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# Micro and nanoformulations of insulin: new approaches

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**ABSTRACT**

Diabetes mellitus is a metabolic disease, which in a severe form needs daily subcutaneous injections of insulin to prevent symptoms, especially diabetic foot ulcers (DFU). However, the emergence of multidrug-resistant (MDR) bacteria in diabetic wounds can lead to complications. The infection of DFUs by MDR bacteria can lead to biofilm formation, and can increase the risk of lower-limb amputation up to 80%. Insulin hormone can activate angiogenesis, migration and proliferation of keratinocytes, and lead to the rapid maturation and closure of wounds. Insulin can promote protein and lipid synthesis, inactivate $NFk\beta^{p50/p65}$, as well as altering cytokine dynamics. However, the uncontrolled and burst release of insulin reduces the therapeutic effects after topical delivery to wound tissues. Therefore a novel strategy for insulin delivery involves various polymeric and liposomal formulations on the micro or nanoscale, for sustained and controlled release of this hormone. In addition, improved sensitivity and selectivity are two major advantages (compared to free insulin) reported for nanoformulations of insulin. This review summarizes the current knowledge about the efficacy and limitations of these formulations to treat infected chronic wounds, especially in diabetics.

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## 1. Introduction

Diabetes mellitus is the 8th most common fatal disease, which can lead to peripheral neuropathy, chronic wounds and local tissue infection [1, 2]. Wounds, especially infected chronic wounds such as diabetic foot ulcers (DFUs), are resistant to treatment owing to poor tissue regeneration, and the presence of pathogens in the wound site [3-6]. The four continuous stages of wound healing, hemostasis, inflammation, proliferation, and remodeling are all affected by hyperglycemia (high blood sugar), weak circulation, and nerve damage in diabetic wounds [7, 8]. Additionally, colonization and formation of biofilms in the wound by multidrug resistant (MDR) bacteria and fungi can inhibit the wound healing process [9-12]. Biofilm formation by MDR bacteria and fungi within DFUs can increase the risk of lower-limb amputation by up to 80% in diabetic patients, because antibiotics are generally ineffective [9, 13]. Antibacterial, antifungal and wound healing agents such as growth factors may be topically applied to DFUs using various formulations, including ointments, creams, hydrogels, wound dressings, or wound fillers to accelerate tissue regeneration in the wound [14, 15].

Insulin peptide can activate angiogenesis, the migration and proliferation of keratinocytes followed by rapid maturation and wound closure. Moreover, insulin can promote protein and lipid synthesis, and

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can inactivate NFkβ$^{p50/p65}$ resulting in altered cytokine dynamics and less inflammation (Figure 1) [16]. Insulin can promote cellular differentiation and growth by increasing the expression of protein kinase B and vascular endothelial growth factor (VEGF). Increased epithelialization in the wound site was observed after topical administration of insulin [17].

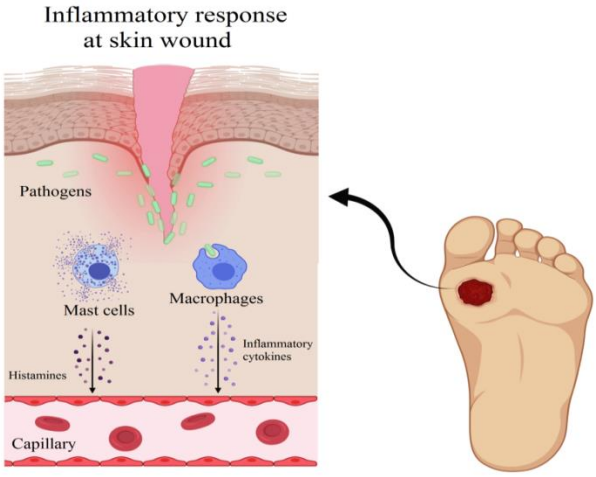


**Fig. 1**. Insulin can have anti-inflammatory activity by changing inflammatory cytokine dynamics (BioRender.com).

When insulin hormone is administered by injection, its activity in the wound site is destroyed by enzymatic degradation [18]. Therefore, controlled and sustained release of the hormone is required to achieve good results along with better patient compliance. Nanomaterials (NMs) possess special properties, such as large surface area to volume ratio (SA:V) and aspect ratio (AR) resulting from their smaller size (< 100 nm) relative to bulk material, and have opened a new window in biomedicine [19-22]. Biocompatibility, circulation half-life, solubility, and biodegradability are influenced by the type of micro or nanocarrier (Figure 2) [23-25]. Liposomal and polymeric micro or nano formulations prepared using biocompatible, bioavailable, and biodegradable components have produced better therapeutic results compared to conventional strategies [26, 27]. Moreover, nanoformulations have also been investigated as vehicles for oral delivery of insulin because they can protect the peptide from degradation in the stomach, and allow it to be absorbed in the small intestine. This review discusses the progress and challenges of recent developments in topical insulin delivery for wound healing.

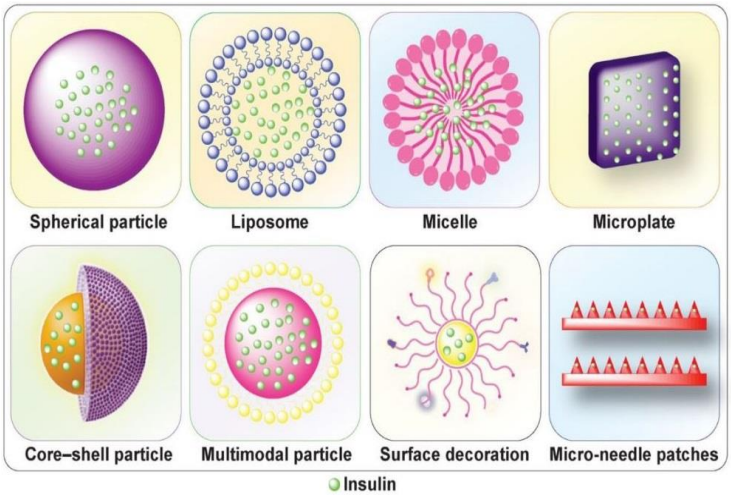


**Fig. 2.** Various micro or nano-delivery systems for loading or encapsulation of insulin [23].

## 2. Micellar and liposomal formulations

Micelles are unilamellar spherical vesicles formed from fatty acids or amphipathic polymers acting as surfactant molecules with hydrophobic tails and hydrophilic head groups. Wound healing aspects of growth factor (GF) delivery by nanoformulations was reviewed in our previous review [14].

Zhu et al described an approach to deliver both insulin and epidermal growth factor (EGF) for improved diabetic wound healing [18]. In a two-step process, a copolymer of poly (ethylene glycol)-b-poly [3-acrylamidophenylboronic acid-co-styrene] (PEG-b-P-PBA-co-St) was used to spontaneously produce micelles loaded with insulin (size of ~230 nm) followed by incorporation of EGF and the micelles into hydrogels composed of succinyl chitosan (SCS) and oxidized hyaluronic acid (OHA) with a size of 30~100 μm. The concentration of blood sugar was relatively reduced by this formulation, accompanied by accelerated wound healing after 12 days compared to gauze control group, attributed to sustained release of insulin from chitosan. It is worth pointing out that the antibacterial activity of white blood cells (WBCs) is weakened under hyperglycemia leading to slower healing of diabetic wounds [28].

The protection of insulin against degradation by peptidases is a complicated topic. Liposomal encapsulation could be employed for controlled and sustained release of insulin after topical delivery. In this regard, encapsulation of insulin in the core of

liposomes can be achieved by preparing them using a solution of insulin in phosphate buffered solution (PBS) at a concentration of 1 mg/mL. Liposomes composed of phosphatidylcholine (PC) and cholesterol (CH) with a diameter range of 219.45 - 365.7 nm were used to encapsulate insulin, where a higher PC:CH molar ratio demonstrated the best encapsulation efficiency up to 96.16%. Moreover, in aqueous dispersion, this formulation remained stable after storage for 6 months at 4°C [29].

### 3. Polymeric nanoparticle formulations

Both natural and synthetic polymers have been employed to produce nanoparticles (NPs) to encapsulate therapeutic agents such as insulin for topical delivery (Figure 3) [30]. Biopolymers such as cellulose and chitosan have gained much attention in the preparation of wound dressings owing to their biocompatibility and biodegradability under physiological conditions. Chitosan is a natural cationic polymer prepared by deacetylation of chitin $(C_8H_{13}O_5N)_n$, and shows antibacterial activity owing to its protonated amino groups. Slow degradation of this polymer can produce biocompatible amino sugar compounds under physiological conditions. Insulin was loaded in chitosan NPs at a concentration ratio of 1:2 mg/mL (with 22 µg/mL of insulin within chitosan NPs) to obtain insulin-chitosan NPs with polydispersity index (PDI), size, and Zeta potential of 0.4, 245.9 nm and 39.3 mV, respectively. These spherical NPs were stable for 56 days at 4 °C, and produced wound closure after 14 days in an animal model. Moreover, angiogenesis and VEGF were induced, and fibroblast migration was stimulated by the chemotactic activity of this formulation [17].

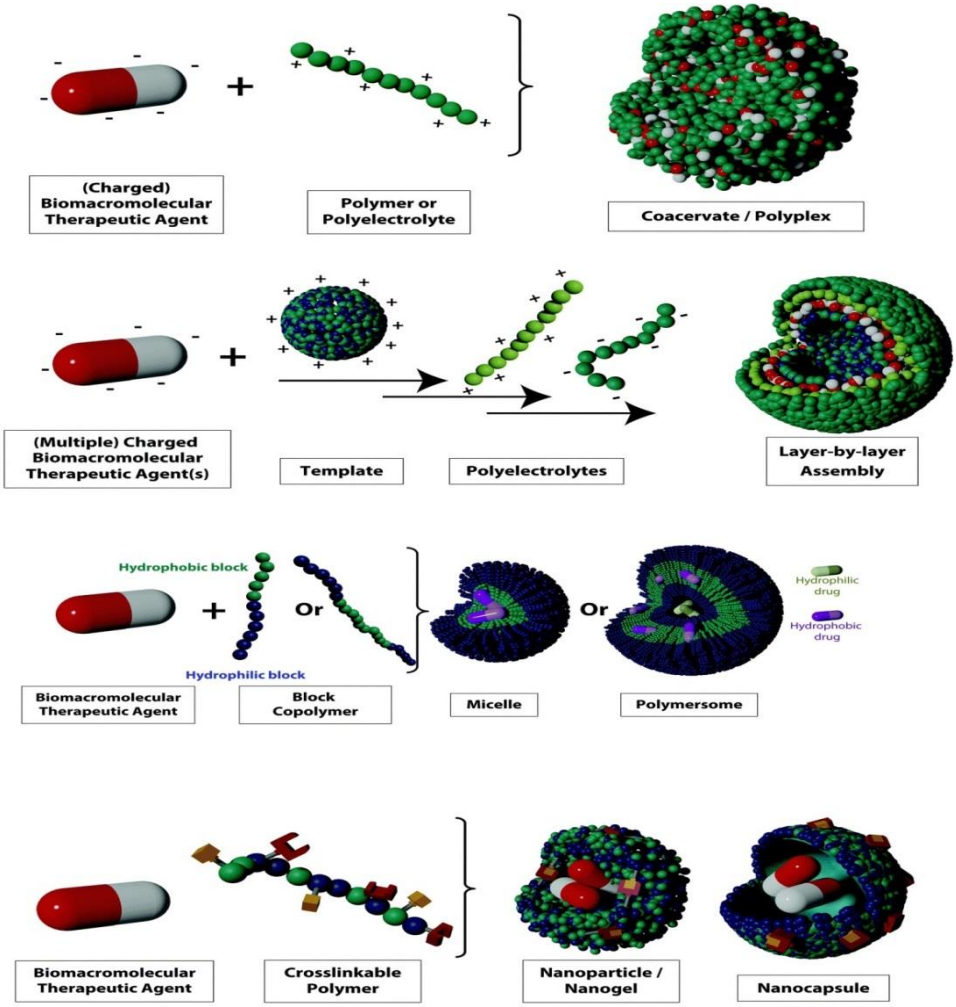


**Fig. 3.** Various strategies for the encapsulation of therapeutic agents in polymeric NPs. Preparation strategies include conjugation, polyplex/coacervate, layer-by-layer assembly. Micelles, polymersomes, nanoparticles, nanogels, nanocapsules can be prepared by covalent binding, electrostatic complexation of charged molecules, or physical encapsulation. (This open access article is licensed under a creative commons attribution 3.0 unported licence [30]).

The combination of synthetic polymers with appropriate mechanical properties with natural polymers is another strategy to prepare effective wound dressings [31-33]. Electrospun nanofibers composed of poly (ε-caprolactone) (PCL) plus collagen were prepared with a mean diameter of 812.68 nm and with loaded insulin (34.7 mg). When this dressing was applied to excisional wounds in rats there was complete closure after 14 days compared to 45% reduction of wound size in sterile gauze controls. In addition to improved mechanical strength, the histological results displayed significant formation of epidermal granulation tissue in treated groups relative to controls [34].

In a two-step process, recombinant human insulin was loaded into poly lactic-co-glycolic acid (PLGA) NPs, and these were encapsulated into polyvinyl alcohol (PVA)-borate hydrogel shells. PEGylation of the PLGA NPs at 5% w/w in this formulation (average size 202.6 nm) was compared relative to a control group without PEG (297.8 nm). Drug loading, direct entrapment efficiency and indirect entrapment efficiency for PEGylated insulin-loaded PLGA NPs were respectively 33.86 µg/mg, 67.7 %, and 69.5 % compared with 28.47 µg/mg, 56.9 % and 69.1 % for the non-PEGylated formulation. In comparison with diabetic wounds treated with free insulin, a shortened inflammatory phase and complete re-epithelialization after 16 days were found for this nanocarrier (Figure 4) [35].

Several benefits have been reported for PEGylation of micro and nanoformulations, including increased drug solubility, reduced immunogenicity, decreased dosage frequency and enhanced serum half-life in physiological conditions. Therefore PEGylation is as an important strategy in the topical delivery of insulin [36]. In another study, NPs were prepared from the anionic polysaccharide alginate modified by the attachment of octa-arginine R8 (cell penetrating peptide), with an average diameter of 300 nm for increasing the intestinal delivery of insulin. In addition to the desired hypoglycemic effect of these NPs, the cellular uptake mode of these NPs was based on energy dependent endocytosis pathway providing 50.75% of the cellular uptake. In contrast, a lower cellular uptake of 47.96% was observed for these formulations without R8 [37].

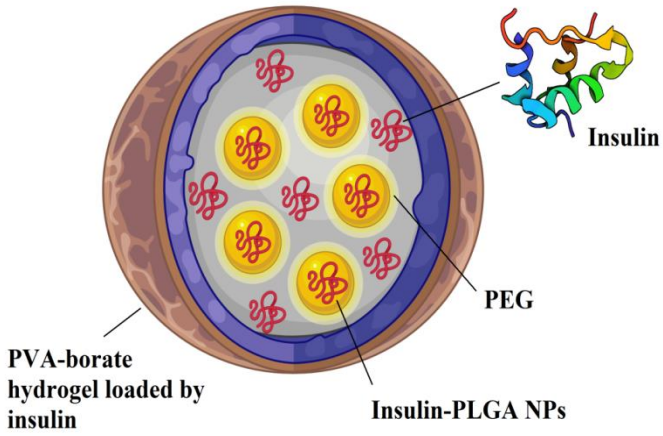


**Fig. 4.** Loading of insulin into PEGylated NPs and then into hydrogel shells to improve wound healing (BioRender.com; [35]).

## 4. Other nanocarriers

Various delivery systems composed of metal/metal oxide NPs or stem cell-derived exosomes, loaded with growth factors can be used to treat diabetic chronic wounds [38-40]. The combination of metal or metal oxide NPs with insulin could improve the therapeutic effects of these NPs inside the body. Silver (Ag) NPs can interact with biological macromolecules in different ways. AgNPs were coated with a 2 nm thickness layer of insulin around these NPs, as shown by unaltered amide-II and III and altered amide-I infrared absorption bands. In physiological conditions, proinflammatory cytokines were decreased (IL-6 and TNFα) while anti-inflammatory cytokine (IL-10) was increased, and accelerated wound healing in the remodeling phase was observed [2]. In contrast to non-diabetic wounds where the pro-inflammatory pathway promotes healing, in chronic diabetic wounds a persistent increase of pro-inflammatory cytokines with a low level of anti-inflammatory cytokines inhibits healing [41-43].

## 5. Conclusions

Diabetes mellitus is a metabolic disorder that needs daily subcutaneous injections of insulin. Although, it is known that insulin can promote wound healing, the best way to deliver the hormone is uncertain. Oral or topical delivery of insulin may be possible by using nanoformulations of this peptide hormone as a more efficient method to treat diabetic patients via improving the bioavailability of insulin. Improved

sensitivity and selectivity are two main advantage of insulin delivery by nanocarriers compared to free insulin. Preparation strategies for polymeric NPs include conjugation, polyplex/coacervate, and layer-by-layer assembly. Micelles, polymersomes, nanoparticles, nanogels, and nanocapsules can be prepared by covalent binding, electrostatic complexation of charged molecules, or physical encapsulation. Various types of wound dressings composed of metal/metal oxide NPs, stem cell-based therapies, and incorporating growth factors can be employed to treat diabetic chronic wounds. In the case of insulin-AgNPs, the balance between pro-inflammatory cytokines (IL-6 and TNFα) and anti-inflammatory cytokines (IL-10) can be affected, leading to accelerated wound healing in the remodeling stage.

**Study Highlights**

- Insulin can promote wound healing, the best way to deliver the hormone is uncertain.
- Oral or topical delivery of insulin may be possible by using nanoformulations of this peptide hormone as a more efficient method to treat diabetic patients.
- Micelles, polymersomes, nanoparticles, nanogels, and nanocapsules can be prepared by covalent binding, electrostatic complexation, or physical encapsulation.
- Various types of wound dressings composed of metal/metal oxide NPs, stem cell-based therapies, and incorporating growth factors can be employed to treat diabetic chronic wounds.

**Abbreviations**

**AR:** Aspect ratio
**DFUs:** Diabetic foot ulcers
**EGF:** Epidermal growth factor
**GF:** Growth factor
**MDR:** Multidrug resistant
**NMs:** Nanomaterials
**NPs:** Nanoparticles
**OHA:** Oxidized hyaluronic acid
**PBS:** Phosphate buffered solution
**PC:CH:** Phosphatidylcholine-Cholesterol
**PCL:** Poly (ε-caprolactone)
**PDI:** Polydispersity index
**PEG-b-P-PBA-co-St:** Poly (ethylene glycol)-b-poly [3-acrylamidophenylboronic acid-co-styrene]
**PLGA:** Poly lactic-co-glycolic acid
**PVA:** Polyvinyl alcohol
**SA:V:** Surface area to volume ratio
**SCS:** Succinyl chitosan
**VEGF:** Vascular endothelial growth factor

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**Conflict of interest**

The authors declare that they have no conflict of interest.

**Ethical approval**

This article does not contain any studies with animals or human participants performed by any of the authors.

**Authors' contribution**

MA: conceptualization and preparing the first drafting; MRH, FM, EA, HK, and IRAM: revising the manuscript.

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