Nitric Oxide for Dermal Application

Subjects: Polymer Science

Contributor: Carolina Gutierrez Cisneros

Nitric oxide (NO•) is a free radical gas, produced in the human body to regulate physiological processes, including skin health. The lack of NO• is known to cause or worsen skin conditions, so an exogenous delivery through NO-donors can compensate its deficiency. This has been incorporated into natural, synthetic and semisynthetic polymeric matrices that have been evaluated for antimicrobial, wound healing and circulatory dermal applications.

Keywords: NO-donor ; topical release ; polymeric matrices

1. Introduction

Nitric oxide is a free radical molecule that is produced endogenously in the human body. Its chemical properties make it suitable for the regulation of several physiological processes, including circulatory, immune, neurological, and antioxidant responses [1]. The metabolic synthesis of NO• results from the controlled oxidation of L-arginine by nitric oxide synthases (NOS) [2][3][4]. NOS enzymes are needed for dermal homeostasis. In addition to the enzymatic release, nitric oxide can be physiologically generated by the chemical reduction of nitrate (NO_3) or nitrite (NO_2). For metabolism, NO_3 is converted by commensal bacteria to NO_2 [5]. Sweat is a nitrate source for the body and given a higher amount of sudoriparous glands in the skin, higher NO• amounts are found there [3][6].

2. Roles and application

There are three bioregulatory roles of NO• in human skin—vasodilation, cutaneous immune response, and tissue regeneration [4][7]. Triggered for defense and repair, most skin cell types can synthetize NO• by one or more NOS for inflammatory, antimicrobial, and apoptotic responses. Another stimulant is exposure to UV, i.e., sunlight, which activates NOS for skin pigmentation [8][9][10][11]. Given its widespread participation in dermal health, inadequate amounts of NO• can result in illness [2]. This has brought special interest in the generation of biomedical strategies that carry and deliver nitric oxide, or its precursors, exogenously. Being a gaseous free radical, it has a short half-life in vivo. Hence, the main challenges for its administration in the clinic are stable storage and controlled release, which has led to the blending of nitric oxide donors with carriers. Numerous of these platforms have been developed where polymeric scaffolds are often used [3].

The most frequently studied and implemented NO-donors are S-nitrosothiols (RNSO) and N-diazeniumdiolates (NONOates) [12]. The discovery of RSNO as endogenous NO-donors encouraged the development of exogenous delivery strategies [13]. On the other hand, NONOates are the most widespread NO-donors given that they do not need to be redox-active for release because they imitate nitric oxide biosynthesis. They consist of structures with a functional NONO-group [1].

The clinical applicability of NO-donors is impeded by a lack of control regarding the release rate and target location. Therefore, their delivery through carriers has enabled the proposal of various pharmaceutical applications. Research has focused at a dermal level on the employment against bacteria and biofilms, but they have also been increasingly investigated for their use in wound healing enhancement and in the treatment of circulatory conditions [2].

Polymers are a strong pillar of drug delivery technologies given that they can offer intrinsic therapeutic activity, be biodegradable to prevent accumulation or toxicity, and enhance release kinetics. Moreover, their molecular structure can be engineered for more biocompatibility and strict control over a wide range of drugs. The inherent properties of the materials vary according to their origin, while synthetic polymers are characterized by their reproducibility and desirable mechanical properties, natural polymers are valuable due to their biocompatibility, biodegradability or antibacterial capacity, for instance [3].

Plentiful polymer-based platforms have been designed, characterized, and tested as carriers of NO-donors for therapeutic applications. For an efficient and functional NO• delivery in biomedical applications, control of the release is needed. A recurrent problem of the available technologies is the unrestrained scattering of nitric oxide or leaching of byproducts produced during the release. Some platforms have aimed to solve these issues by the use of semisynthetic polymers, whose byproducts are often safe, or by the control of release through functionalization or caging the NO-donor. However, even if a more controlled release has been achieved, the developed systems tend to be complicated or not safe yet for clinical use, given a risk of interactions, cell toxicity, or other unknown side effects.

Novel NO-delivery carriers for topical therapies are still to be developed for targeted release. Some recent materials have been proposed as promising alternatives. The development and implementation of these carriers could eventually offset the current challenges of NO-releasing platforms. This could stimulate their clinical testing for approval for administration to patients.

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