REVIEW ARTICLE

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VITAMIN E AND SOLID LIPID NANOPARTICLES (SLNS): PARTNERS IN DIABETIC WOUND HEALING.

VITAMINA E E NANOPARTÍCULAS LIPÍDICAS SÓLIDAS (NLSS): PARCEIRAS NA CICATRIZAÇÃO DA FERIDA DIABÉTICA

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ABSTRACT

Diabetic foot affects 4 to 10% of diabetic patients per year and has a high rate of amputation and mortality (39-80%). Diabetes Mellitus (DM) is among the chronic diseases that increase reactive oxygen species (ROSs) production via glucose oxidation. The use of antioxidants associated with solid lipid nanocarriers (SLNs) is a promising tool for treating poor diabetic healing. This literature review aims to present the impaired diabetic wound healing pathophysiological mechanism and how vitamin E acts to prevent and treat diabetic wounds. Vitamin E-encapsulated SLNs could accelerate the healing process.

Keywords: Diabetes; Wound; Vitamin E; Solid Lipid Nanocarriers (SLN); Oxidative Stress.

RESUMO

O pé diabético acomete de 4 a 10% dos pacientes diabéticos por ano, e apresenta um alto índice de amputação e mortalidade (39-80%). O diabetes mellius (DM) está dentre as doenças crônicas que aumentam a geração das espécies moleculares reativas de oxigênio (EROs) pela oxidação da glicose. O uso de antioxidantes associados a nanocarreadores lipídicos é uma ferramenta promissora no tratamento da cicatrização diabética deficiente. O objetivo dessa revisão de literatura é apresentar o mecanismo fisiopatológico da cicatrização diabética deficiente, e como a vitamina E atua na prevenção e tratamento da ferida diabética, assim como os nanocarreadores lipídicos sólidos (NLS) associados a vitamina E podem auxiliar acelerando o processo de cicatrização deficiente da ferida diabética.

Palavras-chave: Diabetes; Ferida; Vitamina E; Nanocarreadores Lipídicos Sólidos (NLS); Estresse Oxidativo.

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INTRODUCTION

Chronic diabetic wounds occur in approximately 25% of patients with untreated diabetes. The "diabetic foot", as it is more commonly known, affects 4 to 10% of this population per year, with a high rate of amputation and mortality (39-80%). These lesions are characterized by epithelium and dermis loss, which can ultimately reach muscle and bone tissue. The regions most commonly affected by these types of wounds are the lower limbs and plantar and other surfaces subjected to repetitive pressure. Deformities (Charcot's foot) or limited joint mobility are common in diabetic foot [1].

Diabetic neuropathy, vascular diseases and ischemia are among the leading causes of this wound's appearance. The heterodimeric transcription factor hypoxia-inducible factor 1 (HIF-1), composed of HIF-1α and HIF-1β, plays a significant role in angiogenesis, metabolic changes, proliferation, migration, and cell survival. It has been reported that in the diabetic state, hyperglycemia destabilizes HIF-1α, resulting in functional repression, consequently inhibiting HIF-1-mediated signaling [1,2].

Additionally, it has been demonstrated that Diabetes Mellitus (DM) augments the production of reactive oxygen and nitrogen species (ROS and RNS, respectively) due to increased glucose oxidation [5]. Rises in ROS and RNS concentrations can eventually overwhelm the antioxidant defense system and cause oxidative stress [3,4]. Additionally, DM and oxidative stress can both aggravate the inflammatory processes [6].

The ROS-mediated reactions include lipid peroxidation, protein carbonylation and nucleic acid oxidation, among others. An overabundance of these modified biomolecules can activate and/or perturb normal metabolic pathways, leading to cell damage, depleted intracellular antioxidant defenses, and chronic oxidative stress [4,5]. Interestingly, activation of the hexosamine and advanced glycoxidation end product (AGE) pathways, which are involved in collagen degradation, and nuclear transcription factor kappa-B (NF-κB), which upregulates inflammatory cytokine production, are associated with the persistence of inflammatory cells and more significant ROS production [7,8].

Antioxidants are substances that slow or prevent oxidation of a substrate [9]. The oral use of antioxidants such as vitamins C and E, lipoic acid, and N-acetylcysteine has been shown to improve diabetic wound healing, with notable changes observed in extracellular matrix (ECM) synthesis, cytokine production and re-epithelialization [5, 10]. However, it should be pointed out that in 2011, the authors [11] reported increased mortality in women after prolonged antioxidant use. Therefore,

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the effects of long-term antioxidant supplementation need to be evaluated.

Vitamin E has eight stereoisomers, of which α-tocopherol is the most abundant form, with RRR-α-tocopherol exhibiting the highest biological activity. Its synthetic form is composed of a racemic mixture of all eight stereoisomers (all-rac-α-tocopherol) that form vitamin E [12]. Vitamin E is lipophilic, and it is preferentially stored in cell membranes. In the membrane, Vitamin E protects against internal and/or external oxidizing agents. In the present literature review, we found that studies evaluating plasma and tissue vitamin E concentrations in diabetic individuals reported conflicting results [4,10,12]. It is plausible that these discrepancies are at least partially due to bioavailability.

The development of new forms and technologies for drug administration is a challenge for researchers. One solution for improving drug delivery involves using nanotechnology to create materials, devices, and systems at the nanoscale [13]. Nanoparticles or nanocarriers have been shown to act as drug carriers and aid in diagnostic imaging [13]. These systems can improve bioavailability, stabilize bioactive agents [14], and target drugs, reducing toxicity [14, 15].

The nanometric scale delivery systems are classified into two general groups: a) Liquids: nanoemulsions and nanoliposomes, and b) Solids: lipid nanoparticles [solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs)], polymeric nanoparticles (nanospheres and nanocapsules) and nanocrystals [16]. Among these, SLNs have attracted considerable attention for cutaneous applications.

SLNs are colloidal systems derived from oil/water (O/W) emulsions created by simply replacing the oil with a solid lipid, which remains in this state at body temperature [17]. In the 1950s, SLN emulsions were introduced into the clinical routine as emulsions for parenteral nutrition. Currently, there is a second generation of SLNs, represented by NLCs. These systems were developed by blending a solid lipid with a liquid lipid at room temperature [17]. The second generation carriers have greater cargo capacity and better cargo retention during storage than SLNs [18]. The three SLN drug incorporation models are shown in Figure 1 and depend on their solubility (Figure 1).

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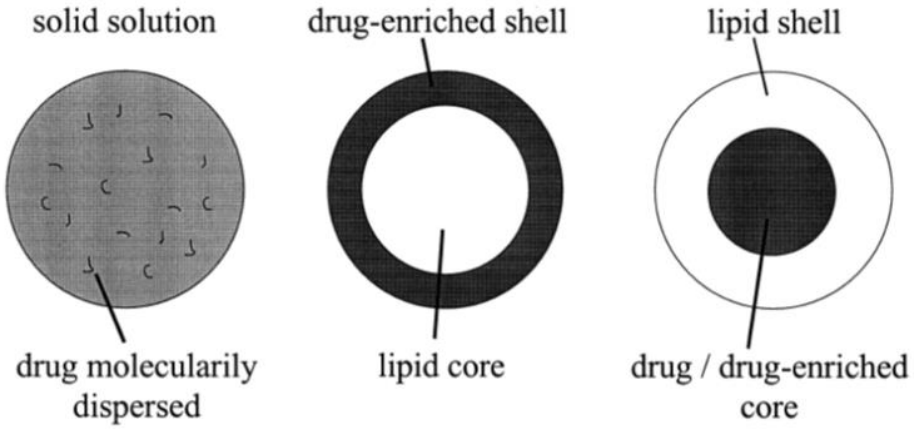
Figure 1 - Models of drug incorporation **into** Solid Lipid Nanoparticles (SLNs).



1. Solid solution model (left); 2. Casing model enriched with drugs, with lipid matrix (center); 3. Lipid shell model, with the drug enriching the matrix (right). Source: Muller et al. [17].

The development of drug-containing nanocarriers involves a series of pre-formulation studies aimed at obtaining truly nanotechnological formulations, with a nanometric particle size, adequate drug encapsulation efficiency, physical-chemical stability and biocompatibility. These features are fundamental to the optimization of the therapeutic action of nanoencapsulated bioactive substances [19,20].

METHODOLOGICAL APPROACH

The present study is a qualitative systematic review carried out from 2018 to 2019. We searched for articles on the Pubmed data platform published between 2000 and 2016. Article selection was based on the description of the molecular and pathophysiological mechanisms of diabetic wounds, the mechanism of action of vitamin E, and the utility of nanocarriers as a tool to accelerate diabetic wound healing.

CONCLUSION

Vitamin E supplementation is currently prescribed for outpatient chronic wound treatment. However, the use of lipid nanocarriers has not gained traction in this clinical setting. Encapsulating this potent antioxidant within SLNs is a promising alternative for the topical treatment of chronic wounds. Indeed, clinical trials have been carried out to evaluate the effectiveness of this association.

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