contraction within 14 days<br>• ↑ collagen deposition and angiogenesis | [143] |
| 8. | Exosome | Engineered Human adipose stem-cell | Ultracentrifugation | SD rats | • ↑ 1.39-folds wound contraction within 15 days<br>• ↑ re-epithelialization, angiogenesis and collagen remodelling action | [134] |
| 9. | Exosome | Human Nrf2-active multipotent stromal cells | Differential ultracentrifugation | Adult $Lepr^{db/db}$ | • DW healing within 14 days<br>• ↓ epithelial gap<br>• ↑ granulation and density of $CD31^{+}$ vessels | [144] |
| 10. | Exosome | mmu_circ_0000250-modified adipose-derived stem cells | Centrifugation followed by Ultrafiltration | Male C57BL mice | • DW healing within 14 days<br>• ↑ microvascular development<br>• ↓ skin tissue apoptosis | [145] |
| 11. | Exosome | hAECs | Ultracentrifugation | Male db/db mice | • ↑ 2.43-folds wound contraction within 14 days<br>• ↑ collagen deposition<br>• ↑ in capillary density | [146] |
| 12. | Exosome | Dia-Exos *AntagomiR-15a-3p* | Ultracentrifugation | C57BL/6J mice | • *Anti-miR-15a-3p* activity<br>• ↑ blood perfusion, collagen synthesis, angiogenesis and fibroblast proliferation | [147] |
| 13. | Exosome (MSCs-Exo oe-H19) | MSCs | Ultracentrifugation | Male C57BL/6J mice | • ↑ 1.3-folds wound contraction within 13 days<br>• ↑ collagen I, VEGF, transforming growth factor-beta (TGF β-1)<br>• ↓ cell apoptosis | [148] |
| 14. | Exosome | Melatonin | Ultracentrifugation | SD rats | • ↑ 1.08-folds wound contraction within 14 days<br>• ↑ anti-inflammatory action, angiogenesis and collagen deposition | [149] |
| 15. | Exosome | PUAO-CPO | Ultrafiltration | Diabetic rats | • ↑ 1.06-folds wound contraction within 14 days<br>• ↑ collagen deposition and angiogenesis | [150] |
| 16. | Exosome | HUC MSCs exosomes encapsulated polyvinyl alcohol/silver nano hydrogel | Ultracentrifugation | SD rats | • ↑ 1.6-folds migration area within 18 days<br>• ↑ formation of epithelium, collagen bundle fibers and hair follicles | [107] |

**Abbreviations:** EPC; endothelial progenitor cells, hAECs; Human amniotic epithelial cells, HUC; Human umbilical cord, MSCs; Mesenchymal stem cells, PUAO-CPO; Polyurethane-Calcium peroxide.

A study was carried out to investigated effect of fibroblast growth factor-2 (FGF-2)/chitosan hydrogel against DW in impaired db/db diabetic mice. On the 10th day, FGF-2/chitosan hydrogel exhibited 1.4-folds wound closure as compared to chitosan treated groups due to neovascularization and angiogenesis at the site of injury [165]. In another study, effect of transforming growth factor- β1 (TGF-β1) hydrogel was checked against DW in female $Lepr^{db}$ diabetic mice. The results showed that TGF- β1 hydrogel was found to exhibit about 1.28-folds increase in proliferating cells at the site of injury as compared to placebo hydrogel treated groups [166]. In one of the studies, potential of recombinant human epidermal growth factor (rhEGF) hydrogel against DW in male SD diabetic rats. Not much advantage could be achieved in this case when compared with rhEGF solution treated as the increase in wound contraction was found to be only by a factor of 1.05-folds after 14 days [167]. In another study, *Sida cordifolia* Linn. (SDL) in the form of its hydrogel was evaluated against STZ induced male albino diabetic rats. SDL hydrogel was found to show 1.35-folds and 4.4-folds increase in wound closure and hydroxyproline content in

a period of 12 days when compared to the diabetic control group respectively [168]. In another study, a hydrogel of sodium carboxymethyl chitosan-recombinant human epidermal growth factor conjugate (NaCMCh-rhEGF) was found to accelerate the DW healing by a 1.58-folds increase in wound contraction and 1.05-folds increase in epithelization as compared to its placebo hydrogel counterpart [169]. Similarly, Thangavel et al., investigated the effect of L-Glutamic acid and chitosan loaded hydrogel (LG + CS hydrogel) against DW in STZ induced male Albino diabetic rat model where they showed 4 days and 6 days faster wound healing rate in comparison to CS hydrogel and diabetic control group. This effect was due to enhanced angiogenesis and collagen deposition at the site of injury [164]. In a similar study, hydrogel of *Moringa oleifera* (MO) leaf extract was tested for its healing properties against DW in STZ induced male Wistar diabetic rat model. Topical application of MO leaf extract loaded hydrogel showed 1.96-folds and 1.22- folds faster DW healing as compared to diabetic control and standard treated groups respectively [170]. In another study, DW healing effect of deferoxamine (DFO) hydrogel was evaluated on db/db diabetic mice where they exhibited 1.13-folds and 1.3-folds increase in epidermal length and 4.25-folds and 2-folds increase in antibacterial activity against *S. aureus* as compared to diabetic control and placebo hydrogel treated groups respectively indicating wound healing potential of the formulation [171]. In another study, Patil et al., investigated the effect of fluorinated methacrylamide chitosan (MACF) hydrogel dressings against DW in male adult db/db diabetic mice model where they observed significant increase in wound closure (1.75-folds

**Table 4**
Preclinical studies of nanohydrogels loaded with various drugs for treating diabetic wounds.

| Sr. No. | Drug | Method of preparation | Animal model | Research highlights | References |
|---|---|---|---|---|---|
| 1. | PVA | Ultraviolet light-initiated polymerization | Female db/db mice | • ↑ 2-folds scar thickness within 22 days<br>↑ angiogenesis and migration of endothelial cells | [177] |
| 2. | Chitosan | Ultraviolet light-initiated polymerization | db/db mice | • ↑ 5-folds wound contraction rate within 16 days<br>• ↑ collagen deposition | [178] |
| 3. | HA | Michael-type addition | Female db/db mice | • 2.2-folds decrease in wound area within 14 days<br>↑ angiogenesis and granulation tissues formation | [179] |
| 4. | IL-8 and MIP-3α loaded gelatin hydrogel | Cross-linking | Male ICR mice | • 5 days faster DW healing as compared to other groups<br>• ↑ neovascularization and collagen deposition | [180] |
| 5 | Glutamine-histidine-arginine-glutamic acid-aspartic acid-glycine-serine | Cross-linking | Male db/db mice | • Complete DW healing within 21 days<br>• ↑ re-epithelialization and angiogenesis | [181] |
| 6. | Neomycin sulfate | Freezing-thawing | Male SD rats | • ↑ 1.07-folds wound contraction within 6 days<br>• ↑ angiogenesis and collagen deposition | [182] |
| 7. | AC | Crosslinking | BKS db mice | • ↑ 1.06-folds wound contraction within 20 days | [183] |
| 8. | Insulin/L929 | Cross-linking | SD rats | • ↑ 1.05-folds wound contraction within 18 days<br>• ↑ collagen deposition | [184] |
| 9. | Sacran | Solvent evaporation | Male albino mice | • ↑ 1.26-folds wound contraction within 12 days<br>• ↑ angiogenesis and collagen deposition | [185] |
| 10. | HP-PEGs, HA-SH and ADSCs | Thiol-ene click reaction | Male SD rats | • ↑ 1.87-folds wound closure within 21 days<br>• ↑ angiogenesis and re-epithelialization | [186] |
| 11. | DFO | Solution polymerization | SD rats | • ↑ 1.5-folds wound contraction within 14 days<br>• ↑ angiogenesis and antibacterial action | [171] |
| 12. | HEP and BEM | Solution polymerization | Female Wistar rats | • ↑ 1.02-folds wound contraction within 21 days<br>• ↑ angiogenesis and neovascularization | [187] |
| 13. | ILM and EGF | Solution polymerization | SD rats | • ↑ 1.11-folds wound contraction within 12 days<br>• ↑ collagen deposition | [188] |
| 14. | aECM and SC | Solution polymerization | Male SD rats | • 4 days faster DW healing as compared to other groups<br>• ↑ extracellular matrix | [189] |
| 15. | Berberine | Solution polymerization | Female SD rats | • ↑ 2-folds wound closure within 13 days<br>• ↑ angiogenesis and anti-inflammatory action | [190] |
| 16. | PAP | Solution polymerization | Male Wistar rats | • ↑ 1.26-folds wound closure within 15 days<br>• ↑ angiogenesis and re-epithelialization, collagen deposition | [175] |
| 17. | PVA-CEC-AGA/Ag | Solution polymerization | Adult male SD rats | • ↑ 1.55-folds wound closure within 20 days<br>↑ angiogenesis and collagen deposition | [191] |
| 18. | Ceffe-γ-PGA hydrogel | Polymerization | Male BKS-Leprem2Cd479/Nju mice | • ↑ 1.19-folds wound closure within 17 days<br>• ↑ capillary density and cell proliferation | [192] |
| 19. | Human Umbical derived mesenchymal stem cells exosomes | Solution polymerization | SD rats | • Complete DW healing in 18 days<br>• ↑ formation of epithelium, collagen bundle fibers and hair follicles | [193] |
| 20. FA | | EDC/NHS cross-linking method | Male C57BL/6 mice | • ↑ 1.22-folds wound closure within 14 days<br>• ↑ angiogenesis and collagen deposition | [194] |

**Abbreviations** AC; Atellocollagen, aECM; Acellular extracellular matrix, ADSCs; Adipose-derived stem cells, BEM; Bemiparin, DFO; Desferrioxamine, EGF; Epidermal growth factor, EDC; Ethylenediamine carbamide, FA; Fayalite, HA; Hyaluronic Acid, HEP; Chitosan functionalized with heparin, HP-PEGs; Hyperbranched multi-acrylated poly (ethylene glycol) macromers, HA-SH; thiolated hyaluronic acid ILM; Insulin-loaded micelles, NHS; N hydroxy succinimide, PVA-CEC-AGA/Ag; polyvinyl alcohol-N-carboxyethyl chitosan agarose/Ag, PAP; *Periplanar Americana* herbal residue, SC; Sacchachitin.

and 2-folds) and angiogenesis (1.71-folds and 2.11-folds) as compared to Aquaderm (marketed formulation) and negative control groups indicating wound healing potential of the developed formulation [172]. Similarly, activity of a hydrogel prepared from edaravone nanoparticles (EDA-NP) was checked against DW in STZ induced male diabetic C57BL/6J mice. The EDA-NP hydrogel (L) was found to exhibit about 1.92-folds, 1.35-folds and 1.01-folds increase in wound healing rate in 15 days as compared to that in diabetic control, EDA-NP (H) and normal control-treated groups respectively. The enhanced activity of EDA-NP hydrogel was attributed to its increased antioxidant and anti-inflammatory effect at the site of injury [173]. In another study, in a 60 days clinical study on 56 patients, Gallelli et al., investigated the effect of quercetin (Qu) and oleic acid (OA) embedded nano hydrogel against DFU in diabetic patients having lower limb skin wound. Only 16 patients (57.1%) treated with 2% w/w hydrogel of Hyaluronic acid showed complete re-epithelization while 26 patients (92.8%) treated with 0.2% hydrogel containing Qu and OA showed complete re-epithelization at the site of injury. Moreover, topical application of HA resulted in some side effects while nano-hydrogel embedded with Qu and OA was found to be devoid of any side effect and thus was considered to be safe to use [174]. In one of the study, Wang et al., compared the wound closure effect of *Periplaneta americana* (PA) hydrogel against DW in diabetic rats with that by Kangfuxin Liquid (KFX), carbomer (CBM)/carboxymethyl cellulose (CMC) gel where they observed 1.03-folds, 1.36-folds and 1.53-folds increase in wound closure as compared to those by KFX liquid, CBM/CBC gel and diabetic control groups respectively indicating wound healing potential of the formulation [175]. In a study on the effect of alginate (Alg)-polydeoxyribonucleotide (PDRN) hydrogel against DW in C57BLKS/J-db/db male diabetic mice, it was found to exhibit 2.05-folds 1.9-folds and 2.18-folds increase and in collagen density and 2 folds, 2.1-folds and 2.8-folds decrease in wound area as compared to Alg, PDRN injection and saline-treated groups respectively [176].

The various nanohydrogels explored so far to treat DW are given in Table 4.

### 4.4. Solid lipid nanocarriers (SLNs)

SLNs are submicron colloidal carriers with size ranging from 50 to 1000 nm. These are generally composed of physiological lipids dispersed in water or aqueous surfactant solution [195]. The examples of lipids used in SLNs are epic cerana, stearic acid, hexadecyl hexadecanoate, caprylic/capric triglyceride, glyceryl monostearate, compritol, docosanoic acid and solid paraffin. The surfactants used in SLNs include egg and soya lecithin, polyoxyethylene, poloxamine, Tween 80, and poloxamer [196]. The advantages of SLNs are their large surface area, small size, and high drug loading capacity, all of which help in improving the therapeutic effects of the drugs contained therein [197,198]. The SLNs explored so far for the treatment of DW are discussed in the subsequent sections.

Recombinant human epidermal growth factor (rhEGF) loaded lipid nanoparticles (SLNs) at a dose of 10 μg were used against chronic wounds in male db/db mice model where they exhibited 1.09-folds, 1.2-folds, 1.3-folds, 1.29-folds and 1.8-folds decrease in inflammation as compared to the treatments in the given doses of rhEGF-SLNs, MS-rhEGF, free rhEGF, empty SLNs and untreated control groups, respectively [199]. In another study, Rajesh et al., have investigated the antibacterial effect of the methanolic extract of *Abutilon indicum* (MEAI) SLNs against microorganisms that causes DFU. The antibacterial effects evaluated in terms of zone of inhibition (mm) against *E. coli*, *Bacillus subtilis* and *P. aeruginosa*. The results revealed that MEAI SLNs exhibited maximum zone of inhibition for *E. coli* ($22 \pm 0.57$ mm for MEAI vs $24.33 \pm 0.33$ mm for MEAI SLNs), *B. subtilis* ($15.33 \pm 0.88$ mm for MEAI vs $18.66 \pm 0.66$ mm for MEAI SLNs) and *P. aeruginosa* ($20.66 \pm 0.88$ mm for MEAI vs $23.66 \pm 0.33$ mm for MEAI SLNs). [200]. Similarly, wound healing effect of SLNs based rutoside ointment (NRO) in STZ induced male Albino Wistar diabetic rat model. Application of NRO accelerated DW healing by promoting hydroxyproline content and antioxidant action at the wound site. Percentage wound size on the 16th day of treatment was found to be 11.35%, 69.5% and 99.9% for NRO, rutoside ointment and ointment base treated groups respectively. In one of the study, application of silence tumour necrosis factor α loaded lipid nanoparticles (siTNFα-loaded LNPs) against DW in STZ induced C57BL/6 diabetic mice model was found to accelerate DW healing by promoting anti-inflammatory action and reducing tumour necrotic factor-alpha (TNF-α) microsomal ribonucleic acid (mRNA) expression in the DW by 40–55%. Percentage of wound contraction was found to be 100% and 70% for siTNFα-loaded LNPs and control groups respectively on the 13th day of treatment [201]. Arantes et al., studied the effect of retinoic acid-SLNs (RA-SLNs) containing chitosan films against DW in STZ induced C57BL/6 male diabetic mice. On the 14th day of study, the percentage of wound healing was found to be 90% and 70% for RA-SLNs surrounded chitosan films, and placebo SLNs surrounded chitosan films respectively which was attributed to enhanced collagen deposition and decreased leukocyte infiltration rate as compared to that by placebo SLNs surrounded by chitosan films [202]. In a similar study on valsartan (Va)-SLNs gel against DFU in STZ induced male SD diabetic rats, the topical application of Va-SLNs gel was found to accelerate DW healing by promoting collagen deposition, angiogenesis and re-epithelization at the site of injury as compared to placebo SLNs gel.

### 4.5. Nanostructured lipid carriers (NLCs)

NLCs are the combinations of solid lipids, liquid lipids and emulsifiers. The ratio of these components is varied to obtain different forms of NLCs such as imperfect type, amorphous type and multiple types [203]. NLCs are reported to minimize the limitations of SLNs such as limited drug loading, entrapment efficiency and drug release during storage [204,205]. Reports on NLCs of drugs to be used for DWs are relatively recent. In 2017, Simvastatin (SV)-stem cells-based NLCs scaffolds were explored for treatment of DW in db/db mice model wherein they exhibited 1.19-folds, 2.56-folds, 1.02-folds and 1.97-folds decrease in wound area as compared to SV, placebo NLCs scaffolds, placebo NLCs + stem cell scaffolds and SV NLCs respectively [206]. In a subsequent clinical trial on 27 patients with DFU phenytoin-NLCs (PHT-NLCs) hydrogel was investigated. The formulation was found to promote collagen deposition, angiogenesis and fibroblast proliferation at the ulcer site. In the eight day study, the percentage of wound healing was found to be $95.82 \pm 2.22\%$, $47.10 \pm 4.23\%$ and $34.91 \pm 28.33\%$ for PHT-NLC-hydrogel, PHT and blank-hydrogel respectively [207]. In another study, Natrajan et al., studied the effect of pioglitazone NLCs loaded collagen/chitosan composite scaffolds (Pio-NLC-COL-CS scaffolds) against DW in STZ induced male Albino Wistar diabetic rat model where they observed 1.45-folds and 1.20-folds increase in wound contraction as compared to control and blank NLC-COL-CS scaffolds treated groups respectively indicating the wound healing potential of the formulation [208]. In another study, taking a cue from the use of aromatic oils in the treatment of DWs, Ghodrati et al., investigated the effect of peppermint essential oil-NLCs (PEO-NLCs) against the infective wound in the BALB/c mice model. On 14th day, PEO-NLCs showed maximum vascularization ($2.66 \pm 0.40$ for PEO-NLCs vs $2.16 \pm 0.40$ for PEO), fibroblast infiltration ($2.83 \pm 0.40$ for PEO NLCs vs $2.33 \pm 0.50$ for PEO) and epithelization ($2.83 \pm 0.20$ for PEO NLCs vs $2.60 \pm 0.30$) as compared to PEO treated groups [209]. Similarly, Khezri et al., have studied the effect of rosemary essential oil NLCs (REO-NLCs) against infected BALB/c mice wound model. On the 12th day, REO-NLCs and REO treated groups showed excellent wound healing while 5 $mm^2$ and 8 $mm^2$ wound area were still left in mupirocin and control groups respectively. The results of antibacterial activity indicated that REO-NLCs showed 1–folds, 3-folds and 4-folds decrease in total bacterial count as compared to REO' mupirocin and control groups respectively [210]. In a study on the effect of poly (lactic-co-glycolic acid)

(PLGA)-Aloe vera (AV) based NLCs against DW in male db/db mice model, it was found to exhibit 1.03-folds and 1.53-folds increase in wound contraction as compared to PLGA-AV and control group (untreated group) respectively. The re-epithelization study revealed that PLGA-AV NLCs exhibited 2.2-folds increase in re-epithelization rate as compared to untreated control group [211]. In one of the study, [w]ound healing effect of epidermal growth factor (EGF)-curcumin (Cur) based NLCs against DW in STZ induced male SD diabetic rats where they showed increase in wound contraction by 1.13-folds, 1.26-folds and 1.30-folds in comparison to EGF, Cur and blank NLCs treated groups respectively [212]. In another study, silicon elastomer-20 (S)-protopanaxadiol-loaded NLCs (PPD-NS) based gel were evaluated against DFU in db/db diabetic mice model where it was observed that PPD-NS based gel exhibited 1.13-folds, 1.39-folds and 1.04-folds decrease in wound closure as compared to control, PPD-S and PPD-N treated groups respectively. The angiogenesis study revealed that PPD-NS based gel exhibited 1.06-folds, 1.37-folds and 2-folds increase in blood vessels as compared to PPD-N, PPD-S and PBS treated groups respectively [213]. In one of the study, wound healing effect of mentha pulegium essential oil (MPO) based NLCs were evaluated against DW in BALB/c mice model. The results revealed that the topical application of MPO based NLCs accelerated DW healing within 15 days by showing 1.6-fold decrease in wound area in comparison to diabetic control group [214].

### 4.6. Nanoparticles

NPs are colloidal solid particles having the size in the nanometer range [215]. Generally, NPs can be zero-dimensional (0-D), one-dimensional (1-D), two-dimensional (2-D) and three-dimensional (3-D) in nature [216]. The basic composition of NPs includes three layers viz. surface layer (polymers, surfactants, small molecules, and metal ions), shell layer, and core [217]. The various NPs such as gold NPs, silver NPs, copper NPs, polymeric NPs, cerium oxide NPs, zinc oxide NPs used to treat DW are discussed in the subsequent sections.

#### 4.6.1. Gold NPs (AuNPs)

AuNPs are extensively used in tissue engineering due to their biocompatibility. Moreover, unlike silver, AuNPs does not impart antimicrobial activity. Thus, AuNPs always used along with other biomolecules for their utility in biomedical applications including DW. For instance, crosslinking of AuNPs with collagen, polysaccharides and peptides are used in integrating GFs without altering the structural integrity of attached biomolecules. These modification in AuNPs results in better biocompatibility and biodegradability [218]. Moreover, in one of the studies, it has been found that when AuNPs were applied to the wound site they exhibit increase in re-epithelization, collagen deposition, granulation tissue formation and ECM deposition. Looking at these benefits various AuNPs explored so far to treat DW are discussed in the subsequent sections [219].

Chen et al., studied the effect of coadministration of AuNPs, epigallocatechin gallate (EGCG) and α-lipoic acid (ALA) (AuEA) against DW in STZ induced male BALB/c diabetic mice. On the 7th day, AuEA exhibited about 2-folds decrease in wound area as compared to vehicle-treated groups indicated wound healing potential of the formulation [220]. Similarly, Jing et al., compared the wound healing effect of nerolidol functionalized AuNPs (N-AuNPs) against DW in male Albino diabetic rats with that by antimicrobial peptide (LL37) AuNPs and diabetic control groups. Application of N-AuNPs accelerated DW contraction by 1.2-folds and 1.03-folds as compared to control and LL37 AuNPs treated groups [221]. In another study, the wound healing effect of LL37/*pDNAs* AuNPs were evaluated against DW in STZ induced male C57BL/6 diabetic mice. The results revealed that LL37/*pDNAs* AuNPs treated groups exhibited 2.25-folds, 2.57-folds and 1.8-folds increase in wound closure within 10 days as compared to control, *pDNAs* and LL37 treated groups respectively [222]. In another study, Ponnanikajamideen et al., compared the wound healing effect of *Chamaecostus cuspidatus* (CC) AuNPs against DW in STZ induced adult male Wistar diabetic mouse model with that by CC (plant extract) treated groups. The results revealed that CC AuNPs treated groups exhibited about 1.03-folds increase in wound contraction as compared to plant extract treated group [223]. In one of the study, effect of dual-functional AuNPs i.e., 11-mercaptoundecyl-N, N, N-trimethylammonium bromide (11-MTA)/-VEGF-A165 AuNPs were evaluated against DW in db/db diabetic mice. On the 12th day, dual-functional AuNPs exhibited 5-folds and 5.5-folds decrease in wound size as compared to 11-MTA and untreated groups respectively [224]. In another study, wound closure and re-epithelization potential of keratinocytes growth factor (KGF) AuNPs against DW in STZ induced female SD diabetic rats. The results were compared with control, KGF and AuNPs alone. The results revealed that KGF AuNPs treated groups exhibited about 1.58-folds, 1.26-folds and 1.46-folds increase in percentage wound healing and about 3.75-folds, 1.5-folds and 3.4-folds increase in re-epithelization as compared to control, KGF and AuNPs alone treated groups respectively [225]. Similarly, wound closure activity of calreticulin conjugated AuNPs were evaluated against DW in STZ induced male BALB/C diabetic mice, it was found to exhibit 1.39-folds increase in percentage wound closure within 10 days as compared to Au NPs alone treated groups [226]. In another study, effect of *DsiRNA*-loaded AuNPs based thermoresponsive gel were evaluated against DW in *In vitro* cultured human dermal fibroblasts cells. The results revealed that *DsiRNA*-loaded AuNPs exhibited 98% of cell viability and promoted an increase in cell migration and proliferation rate that helped in wound healing [227].

#### 4.6.2. Silver NPs (AgNPs)

Silver is a bactericidal agent and is frequently used to treat wounds, burns and various ulcers. For example, silver in the form of nitrate is used to treat non-healing chronic wounds. Furthermore, silver is also coated on dressings to distribute drug efficiently, which plays a key role in healing wounds. Moreover, the application of AgNPs based dressings on the wound site is devoid of toxicity which makes them more advantageous in terms of dressings. In addition, the co-administration of AgNPs with collagen enhances antibacterial activity and make them as a suitable biomaterial for wound dressings. In some of the studies it has been reported that AgNPs reduces oxidative stress and inflammatory cytokines as well, which aids in wound healing. Various uses of AgNPs in treating DW is highlighted below.

Tehrani et al., have studied the antibacterial effect of AgNPs coated leather and leather without AgNPs coating on different strains of gram-positive and gram-negative bacteriae isolated from foot ulcers of 95 diabetic patients. The results revealed a significant decrease in the number of counts of bacteriae treated with AgNPs coated leather as compared to the non AgNPs coated leather indicating the antibacterial potential of AgNPs [228]. In one of the study, wound healing effect of *Azadirachta indica* (AI) AgNPs were evaluated against DW in STZ induced male Swiss Albino diabetic mice. On the 21st day AI AgNPs exhibited increase in wound contraction by 1.13-folds and 1.78-folds in comparison to SSD and control groups respectively [229].

Hernandez1 et al., conducted a clinical trial in which the effect of AgNPs was investigated against DFU. In this study, wound healing rate (days) of AgNPs were evaluated in two patients with Wagner third grade foot ulcer (W3GFU) and Wagner second grade foot ulcer (W2GFU) respectively. To treat these patients, AgNPs were applied topically at the site of the injury. The results revealed that topical application of AgNPs showed complete wound healing in W3GFU patient within 21 days by promoting re-epithelization and anti-inflammatory action. While in the case of a patient having W2GFU AgNPs took 26 days to completely heal the wound. The outcomes of the study inferred that AgNPs exhibited about 1.23-folds faster wound healing rate in the patient having W3GFU as compared to a patient having W2GFU [230]. In one of the study, wound healing activity of bamboo cellulose nanocrystals (BCNCs) co-administered AgNPs were evaluated against DW in STZ induced

Swiss albino diabetic mice. Application of BCNCs co-administered AgNPs at the wound site exhibited increase in percentage wound closure by 1.1-folds and 1.06-folds as compared to AgNPs and BCNCs treated groups respectively [231]. In another study, Shi et al., compared the wound healing effect of AgNPs composed of thiolated chitosan (C), N-acetyl-L-cysteine (N) and maleic acid-grafted dextran (DM) (AgNPs-CNDM) against DW in STZ induced male SD diabetic rats where they observed on 10th day, AgNPs-CNDM exhibited about 5-folds, 2-folds, 4.8-folds decrease in wound area as compared to control, AgNPs and CNDM treated groups [232]. In another study, activity of AgNPs impregnated chitosan (CS)- poly ethylene glycol (PEG) hydrogel was evaluated against DW in alloxan monohydrate induced diabetic rabbits. The results showed that AgNPs impregnated CS-PEG hydrogel exhibited about 1.58-folds and 1.18-folds increase in percentage wound contraction as compared to AgNPs alone and CS treated groups respectively [233]. Similarly, effect of co-administration of hypochlorous acid (HClO), chitin-nanofiber sheet (CNFS) and AgNPs were evaluated against DW in db/db diabetic mice. The results revealed that co-administration of HClO), chitin-nanofiber sheet (CNFS) and Ag NPs treated groups exhibited about 1.66-folds and 1.37-folds increase in angiogenesis and length of granulation tissue as compared to combination of HClO and CNFS treated groups respectively. This indicated the potential of AgNPs in the therapy [234]. In one of the study, Kumar et al., have investigated the wound healing effect of *Aloe arborescens* AgNPs against diabetic wounded fibroblast cells (WS1) using the scratch assay. The results revealed an accelerated wound healing within 48 h when *Aloe arborescens* AgNPs were used against WS1 human skin fibroblast [235]. In another study, antibacterial effect of *Aerva lanata* (AL) AgNPs were tested against microorganisms isolated from the foot of the DFU patients. The microorganisms isolated from DFU patient foot were *E. coli*, (PA), *Bacillus Subtilis* (BS) and *S. aureus*. These isolated microorganisms were tested against AL AgNPs. The results revealed that AL AgNPs showed antibacterial action against these DFU bacterial isolates and showed minimum bactericidal concentration (MBC) and minimum inhibitory concentration (MIC) of 10–20 μg/mL and 5–15 μg/mL respectively. Besides these, AL AgNPs also showed an increase in accumulation of intracellular reactive oxygen species (ROS), augmented membrane leakage, modified membrane integrity, and drastically ruptured membrane which helps in wound healing [236]. Similarly, activity of co-administration of synthetic chitosan-based composite hydrogel ($SNP_ECHG$) and EGF AgNPs were evaluated against DW in STZ induced male SD diabetic rats, it was found to exhibit about 1.18-folds and 1.35-folds increase in percentage wound closure as compared to HeraDerm (commercial) and gauze treated groups. Additionally, $SNP_ECHG$ co-administered EGF AgNPs exhibited about 1.24-folds and 1.55-folds increase in collagen content as compared to HeraDerm (commercial) and gauze treated groups [237].

#### 4.6.3. Copper NPs (CuNPs)

Copper NPs are gaining tremendous attention in the treatment of chronic wounds. They are essential for modulation of various GFs and cytokines as well participate in all phases of wound healing [238]. Furthermore, they can promote angiogenesis by affecting the hypoxia inducible factor-1a (HIF-1a) and regulates VEGF secretion [239]. Moreover, CuNPs also exhibit antimicrobial effect which play key role in wound healing. In addition, several studies revealed that CuNPs also promote cell migration and cell proliferation which is helpful in accelerating wound healing process. Utilizing these remarkable potential various CuNPs are used to treat DW which are discussed in the subsequent sections [240].

In another study, the effect of CuNPs was examined on a 58-year-old patient with T2DM, micro and macrovascular complications, critical limb ischemia, diabetic retinopathy, peripheral artery disease, chronic renal disease of stage II and ulcer in the right heel as well as necrotic injuries in the 2nd, 3rd, and 4th toes. Due to these complications, the patient was programmed for a supracondylar amputation. To avoid amputation, this patient was included in the clinical trial and given the treatment of CuNPs. When the CuNPs were applied at the site of injury, it was observed that within three months, the ulcer gets healed. The patient was saved from supracondylar amputation. This effect was due to antibacterial action, epithelization and stimulation of autolytic debridement at the site of injury [241]. Similarly, wound healing activity of folic acid-based CuNPs (F-HKUST-1) were tested against DW in STZ induced diabetic mice with that by HKUST-1, PBS and folic acid-treated groups. Topical application of F-HKUST-1 at the wound site exhibited about 1.05-folds, 1.11-folds and 1.26-folds increase in wound contraction as compared to HKUST-1, PBS and folic acid respectively [242]. In a study on the effect of yeast extract (YE)-immobilized-copper (Cu) nanoparticle (NP)-dispersed carbon nanofibers (CNFs) was checked against DW in STZ induced female Wistar diabetic rats. On the 14th day, YE-immobilized CuNPs dispersed CNFs demonstrated 1.09-folds and 1.28-folds increase in wound contraction as compared to CNFs and control groups respectively [243]. In one of the study, antibacterial effect of herbal extract-based CuNPs ointment were tested against microorganisms isolated from the foot of DFU patient. The microorganisms isolated from the foot of the DFU patient were *E. coli* and *S. aureus*. The results revealed that CuNPs ointment showed antibacterial action against *S. aureus* and *E. coli* with a zone of inhibition of 14 mm *(S. aureus*) and 15 mm (*E. coli)*, respectively [244]. In another study, Zhang et al., compared the wound closure and angiogenesis activity of copper-based metal−organic framework (HKUST-1) against DW in C57BL/6J diabetic mice where they exhibited about 2-folds decrease in percentage wound area as compared to control groups. Additionally, HKUST-1 treated groups showed increase in length of blood vessels by 2.1-folds in comparison to control groups [245]. Similarly, Liu et al., investigated the effect of ultrasmall CuNPs (Cu5.4O USNPs) against DW in a male BALB/c diabetic mouse model. On the 15th day, Cu5.4O USNPs exhibited about 2.6-fold increase in wound contraction as compared to control (PBS) treated groups respectively [246].

#### 4.6.4. Cerium oxide NPs (CONPs)

CONPs are gaining remarkable attention in the field of tissue engineering. Because they promote growth of vasoendothelial cells (VECs), keratinocytes and fibroblasts, which are essential for wound healing. Moreover, CONPs exhibit antioxidant effect by scavenging reactive oxygen species (ROS). In addition, CONPs also promote angiogenesis and anti-inflammatory action [269]. CONPs also helps in the modulation of intracellular oxygen environment [247]. Looking at these potentials various CONPs used to treat DW are discussed in the subsequent sections.

In a study on the effect of CONPs conjugated small non-coding RNA (MicroRNA-146a) against DW in STZ induced diabetic porcine model. Application of CONPs conjugated MicroRNA-146a accelerated DW healing within 14 days by 1.51-folds as compared to diabetic control groups [248]. Similarly, Augustine et al., compared the wound healing effect of CONPs loaded electrospun Poly (3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) membranes against DW in male SD rats where they found that on the 30th day, CONPs loaded PHBV treated groups exhibited about 1.14-folds increase in percentage wound contraction as compared to PHBV [249]. In another study, effect of CONPs based gel were checked against neuropathic DFU. A 62-year--old patient having a history of T2DM was selected for the study. The patient was suffering from T2DM for the last 20 years and had multifactorial diabetic complications such as retinopathy, neuropathy and microangiopathy of the lower limb. The patient also had hypertension and dyslipidemia. To treat diabetic complications, the patient had received insulin therapy and for hypertension perindopril. Atorvastatin was administered to manage dyslipidemia. Despite these ongoing treatment strategies, the foot ulcer got developed in the plantar region of the foot. For the treatment of foot ulcer, Trikacide 1500 mg orally per day was given along with gauze with the hypertonic solution (0.45% NaCl), and bandages were applied at the ulcer area for two months.

However, these treatments were failed to heal the wound. Finally, CONPs based gel was applied topically at the site of the foot ulcer. The treatment with CONPs based gel accelerated wound healing within 2 months by showing anti-inflammatory, antioxidant, bacteriostatic, and tissue regenerative activity at the site of injury [250]. In one of the study, activity of zwitterionic cryogel *miRNA146a*-conjugated CONPs were examined against DW in female db/db diabetic mice. The results were compared with the control zwitterionic cryogel. Topical application of zwitterionic cryogel *miRNA146a*-conjugated CONPs accelerated DW within 14 days by 1.43- as compared to control zwitterionic cryogel treated groups [251]. Similarly, in a study on the effect of nano silk (NS) co-administered CONPs conjugated *miRNA146a* against DW in female diabetic mice. The results revealed that NS co-administered CONPs conjugated *miRNA146a* treated groups exhibited 2.3-folds faster-wound healing as compared to diabetic control groups [252].

#### 4.6.5. Zinc oxide NPs (ZnO NPs)

Zinc is an important micronutrient which plays key role in human physiology. It acts as a cofactor for various metalloenzymes which are necessary for immunomodulation, cell growth, proliferation and cell membrane repair. The deficiency of Zn is responsible for skin lesions, decrease in immunity, growth retardation and impede wound healing process. Moreover, Zn helps in the regulation of ECM and also exhibit antioxidant effect [253]. The various ZnO NPs explored so far to treat DW are discussed in the subsequent sections.

Antibacterial effect of *Aristolochia indica* (*A. indica*) loaded ZnO NPs were tested against micro-organisms isolated from the foot of the DFU patients. The microorganism isolated from the foot of the patients were coagulase-negative *staphylococci* (CNS) (0.44%), *E. coli* (45%), *E. faecalis* (1.16%), *Acinetobacter baumannii* (*A. baumannii)* (10%), *S. aureus* (15%) and *Klebsiella pneumoniae* (*K. pneumonia)* (8.4%). The results revealed a significant decrease in the number of counts of bacteriae i.e., 99.9% killing rate within 6 h when treated with *A. indica* loaded ZnO NPs as compared to vancomycin indicating the antibacterial potential of ZnO NPs [254]. In another study, wound healing effect of mucin-ZnO NPs based hydrogel were checked against DW in alloxan monohydrate induced male Wistar diabetic rats where they exhibited 1.21-folds, 1.17-folds, 1.08-folds and 1.03-folds increase in wound contraction in comparison to blank hydrogel, gentamicin, mucin and ZnO NPs treated groups respectively [255]. In one of the study, antimicrobial effect of radish root extract-based ZnO NPs against DFU. In this study, radish root extract-based ZnO NPs were tested against microorganisms isolated from the foot of the DFU patients where they exhibited 2.5-folds, 1.5-folds, 2.1-folds and 2-folds increase in zone of inhibition against *E. coli*, *E. faecalis*, *P. aeruginosa and* MDR–*A. baumannii as* compared to radish root extract alone respectively [256].

#### 4.6.6. Poly (lactic-co-glycolic acid) NPs (PLGA-NPs)

PLGA is a copolymer and is extensively used in wound healing due to their biocompatibility and biodegradability. Moreover, PLGA helps in angiogenesis by releasing exogeneous lactate and accelerates wound healing process [257]. Several studies also revealed that when PLGA NPs is used along with other biomolecules it allows cell proliferation, migration as well as exhibit anti-inflammatory and antioxidant effect. In addition, promotes neovascularization, keratinocytes and fibroblasts migration, re-epithelization and collagen deposition at the site of injury. Looking at these benefits various PLGA NPs explored so far to treat DW are discussed below.

Activity of scaffolds/growth factor (GF) loaded PLGA NPs were evaluated against DW in male db/db diabetic mice. The results were compared with the control group and scaffolds/unloaded NPs. On the 15th day, scaffolds/GF-loaded PLGA NPs exhibited 1.41-folds and 4.25-folds increase in wound closure as compared to scaffolds/unloaded NPs and control scaffolds respectively [258]. In another study, effect of PLGA combined VEGF NPs were evaluated against DW healing in leptin receptor-deficient diabetic db/db mice. The results revealed that PLGA combined VEGF NPs exhibited 1.05-folds, 1.53-folds and 1.48-folds increase in wound contraction as compared to PLGA-NPs, control and VEGF alone treated groups respectively indicating wound healing potential of the formulation [259]. Similarly, wound heling effect of ferulic acid PLGA-NPs (FA PLGA-NPs) were evaluated against DW in male Wistar diabetic rats. Topical application of FA PLGA-NPs accelerated DW healing within 14 days by 3.1-folds, 1.6-folds, 3.1-folds and 2.4-folds as compared to the control group, oral ferulic acid nanosuspension, mupirocin ointment and oral metformin-treated groups respectively [260]. In a study on the effect of insulin loaded PLGA NPs based hydrogel for DW healing in male SD diabetic rats. The results revealed that the percentage of wound injury index got reduced by 20-fold with insulin loaded PLGA NPs as compared to diabetic control groups. This wound healing effect was attributed to angiogenesis, collagen deposition and anti-inflammatory action at the site of injury [261]. Similarly, Hasan et al., compared the wound healing effect of polyethylenimine/diazeniumdiolate (PEI/NONOate)-doped PLGA nanoparticles (PLGA-PEI/NO NPs) against methicillin-resistant *S. aureus* (MRSA) biofilm-infected wounds in male BALB/c diabetic mice. On the 12th day, the percentage of wound closure of mice treated with PLGA-PEI/NO NPs was found to be 95.5%. However, control and PLGA-PEI/NO NPs treated groups showed negative effect [262]. In another study, sesamol-PLGA (SM-PLGA) nanosuspension were evaluated against DW in STZ induced male Wistar diabetic rats, it was found to exhibit about 1.33-folds, 1.25-folds and 1.11-folds increase in percentage wound closure as compared to DFU control, SM-50 and SM-100 treated groups respectively. Additionally, SM-PLGA nanosuspension exhibited about 1.3-folds and 1.5-folds decrease in TNF-α levels as compared to SM-100 and SM-50 treated groups respectively [263]. In one of the study, rate of granulation and angiogenesis activity of *Archidendron pauciflorum* (AP) PLGA NPs ointment were evaluated against DW in STZ induced male Swiss-Webster diabetic mice. The results revealed that AP PLGA NPs ointment exhibited about 1.25-folds and 1.05-folds increase in the average area of granulation tissues and blood vessels in comparison to AP alone treated group [264]. Similarly, activity of PLGA/GE electrospun nanofibrous mats loaded liraglutide were evaluated against DW in STZ induced male SD diabetic rats. The results showed that PLGA/GE electrospun nanofibrous mats loaded liraglutide showed 1.33-folds, 2-folds and 1.42-folds increase in percentage wound closure, blood vessels and cell migration rate as compared to control groups respectively [265].

### 4.7. Wafers

Wafers is a novel class of delivery system that have been applied directly on the suppurating wounds. These wafers adhere instantly at wound the surface and absorb exudate. Wafers are formed by using polymers such as sodium alginate, carrageenan, xanthan gum, methylcellulose and chitosan [266]. The Wafers used so far to treat DW have been discussed in the subsequent sections.

Antimicrobial effect of ciprofloxacin-loaded calcium alginate wafers was tested against microorganisms isolated from the foot of the DFU patients. The isolated microorganisms were found to be *P. aeruginosa*, *S. aureus* and *E. coli*. The results showed that ciprofloxacin-loaded calcium alginate wafers exhibited 45-folds, 1.09-folds and 45-folds increase in zone of inhibition against *E. coli*, *S. aureus* and *P. aeruginosa* as compared to commercial Algisite Ag® treated groups [267]. Similarly, Atia et al., compared the wound healing effect of diosmin nanocrystals loaded wafers against DW in STZ induced SD diabetic rats where they exhibited 1.25-folds, 1.15-folds and 1.50-folds decrease in ulcer area as compared to placebo wafers, diosmin powder gel and diabetic control groups respectively [268].

### 4.8. Dendrimers

Dendrimers are highly branched star-shaped macromolecules with

dimensions of nanometer-scale. These consist of three components a central core, an interior dendritic structure (the branches) and an exterior surface with functional groups [269]. They serve as a novel carrier due to their various advantages such as a capacity for improving solubility, absorption, bioavailability and target specificity [270]. Looking at these benefits various dendrimers explored so far to treat DW are discussed below.

In a study on the effect of polyamidoamine-starburst (PAM-RG4)/minicircle (MC) VEGF165 *deoxyribose nucleic acid (DNA*) complex dendrimer (PAM-RG4/MC VEGF165 *DNA* complex dendrimer) against DW in STZ induced male C57BL/6J diabetic mice. The results revealed that PAM-RG4/MC VEGF165 *DNA* complex dendrimer treated groups accelerated DW healing within 12 days and exhibited about 1.1-fold decrease in wound area as compared to diabetic control-treated groups [271]. In another study, wound healing potential of peptide dendrimers ($AK_{21}$) were evaluated against DW in STZ induced male Kunming diabetic mice. Wound healing studies revealed that the $AK_{21}$ treated groups showed decrease in wound area by 10.8-folds than that of diabetic control groups due to increased re-epithelization at the site of injury [272].

### 4.9. Hydrogel nanotubes

The hydrogel nanotubes are formed by crosslinking of nanotubes with hydrogel in order to increase the three-and-four-dimensional printability, tunability, stiffness and electrical conductivity. Moreover, hydrogel nanotubes are gaining attention in the field of tissue engineering due to its biocompatibility and wound healing properties [273].

Activity of HNTs were evaluated against DW in male Wistar diabetic rats. Topical application of HNTs accelerated DW healing within 16 days by 1.33-folds as compared to diabetic control-treated groups. In addition, HNTs treated groups exhibited 1.3-folds, 1.8- folds and 1.6-folds decrease in IL-6 levels, TNF-α levels and IL-10 levels as compared to diabetic control groups respectively [274].

## 5. Biomaterials

### 5.1. Scaffolds

Scaffolds are three-dimensional polymeric structures consisting of biocreamics, hybrid materials and polymers which helps in tissue rejuvenation [275,276]. Based on tissue response, biocreamics are divided into three categories *viz.* bioactive (bioactive glass), nearly inert (zirconia and alumina), and resorbable ceramics (β- and α tricalcium phosphate, TCP) [277]. Besides these, polymers used in the scaffolds are of two types, either synthetic or natural origin. The polymers that come under the synthetic category are polyphosphazene, poly (propylene) fumarate (PPF), polycaprolactone, polyanhydride, polyether ether ketone (PEEK), polyglycolic acid (PGA) and polylactic acid (PLA) [278]. The natural polymers used in scaffolds are chitosan, fibrin, collagen, and hyaluronic acid [279]. Some of the studies wherein, scaffolds have been used to treat DW are discussed below.

Effect of collagen-based VEGF scaffolds were evaluated against DW in STZ induced diabetic rats. Application of collagen-based VEGF scaffolds accelerated DW healing by 1.23-folds as compared to VEGF alone treated groups [280]. In another study, Lee et al., studied compared the wound healing effect of glucophage loaded collagen/PLGA scaffolds membranes against DW in STZ induced male SD diabetic rats with that by gauze sponge. The results showed that glucophage loaded PLGA scaffolds membranes exhibited about decreases in wound area by 3.5-folds within 14 days in comparison to gauze sponge treated groups [281]. In another study activity of prolyl hydroxylase domain protein 2 (PHD2) *siRNA* scaffolds were evaluated against DW in STZ induced SD diabetic rats. The results showed that PHD2 *siRNA* scaffolds exhibited about 2-folds increase in relative VEGF protein content as compared to SCR-siNPs [282]. Similarly, activity of perclan-VEGF chitosan scaffolds were tested against DW in male Lewis diabetic rats, it was found to exhibit about 3.3-folds and 2.5-folds increase in reepithelization and angiogenesis as compared to the diabetic control group respectively [283]. In a study on the effect of co-administration of Eudragit RL, gentamicin and rhEGF scaffolds against DW in STZ induced female C57BL/6 diabetic mice where they exhibited decrease in open wound area by 1.63-folds within 12 days as compared to Eudragit RL alone treated groups [284]. Similarly, activity of laminin heparin peptide bonded GF scaffolds was tested against DW in STZ induced db/db diabetic mice. The results revealed that laminin heparin peptide bonded GF scaffolds exhibited about 2-folds and 1.8-folds increase in percentage wound closure and granulation tissue thickness within 10 days as compared to fibrin treated groups [285]. In another study, effect of co-administration of konjac glucomannan, keratin and *Avena sativa* extract (KGM/KER/OAT) hydrogel scaffolds were evaluated against DW in STZ induced healthy male Wistar diabetic rat model. The results revealed that KGM/KER/OAT hydrogel scaffolds showed complete wound healing within 16 days, whereas KGM/KER scaffolds and control group took 20 and 24 days for complete wound healing respectively. In addition, co-administration of KGM, KER and OAT hydrogel scaffolds showed 2.08-folds increase in antioxidant activity as compared to diabetic control group [286]. Similarly, activity of psyllium seed husk polysaccharide (PSH), KER and 1% morin (MOR) co-loaded scaffolds were evaluated against DW in STZ induced male Wistar diabetic rat model. Topical application of PSH, KER and 1% MOR co-loaded scaffolds accelerated DW healing within 16 days by showing 2.4-folds, 1.07-folds and 2.15-folds increase in wound closure as compared to diabetic control, PSH, KER and 0.5% MOR co-loaded scaffolds and combination of PSH and KER scaffolds treated groups respectively [287]. Similarly, wound healing effect of acellular dermal matrix PEGylated graphene oxide-mediated quercetin (ADM-GO-PEG/Que) modified collagen hybrid scaffolds were evaluated against DW in STZ induced ICR diabetic mice where they showed 1.38-folds, 1.22-folds and 1.03-folds increase in wound closure as compared to diabetic control, ADM, and GO-PEG/Que scaffolds treated groups respectively [288]. Similarly, activity of peritoin (PN) and connective tissue growth factor (CCN2) scaffolds were evaluated against DW in db/db diabetic mice. The results revealed that CCN2 scaffolds exhibited about 1.75-folds, 3.5-folds and 4.66-folds increase in vessel density as compared to PN, collagen and control-treated groups respectively [289]. In another study effect of gelatin-curcumin (GC)/lithospermi radix extract (L)/chitosan (C) nanofibrous scaffolds against DW in STZ induced male SD diabetic rat model, it was found to exhibit about 1.01-folds, 1.04-folds, 1.01-folds, 1.07-folds and 1.02-folds increase in wound recovery rate as compared to GC/L, GC, GC/C, Comfeel® and gauze (control) treated groups respectively [290]. In one of the study, Han et al., compared the wound healing effect of *Asiatic acid* (AA) scaffolds against DW in STZ induced male C57BL/6J diabetic mice with that by diabetic control groups. The results revealed that the AA scaffolds treated groups increase in the wound closure and collagen content by 2-folds and 1.58-folds respectively in comparison to diabetic control groups [291,292]. Similarly, angiogenesis activity of platelet-derived growth factor-BB (PDGF-BB) co-loaded scaffolds were evaluated against DW in female C57BL/6JNju DIO type II diabetic mice. It was found to exhibit about 2-folds increase in angiogenesis rate as compared to placebo scaffolds [293]. In a study on the effect of rGO-ADM-mesenchymal stem cells (MSCs) scaffolds were tested against DW in STZ induced male ICR diabetic mice. Topical application of rGO-ADM-MSCs scaffolds accelerated DW healing within 14 days by showing 1.17-folds, 1.13-folds and 1.03-folds increase in wound closure as compared to control, ADM-MSCs scaffolds and ADM-GO scaffolds treated groups respectively [294]. Similarly, Jiang et al., compared the wound healing effect of silicon-doped amorphous calcium phosphate scaffolds against DW in STZ induced diabetic mice with that by diabetic control groups. It was found from the study that silicon-doped amorphous calcium phosphate scaffolds exhibited about 1.26-folds increase in wound closure within 15

days as compared to control groups [295]. In another study, effect of co-administration of the collagen-binding domain (CBD)/vasoendothelial growth factor (V)/stromal-derived growth factor-α (S) scaffolds against DW in STZ induced male SD diabetic rats. The DW healing studies revealed that CBD/V/S scaffolds showed 1.11-folds and 1.23-folds increase in wound healing as compared to control and placebo scaffolds treated groups respectively [296]. In one of the study, activity of polylactic acid (PLA)/chitosan (CS) nano scaffolds loaded cod liver oil (30%) were evaluated against DW in STZ induced diabetic rats. Topical application of PLA/CS nano scaffolds loaded cod liver oil (30%) exhibited increased in wound closure by 2.25-folds and 1.57 -folds in comparison to control and PLA/CS nano scaffolds alone treated groups respectively [297]. In one of the study, curcumin and zinc ion eutectic metal-organic frameworks-based scaffolds were evaluated against DW in STZ induced male C57 diabetic mice. The results revealed that curcumin and zinc ion eutectic metal-organic frameworks-based scaffolds exhibited about 3.18-folds and 2.28-folds increase in blood vessels and wound closure as compared to control groups respectively [298]. In another study, Yao et al., compared the wound healing potential of SDF-1 scaffolds against DW in STZ induced male SD diabetic rats with that by diabetic control and commercial wound dressing (Comfeel). It was found that SDF-1 scaffolds accelerated DW healing within 14 days by promoting 1.06-folds and 1.23-folds increase in wound closure as compared to diabetic control and Comfeel treated groups respectively [299]. In a study on the effect of dual growth factors (bFGF and VEGF) carrying NPs-based scaffolds against DW in STZ induced Swiss Albino diabetic mice. The results demonstrated that dual growth factors carrying NPs-based scaffolds exhibited about 1.06-folds and 1.22-folds increase in percentage wound closure as compared to bFGF and VEGF alone and diabetic control-treated groups respectively [300].

Various scaffolds used to treat DW are depicted in Table 5.

### 5.2. Nanofibers

Nanofibers are considered as the novel class of biomaterial that help in tissue rejuvenation and possess tunable features such as hydrophilic surface, suitable biocompatibility, controllable biodegradability and porosity [311,312]. They can be fabricated by using natural and synthetic polymers. The natural polymers include silk fibroin, cellulose, collagen, keratin, polysaccharides, gelatin, chitosan and alginate. The synthetic polymers include polyurethane (PU), poly (lactic acid) (PLA), polycaprolactone (PCL), poly (lactic-co-glycolic acid) (PLGA), poly (ethylene-co-vinyl acetate) (PEVA), poly (3-and hydroxybutyrate-co-3-hydroxy valerate) (PHBV) [312]. Some of the studies wherein nanofibers have been explored to treat DW are discussed in the subsequent sections.

Choi et al., investigated the effect of rhEGF-nanofibers at the dose of 10% w/w against DW in STZ induced female C57BL/6 mice. Topical application of rhEGF nanofibers accelerated DW healing within 14 days by 1.6- folds, 1.9-folds and 1.18-folds as compared to rhEGF/nanofibers (10% w/w), nanofibers alone and normal control groups respectively [313]. Similarly, wound healing potential of curcumin-PCL nanofibers were evaluated against DW in STZ induced male C57/B6 diabetic mice. Wound healing study revealed that the curcumin-PCL nanofibers treated group exhibited about 1.33-folds increase in wound closure as compared to PCL nanofibers alone treated groups [314]. In a study on the effect of Poly-N-Acetyl glucosamine (sNAG) membranes against DW in genetically modified diabetic Lep/r-db/db mice, it was found to exhibit about 1.2-folds increase in wound contraction as compared to non-treated groups. The granulation study revealed that sNAG membranes treated groups exhibited about 3-folds and 3.75-folds increase in granulation tissue as compared to non-treated groups and cellulose treated groups respectively [315]. In one of the study, potential of multiple growth factors (bFGF and EGF) based nanofibers were tested against DW in C57BL/6 diabetic mice. The results demonstrated that multiple growth factors-based nanofibers exhibited about 1.2-folds, 1.3-folds and 1.8-folds increase in percentage wound contraction as compared to bFGF nanofibers, EGF nanofibers and blank nanofibers treated groups respectively [316]. In another study, activity of multiple growth factors (VEGF, PDGF, bFGF and EGF) composite nanofibers were evaluated against DW in STZ induced male SD diabetic rats, it was found to exhibit 1.3-folds and 1.13-folds increase in wound contraction and the number

**Table 5**
List of scaffolds prepared till date to treat diabetic wounds.

| Sr. No. | Drug | Method of preparation | Animal model | Research highlights | References |
|---|---|---|---|---|---|
| 1. | Curcumin and Zinc ion | Electrospinning | Male C57 mice | • ↑ 3.18-folds wound healing rate in 15 days<br>• ↑ collagen deposition, re-epithelization and angiogenesis | [301] |
| 2. | Insulin and poly-D-L-lactide-glycolide | Coaxial electrospinning | SD rats | • 3.16-folds decrease in wound area in 14 days<br>• ↑ collagen deposition, epithelial cell proliferation and fibroblast migration | [302] |
| 3. | Polydopamine Biactive glass | Electrospinning | Diabetic mice | • 1.35-folds decrease in wound area within 14 days<br>• ↑ angiogenesis, re-epithelization and collagen deposition | [303] |
| 4. | Genipin and SDF-1 | Freeze-drying | Male SD rats | • 1.06-folds increase in wound healing in 14 days<br>• ↑ angiogenesis, collagen synthesis and neovascularization | [304] |
| 5. | Bone marrow MSCs | Electrospinning | Male C57BL/6 mice | • 2.5-folds increase in re-epithelization rate within 7 days<br>• ↑ ECM deposition, angiogenesis, re-epithelization and antiinflammatory action | [305] |
| 6. | Collagen-based Bcl-2-modified adipose-derived stem cells | – | Female db/db mice | • 1.92-folds increase in wound healing within 14 days<br>• ↑ neovascularization, angiogenesis, cellularity and re-epithelialization | [306] |
| 7. | Timolol | – | Db/db mice | • 1.59-folds increase in re-epithelization rate within 14 days<br>• ↓ MMP-9 | [307] |
| 8. | Bilayered fibrin/poly(ether) urethane scaffolds loaded with platelet lysate | Combined apparatus | Male db/db mice | • 3.47-folds decrease in wound area with 14 days<br>• ↑ re-epithelization and collagen deposition | [308] |
| 9. | 2,2,6,6-tetramethyl-1-piperidinyloxy)/ Sacchachitin | Mechanical disintegration | SD rats | • DW healing within 14 days<br>• ↑ neovascularization, collagen deposition and fibroblast migration | [309] |
| 10. | Poly-3- hydroxybutyrate and gelatin | Electrospinning | Male Wistar rats | • 7.5-folds decrease in wound area within 14 days<br>• ↑ collagen synthesis, cell attachment and proliferation | [310] |

of blood vessels at the site of injury within 6 weeks as compared to diabetic control groups [317]. Similarly, Antibacterial activity of silver-containing nanofibres were evaluated against DW in STZ induced male Swiss albino diabetic mice. The results of the study showed that silver-containing nanofibres demonstrated increase in percentage healing factor by 1.1-folds and 1.2-folds as compared to AgNPs and insulin-treated groups [318]. In one of the study, Mohammadi et al., compared the wound healing potential of curcumin-loaded poly(ε-caprolactone) (PCL)/gum tragacanth (GT) (PCL/GT/Cur) nanofibers against DW in STZ induced male SD diabetic rats where they observed 5-folds increase in wound closure as compared to diabetic control groups indicated wound healing potential of the formulation [319]. In another study, effect of heparin mimetic peptide (GAG-PA/KP) nanofibers were evaluated against DW in STZ induced male SD diabetic rats, it was found to exhibit about 1.33-folds increase in percentage wound closure as compared to control groups. Additionally, it was observed from the study that GAG-PA/KP treated groups showed about 1.28-folds increase in granulation tissue per unit area in comparison to diabetic control groups [320]. Similarly, wound healing potential of CuNPs-yeast-carbon nanofibers were tested against DW in female Wistar diabetic rats. The results revealed that CuNPs-yeast-carbon nanofibers exhibited about 1.01-folds, 1.09-folds and 1.28-folds increase in percentage wound contraction as compared to CuNPs-carbon nanofibers, carbon nanofibers and control groups respectively [243]. In another study, Grip et al., compared the wound healing potential of β-glucan-loaded nanofibers against DW in male diabetic db/db mice with that by fiber carrier. It was observed from the study that β -glucan-loaded nanofibers exhibited about 3.5-folds decrease in open wound area within 24 days in comparison to fiber carrier treated groups [321]. In a study on the effect of neurotensin-loaded poly-lactide–polyglycolide/cellulose nanocrystals (PLGA/CNC) composite nanofiber membranes against DW in adult male Wistar rats. Topical application of neurotensin loaded PLGA/CNC composite nanofiber accelerated wound healing within 14 days by 5.5-folds in comparison to diabetic control groups [322]. In one of the study, activity of nanofiber-expanded human $CD34^+$ cells were tested against DW in STZ induced NOD/SCID diabetic mice. The results revealed that nanofiber-expanded human $CD34^+$ cells exhibited 1.3-folds, 2.1-folds and 2.8-folds increase in percentage wound contraction, vascular density and collagen density as compared to $CD34^+$ cells therapy alone treated groups respectively [323]. In another study, effect of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) co-loaded sacchachitin nanofibers (SCNF) were evaluated against DW in STZ induced SD diabetic rats, it was found to exhibit 5.5 days and 2.5 days faster-wound healing in comparison to gauze and hydrogel treated groups respectively [307]. Similarly, potential of gelatin (GEL)-bacterial cellulose (BC)-glibenclamide (Gb) nanofibers and GEL-BC-metformin (Met) nanofibers were evaluated against DW in male SD diabetic rats. The wound healing study revealed that GEL-BC-Gb nanofibers exhibited about 1-fold, 1.6-folds and 1.9-folds decrease in wound area as compared to GEL-BC-Met, GEL-BC and diabetic control respectively. In addition, anti-inflammatory study demonstrated that GEL-BC-Gb nanofibers treated groups showed about 2.1-folds, 1.6-folds and 1.1-folds decrease in TNF-α levels as compared to diabetic control, GEL-BC nanofibers and GEL-BC-Met nanofibers treated groups respectively [324]. In a study on the effect of sesamol-cellulose acetate (CA)/zein composite nanofibers (H) at a dose of 5% w/v against DW in STZ induced male C57BL/6J diabetic mice. It was observed from the study that H treated groups exhibited about 1.25-folds, 1.66-folds and 1.02-folds increase in percentage wound closure within 9 days as compared to placebo nanofibers (M), diabetic control groups (S) and sesamol-CA/zein nanofibers (2% w/v) (L) treated groups [325]. Similarly, Samadian et al., compared the collagen density of cellulose acetate/gelatin/berberine (CA/Gel/Beri) nanofibers against DW in STZ induced adult Wistar rat model with that by sterilized CA/Gel and negative control groups. The results revealed that CA/Gel/Beri nanofibers accelerated DW healing within 16 days by showing 1.23-folds and 3.01-folds increase in collagen density as compared to sterilized CA/Gel and negative control groups respectively [326]. In a study on the effect of *Malva sylvestris* extract-based nanofibers against DW in STZ induced male Wistar diabetic rats. Topical application of *Malva sylvestris* extract-based nanofibers accelerated DW healing by promoting myofibroblasts contraction at the site of injury. Additionally, it was observed from the study that *Malva sylvestris* extract nanofibers exhibited about 2.9-folds increase in percentage wound closure as compared to gauze treated groups [327]. Activity of oxygen-generating polycaprolactone-sodium per carbonate (PCL-SPC) nanofibers were evaluated against DW in STZ induced male SD diabetic rats. On the 27th day, PCL-SPC nanofibers exhibited about 1.05-folds and 1.28-folds increase in wound closure as compared to control and PCL + control-treated groups respectively [328]. In another study, effect of desferrioxamine (DFO) nanofibers against DW in STZ induced diabetic rats, it was found to exhibited 1.4-folds increase in percentage wound closure as compared to diabetic control groups [329]. In another study, Razzaj et al., compared the wound healing potential of cephradine (Ceph)-loaded gelatin (GE)/polyvinyl alcohol (PVA) electrospun nanofibers against DW in male NcZ10 diabetic mice with that by Ceph treated groups. The results revealed that on the 11th day, Ceph-loaded GE/PVA) electrospun nanofibers exhibited about 1.87-folds decrease in percentage wound areas compared to Ceph treated groups [330].

### 5.3. Nanocomposites

Nanocomposite system is consisting of NPs encapsulated in a matrix such as a nanofiber, hydrogel, foam, nanocrystals and films. These are popularly used in wound dressings for enhanced wound healing. These nano-based dressings possess higher porosity (surface to volume ratio). In addition to this, their structure causes stimulation of the topographic appearance of ECM that allows attachment and spreading of fibroblast and keratinocytes. Thus, it facilitates collagen synthesis and reepithelization of the wounds [331,332]. The various nanocomposites used against DW are discussed in the subsequent sections.

Activity of viscose/silver/alginate/nicotinamide/calcium (Vis/AgA167NPs/ALG/NIC/$CaCl_2$) nanocomposites was evaluated against DW in STZ induced diabetic rabbits. It was observed from the study that Vis/Ag-167NPs/ALG/NIC/$CaCl_2$ treated groups exhibited about 1.51-folds and 1.29-folds increase in percentage wound closure as compared to Vis/Ag-NPs/ALG and Vis/Ag-NPs/ALG/NIC treated groups respectively [333]. In another study, effect of bioactive glass (BG)/patterned electrospun membrane (PEM) nanocomposite against DW in STZ induced female C57/BL6 diabetic mice. On the 13th day, BG/PEM nanocomposites exhibited about 1.40-folds and 1.42-folds increase in wound contraction as compared to PEM and control groups respectively [334]. In another study, wound healing activity of reduced graphene oxide (rGO)-isabgol (Isab) nanocomposites were evaluated against DW in STZ induced male Wistar rats, it was found to exhibit DW healing within 20 days by 1.49-folds as compared to diabetic control groups [335]. In a study on the effect of AuNPs–calreticulin nanocomposites against DW in STZ induced male BALB/C mice. Topical application of AuNPs–calreticulin nanocomposites accelerated DW healing within 20 days by promoting collagen deposition, re-epithelization, keratinocytes and fibroblasts migration at the site of injury. On the 20th day, AuNPs–calreticulin nanocomposites exhibited about 1.11-folds, 1.08-folds and 1.07-folds increase in wound closure as compared to PBS, insulin and AuNPs treated groups respectively [231]. Similarly, activity of edaravone loaded alginate-based nanocomposite hydrogel were evaluated against DW in STZ induced male C57BL/6J mice where they exhibited 1.58-folds increase in wound contraction as compared to diabetic control groups [173]. In another study, effect of iron (Fe)-copper (Cu) nanocomposite were evaluated against DW in STZ induced Wistar albino diabetic rats, it was found to exhibit about 1.1-folds and 2-folds decrease in wound area in comparison to antibiotics and iodine solution treated groups respectively. Additionally, it

was observed from the study that Fe–Cu nanocomposites showed a 1.3-folds and 1.1-folds decrease in IL-1 β level as compared to iodine solution and antibiotic-treated groups respectively [336]. In one of the study, Li et al., compared the wound healing effect of polyethylene glycol diacrylate (P)/sodium alginate (A)/bioactive glass nanoparticles containing copper (BC) scaffolds (PABC scaffolds) against DW healing in male ICR mice with that by PAB and PA treated groups. Topical application of PABC scaffolds accelerated DW healing within 21 days by promoting angiogenesis, collagen deposition and neovascularization at the wound site. On the 21st day, PABC scaffolds exhibited about

**Table 6**
Clinical trials carried out till date for various therapeutics used to treat diabetic wounds.

| Sr. No. | Drug | Delivery system | No. of patients | Research outcome | References |
|---|---|---|---|---|---|
| 1. | CT-102 activated platelet supernatant | – | 13 | 1.28-folds decrease in ulcer area as compared to placebo-treated groups | [339] |
| 2. | Repifermin | – | 94 | 1.41-folds increase in percentage wound closure as compared to placebo-treated group | [340] |
| 3. | Pomegranate | Extract | 60 | Promoted wound healing by showing antibacterial, antioxidant and neovascularization at the wound site | [341] |
| 4. | Acellular biomaterial derived from pig small intestine submucosa (OASIS) | Matrix | 73 | 1.49-folds increase in wound closure as compared to marketed formulation (Regranex gel). | [342] |
| 5. | Connexin43-based peptide | Hydrogel | 92 | 1.26-folds increase in mean per cent wound closure within 12 weeks | [343] |
| 6. | Autologous platelet-rich plasma | Gel | 129 | 1.59-folds increase in wound closure as compared to control groups | [344] |
| 7. | Nitric oxide | Patch | 90 | – | [345] |
| 8. | Protease-modulating matrix and autologous growth factors + collagen biomaterials | – | 54 | 1.59-folds decrease in ulcer depth within 8 weeks as compared to collagen biomaterials | [346] |
| 9. | Mucopolysaccharide + chitosan | Dressing | 85 | 4.5-folds increase in wound closure as compared to gauze treated groups | [347] |
| 10. | Bemiparin | – | 70 | 1.54-folds increase in ulcer healing rate as compared to placebo-treated groups | [348] |
| 11. | Microcyn Rx | Superoxidized solution | 67 | 1.65-folds increase in wound closure as compared to oral levofloxacin + saline-treated groups | [349] |
| 12. | HYAFF | Scaffolds | 180 | 1.16-folds increase in wound closure as compared to the control group | [350] |
| 13. | Dehydrated human amniotic membrane allografts | – | 25 | 11.5-folds increase in wound healing rate compared to SOC | [351] |
| 14. | Granulocyte stimulating factor mobilized peripheral blood $CD34^{+}$ cell | – | 5 | The maximum time taken by the patient to heal the wound was 26 weeks. All the patients were relieved from pain after the treatment. | [352] |
| 15. | Platelet | Gel | 117 | 1.26-folds increase in wound closure as compared to control group | [353] |
| 16. | Clostridial collagenase | Ointment | 55 | Promoted wound healing by 1.11-folds as compared to placebo-treated groups. | [354] |
| 17. | Honey | Dressings | 348 | 1.32-folds increase in DW healing within 18 days | [355] |
| 18. | Human acellular dermal matrix | – | 168 | 1.16-folds increase in wound healing rate as compared to conventional care | [356] |
| 19. | Flaxseed oil omega-3 fatty acids | – | 60 | 1.8-folds decrease in ulcer width as compared to placebo-treated groups | [357] |
| 20. | Zinc supplementation | – | 60 | 1.07-folds decrease in ulcer length within 12 weeks as compared to placebo-treated groups | [358] |
| 21. | Silver | Nanoparticles | 2 | Accelerated diabetic wound healing within 25 days due to re-epithelization and antimicrobial action | [230] |
| 22. | Copper | Nanoparticles | 1 | Healed DFU within 3 months by showing epithelization and antibacterial action | [241] |
| 23. | Recombinant human epidermal growth factor | Spray | 167 | 1.46-folds increase in healing rate as compared to placebo-treated groups | [359] |
| 24. | Cryopreserved placental membrane | – | 26 | 65.4% patients showed wound closure within 5 weeks | [360] |
| 25. | Sodium Alginate | Hydrogel | 7 | In the 12th week patients showed a remarkable reduction in DFU | [361] |
| 26. | Platelet-rich fibrinogen | 3D printed scaffold | 1 | DW healing within 14 days due to re-epithelization and neo-granulation | [362] |
| 27. | Allogeneic Adipose-Derived Stem Cell | Hydrogel | 59 | Accelerated diabetic wound healing within 12 weeks and the formulation was biocompatible | [363] |
| 28. | Phenytoin | Nanostructured lipid carriers | 27 | Promoted angiogenesis, neovascularization and collagen deposition | [207] |
| 29. | Aloe vera/Plantago Major | Gel | 40 | Healed the wound within 4 weeks and gel showed no side effects | [364] |
| 30. | Erythropoietin | Hydrogel | 20 | Promoted angiogenesis, re-epithelization, proliferation and differentiation of keratinocytes at the site of injury | [365] |
| 31. | Cerium dioxide | Nanoparticles | 1 | Increased antimicrobial, anti-inflammatory and antioxidant effect | [250] |
| 32. | Esmolol Hydrochloride | Gel | 350 | DW healed within a period of 12 weeks | [366] |
| 33. | rhEGF | – | 610 | Healed DW within 12 weeks | [367] |
| 34. | Hypothermically stored amniotic membrane (HSAM) | Membrane | 76 | HSAM treated groups exhibited about 60% reduction in wound area as compared to standard of care (SOC) | [368] |
| 35. | *Quercus infectoria* | Solution | 56 | 1.20-folds increase in wound closure within 8 weeks as compared to the control group | [369] |
| 36. | Cu/TiO2–SiO2 | Nanogel | 1 | DFU got healed completely within 10 months due to re-epithelization and anti-inflammatory action | [370] |
| 37. | Quercetin and oleic acid | Nanohydrogel | 56 | Increased wound contraction rate by promoting antioxidant and antimicrobial action | [174] |
| 38. | Plerixafor | S.C injection | 26 | Only 38% of patients showed wound healing and the trial terminated | [371] |
| 39. | Omega-3-rich fish skin grafts | – | 49 | 2.09-folds increase in wound healing rate as compared to SOC | [372] |

1.5-folds and 1.63-folds increase in wound closure as compared to PAB and PA treated groups respectively [337]. In a study on the effect of methacrylated kappa-carrageenan (KaMA)-polydopamine (PD) modified ZnO/L-glutamic acid nanocomposite spray dressings against DW in female Wistar diabetic rats. Wound healing study showed that KaMA-PD modified ZnO/L-glutamic acid nanocomposite spray dressings treated group showed increase in wound contraction by 1.25-folds in comparison to control groups [338].

Various clinical as well ongoing clinical trials that have conducted recently on DW are depicted in Table 6 and Table 7. A list of patents that have been implicated for DW healing are given in Table 8.

## 6. Conclusion

The treatment of DW is still a major challenge due to the inability of the current therapies to provide a favorable environment for tissue rejuvenation. However, advancement in recent years has provided new insights in the field of DW healing. Taking these things into consideration, the present manuscript emphasized the advancement in the conventional and novel therapeutic moieties using NDDS and nanomaterials. A series of NDDS that have been designed to treat DW include liposomes, exosomes, niosomes, transfersomes, NE, nano hydrogel, SLNs, NLCs, Metallic NPs, Polymeric NPs, dendrimers, hydrogel nanotubes and wafers. These nanocarriers provide sustained release, protection of the drug from the enzymatic degradation, target specificity and enhancement in the solubility. Owing to these benefits, offered by NDDS, the therapeutic agents loaded in them provide enhanced neo-vascularization, re-epithelization, antibacterial activity, collagen deposition and angiogenesis. The study also entailed the role of nanomaterials alone and in combination with NDDS to effectively treat DW. The nanomaterials covered in this article include scaffolds, nanofibers and nanocomposites. The advantages of nanomaterials such as biocompatibility, biodegradability, renewability, retention property at the wound site and less toxicity make them unique materials to be used for DW healing. Despite these enormous potentials, these delivery systems are associated with some limitations such as tedious preparation procedure, lack of international standards and less availability of evaluation methods for toxicological studies. The major issue is related to achieving a good in vitro-in vivo correlation because the in vitro experiments are performed in a controlled environment. In contrast, there are many biological barriers that impediment the passage of formulations under in vivo condition. Further, the physicomechanical and

**Table 7**
Patents filed till date for various therapeutics used to treat diabetic wounds.

| Sr. No. | Therapeutic moiety | Delivery system | Patent no. | Key Claims/finding | Reference |
|---|---|---|---|---|---|
| 1. | Platelet-rich plasma | Gel | ES2600793T3 | Accelerated wound healing by promoting increase in granulation tissue number, collagen deposition and vascularization | [373] |
| 2. | *Ulmus macrocarpa* | Extract | KR20080071385A | Accelerated wound healing by promoting immunomodulation, granulation tissue and anti-inflammatory action at the wound site | [374] |
| 3. | Stem/progenitor cells | Scaffolds | CN101330935B | Complete healing of DW within 26 days | [375] |
| 4. | EGF | Cream | US7517528B2 | Exhibited wound healing within 3-weeks | [376] |
| 5. | Adipsin | Solution | US7638484B2 | Increased epidermal migration and epidermal closure | [377] |
| 6. | Exogenous polypeptide (KGF-2) | Gel | US20180311414A1 | Helped in wound healing by showing antibacterial action | [378] |
| 7. | HIF-1 modulator | Gel | US10751304B2 | Promoted wound healing by showing angiogenesis and neovascularization at the site of injury. Additionally, HIF-1 modulator treated groups showed 2 days faster wound healing as compared to control group | [379] |
| 8. | Treprostinil | Solution | US8563614B2 | In this study, 10 patients with peripheral arterial disease were considered. The results revealed that out of 10 patients, 5 patients showed no sign of pain, 2 patients cured fully and 2 patients partly cured. | [380] |
| 9. | Collagen | Biofabric | US7928280B2 | Out of 45 patients, 15 patients showed complete wound healing | [381] |
| 10. | Adipose derived stem cells | Injection | US8105580B2 | Accelerated DW healing within 7 weeks and also promoted hair growth at the wound site | [382] |
| 11. | Cellulose/nano-silver sodium alga acid composite membrane dressings | Composite | CN103041438B | Accelerated wound healing by showing antibacterial action and exudate absorbing property | [383] |
| 12. | Ulcer recovering oil (Dragon's blood, bletilla striata, frankincense, myrrh and catechu) | Oil | CN103479883B | Promoted 75% of the wound healing within 14 days | [384] |
| 13. | Elastomeric matrix element (A61F2/02) | Matrix | US9050176B2 | Accelerated wound healing by promoting angiogenesis and collagen deposition at the wound site | [385] |
| 14. | Poly-N-acetylglucosamine | Nanofibers | US10561677B2 | Exhibited wound healing by showing anti-inflammatory and antibacterial action against S. aureus | [386] |
| 15. | Alimentary Protein-Based Scaffolds | Scaffolds | US8790921B2 | Accelerated wound healing by promoting angiogenesis, collagen deposition, hydration and antibacterial action at the wound site | [387] |
| 16. | Dichlorine monoxide | Solution | US20170049813A1 | Helped in wound healing by antibacterial action | [388] |
| 17. | Borate glass-based particles | Fibers | US9486554B2 | Helped in wound closure after 22 days by promoting angiogenesis and antibacterial action | [389] |
| 18. | Silver | Hydrogel | US9327029B2 | Accelerated wound healing by promoting hydration, antibacterial action and relieved pain | [390] |
| 19. | Anti-connexin polynucleotide | Gel | US20170240905A1 | Healed venous ulcer within one month by showing anti-inflammatory action | [391] |
| 20. | Nanofibrillary polysaccharide | Hydrogel | DK2958599T3 | Maintained hydration, epithelization, contraction and antibacterial action at the site of injury | [392] |
| 21. | Vesicles comprising EGF | Liposomes | US20180015145A1 | Promoted wound healing by showing epithelization | [393] |
| 22. | CRM1 inhibitor | Hydrogel | EP2968278B1 | Accelerated DW healing within 14 days | [394] |
| 23. | *miR-92* inhibitor | Gel | US10280422B2 | Promoted wound healing by promoting angiogenesis, granulation and re-epithelization | [395] |
| 24. | Carnosine | Injection | CN105189531B | Promoted DW healing by providing strength to ECM, potentiate collagen deposition and increase insulin like growth factor-1 | [396] |
| 25. | Bismuth-thiols | Nanosuspension | US10835510B2 | Accelerated wound healing by promoting migration of keratinocytes and fibroblasts at the site of injury | [397] |

**Table 8**
Ongoing clinical trials till date for various therapeutics used to treat diabetic wounds.

| Phase | Intervention | Condition | No. of participants | Allocation | Study start date | NCT number | Reference |
|---|---|---|---|---|---|---|---|
| NA | Lipoaspirate Injection | Investigate the effect of Lipoaspirate injection in diabetic lower extremity wound | 250 | Randomized | February 2009 | NCT00815217 | [398] |
| Phase2 | Isoniazide | Investigated the safety and efficacy of isoniazide on DFU | 60 | Randomized | July 2011 | NCT01342497 | [399] |
| Phase1 | Esmolol hydrochloride gel | Investigated the efficacy of esmolol hydrochloride gel on DFU | 50 | Randomized | February 2014 | NCT01113515 | [400] |
| Phase4 | DermaPure | Study the effect of DermaPure against DFU | 50 | Randomized | August 2014 | NCT02081352 | [401] |
| NA | Cold plasma therapy | Investigate the effect of cold plasma therapy against DFU | 65 | Randomized | August 17, 2016 | NCT04205942 | [402] |
| Phase1 | Autologous ADSC stem cells in fibrin gel | Study safety and efficacy of autologous ADSC stem cells in fibrin gel against DFU | 20 | Non-Randomized | September 3, 2018 | NCT03865394 | [403] |
| – | *miR-200b and miR-21* | Study the effect of *miR-200b* and *miR-21 in DW* | 124 | No | August 12, 2019 | NCT02581098 | [404] |
| Phase3 | Platelet-rich plasma-fibrin glue in combination with vitamin E and C | Reduce oxidative stress by co-administration of Platelet-rich plasma-fibrin glue with vitamin E and C | 24 | Randomized | August 28, 2019 | NCT04315909 | [405] |
| – | Platelets rich plasma | Investigated the efficacy of platelets rich plasma against DFU | 60 | – | July 30, 2019 | NCT03890172 | [406] |
| – | Negative pressure wound therapy | Investigate the effect of negative pressure wound therapy against DFU | 40 | – | November 2019 | NCT04093635 | [407] |
| NA | Omega 3 wound fish skin graft | To investigate the effect of omega3 wound fish skin graft against DFU | 100 | Randomized | July 31, 2019 | NCT04133493 | [408] |
| NA | Kerecis Omega3 wound dies | Investigated the efficacy of Kerecis Omega3 wound dies in DFU | 229 | Randomized | July 2, 2020 | NCT04537520 | [409] |
| – | Biofilm modified macrophage | Study the effect of biofilms on DW | 28 | Non-Probability Sample | February 1, 2020 | NCT03271580 | [410] |
| NA | Topical Oxygen Chamber | Investigate the effect of oxygen therapy on DW | 40 | Randomized | February 1, 2020 | NCT02313428 | [411] |
| Phase2 | Donepezil tablets | Investigate the effect of Donepezil tablets on DW | 20 | Randomized | August 30, 2020 | NCT04505670 | [412] |
| Phase1 | Treprostinil iontophoresis | Investigate the effect of treprostinil iontophoresis against DFU | 60 | Randomized | January 28, 2020 | NCT03654989 | [413] |
| NA | Kelulut honey | Investigate the effect of Kelulut honey vs conventional dressings on DW | 76 | Randomized | June 2021 | NCT04849143 | [414] |
| Phase2 | DFO gel | Investigate the effect of DFO gel on DFU | 174 | Randomized | August 30, 2021 | NCT03137966 | [415] |
| Phase1 | Nitric oxide foot bath | Investigated the safety and efficacy of nitric oxide solution delivered as a foot bath to treat DFU | 40 | Randomized | February 23, 2021 | NCT04755647 | [416] |
| Phase2 | Folic acid | Investigate the efficacy and safety of folic acid against DFU | 30 | Randomized | March 1, 2021 | NCT04723134 | [417] |
| NA | Celliant socks | Investigate the effect of Celliant socks against DFU | 254 | Randomized | June 1, 2021 | NCT04709419 | [418] |
| NA | Hybrid scale fiber matrix | Investigate the effect of hybrid-scale fiber matrix against DFU | 40 | Randomized | May 5, 2021 | NCT04918784 | [419] |
| Phase3 | Umbical cord blood mononuclear cell gel | To investigate the effect of umbical cord blood mononuclear cell gel against DFU | 40 | Randomized | March 30, 2021 | NCT04689425 | [420] |

storage instability, toxicity, poor drug loading and yield, poor site specificity and expensive manufacturing procedures restrict the use of nanocarriers/nanomaterials clinically. However, it is an in-escape trend for the researcher to further harness the potential of these delivery systems. Outlooking at the technical problems thereby, NDDS provide tangible advantages to improve patient compliance. In future, one should look for overcoming the aforementioned barriers and regulatory issues related to NDDS so that their better translation in market should be achieved. The conduct of exploratory clinical trials could further help in resolving these issues. These delivery systems are bound to establish the most favorable and economic therapies to treat the DW in the future.

## Declaration of competing interest

Declared none.

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