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Pharmacological Applications of Nitric Oxide-Releasing Biomaterials in Human Skin

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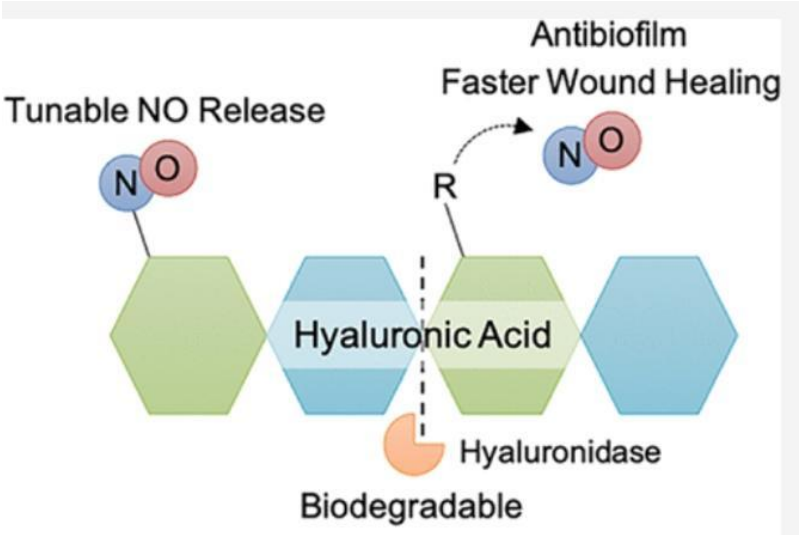
Abstract: *The gaseous free radical nitric oxide (NO) is a key endogenous found molecule involved in several physiological and pathophysiological processes in different organs and tissues . The use of nitric oxide (NO) is emerging as a promising, novel approach for the treatment of antibiotic resistant bacteria and biofilm infections. Depending on the concentration, NO can induce biofilm dispersal, increase bacteria susceptibility to antibiotic treatment, and induce cell damage or cell death via the formation of reactive oxygen or reactive nitrogen species. In detail, NO-donor prodrugs have been attached and loaded to diverse biomaterials to fabricate nanoparticles, hydrogels, and coating platforms by means of physical, chemical, or supramolecular techniques*

Keywords: NO, novel approach , concentration, antibiotic , prodrug, supramolecular techniques

I. INTRODUCTION

Nitric oxide (NO) is an important endogenous molecule that plays several roles in biological systems. NO is synthesized in human skin by three isoforms of nitric oxide synthase (NOS) and, depending on the produced NO concentration, it can actuate in wound healing, dermal vasodilation, or skin defense against different pathogens, for example. Besides being endogenously produced, NO-based pharmacological formulations have been developed for dermatological applications targeting diverse pathologies such as bacterial infection, wound healing, leishmaniasis, and even esthetic issues such as acne and skin aging.

No healing and chronic wounds represent a major problem for the quality of life of patients and have cost implications for healthcare systems. The pathophysiological mechanisms that prevent wound healing are usually multifactorial and relate to patient overall health and nutrition, vascularity of the wound bed, and coexisting infection/colonization.



Higher NO payloads corresponded with a higher degree of antimicrobial efficacy.

Chronic no healing wounds represent a substantial global problem for the quality of life of patients and treatment options for clinicians and healthcare workers. In the UK alone, it is estimated that 3.8 millions patients are undergoing

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treatment by the National Health Service (NHS) and the number of chronic wounds is rising at a rate of 12% per year. (1) Wound management costs the NHS £8.3 billion, which can be broken down into £2.7 billion for healed wounds and £5.6 billion for unhealed wounds.

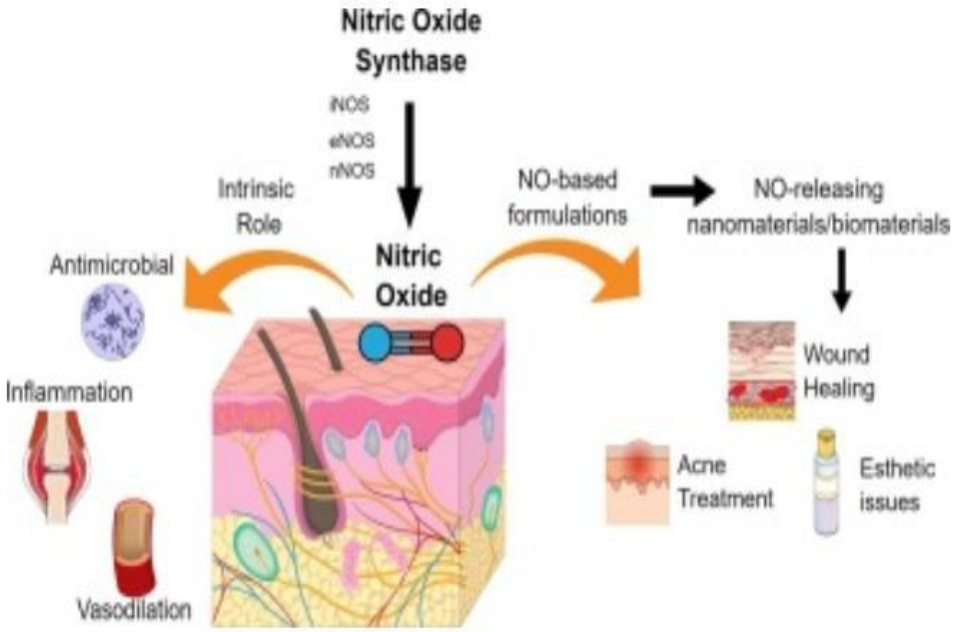
Currently, the gold standard in antimicrobial wound care, without using antibiotics, involves the use of silver-based dressings. (2) While these dressings have made great strides in reducing microbial bioburden, they do not actively promote wound healing. (3) NO is a promising alternative to antibiotics as it has shown potent antibacterial activity. As it has many mechanisms of action against bacteria, it is difficult for bacteria to develop resistance against this multipronged assault.

Importance of NO in the human skin:

Nitric oxide (NO) is a free radical gas and pleiotropic physiological regulator actively produced in several tissues of the human body. This exciting molecule can play vital participation in a variety of metabolic effects which are induced by NO. Endogenously, NO is enzymatically synthesized through nitric oxide synthase (NOS) by the oxidation of L-arginine to produce L-citrulline and NO in the same proportion (Stuehr, 2004).

NO-releasing biomaterials in the treatment of skin diseases/infections:

Innovative technologies discovered in material and pharmaceutic areas yield advanced wound dressings with a more active role that can help in different steps of the healing process. NO-releasing devices could conform to suitable systems due to their wide range of biological activities in which antimicrobial activity is important to ensure well-performed healing, avoiding, or fighting infections.



Molecules to deliver NO to biologicals:

NO has an extremely short half-life of 1–5 s, as it is a free radical and a molecule of a gaseous nature. The duration of NO exposure to the target site, and its kinetics behavior are essential for biological applications. However, NO-based therapies are limited because of their short half-life, aimlessly diffusion, and insufficient capacity to accumulate in target tissues. To increase NO stability and therefore enable its use, NO donors have been synthesized (Seabra, 2017).

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Key Application:

- Treatment of osteoarthritis, cardio metabolic and inflammatory disorders
- Treatment of Glaucoma and diabetic
- Macular edema
- Wound healing and pain management
- NO and drug eluting stents/coatings
- Treatment of skin disorders

Key Attributes:

Drug molecules and NO releasing moiety attached via hydrolytically degradable linker
Controllable release profiles

Applications:

Treatment of Glaucoma, Osteoarthritis, Cardio-metabolic and inflammatory disorders
NO releasing coatings

Antibacterial Activity of PL/CS and GSNO-PL/CS Hydrogels:

The antimicrobial properties of PL/CS and GSNO-PL/CS hydrogels were investigated against gram-negative bacteria, Pseudomonas aeruginosa (PAR). PAR is an important human pathogen, responsible for a wide range of chronic and acute infections, such as diabetic foot infections, burn wounds and pneumonia in cystic fibrosis patients [88,89,90,91,92,93,94]. PAR is particular resistant bacteria against β-lactans antibiotics due to its intrinsic capability of expressing β-lactamases and efflux pumps [91].

Both MIC and MBC values for PL/CS hydrogel were found to be 2.1 μg·mL−1, whereas both MIC and MBC values for GSNO-PL/CS hydrogel were found to be 0.5 μg·mL−1 (this concentration corresponds to 1 mmol·L−1 of GSNO) (Table 2). The sole PL/CS hydrogel had a bacterial effect; however, the incorporation of GSNO into the hydrogel decreased both MIC and MBC values by four times. Thus, as expected, the PL/CS hydrogel demonstrated antibacterial activity (due to the presence of CS), and this activity was enhanced by GSNO incorporation into the hydrogel matrix. Interesting, by comparing Table 2 and Figure 6, the hydrogel concentration required to achieve an anti-bacterial effect was not found to be cytotoxic (as related to a cytotoxicity pattern in Vero cells). Therefore, there is a concentration range that the GSNO-containing PL/CS hydrogel that can be safely administered to the patient, without damaging mammalian cells, and with a promising antibacterial effect.

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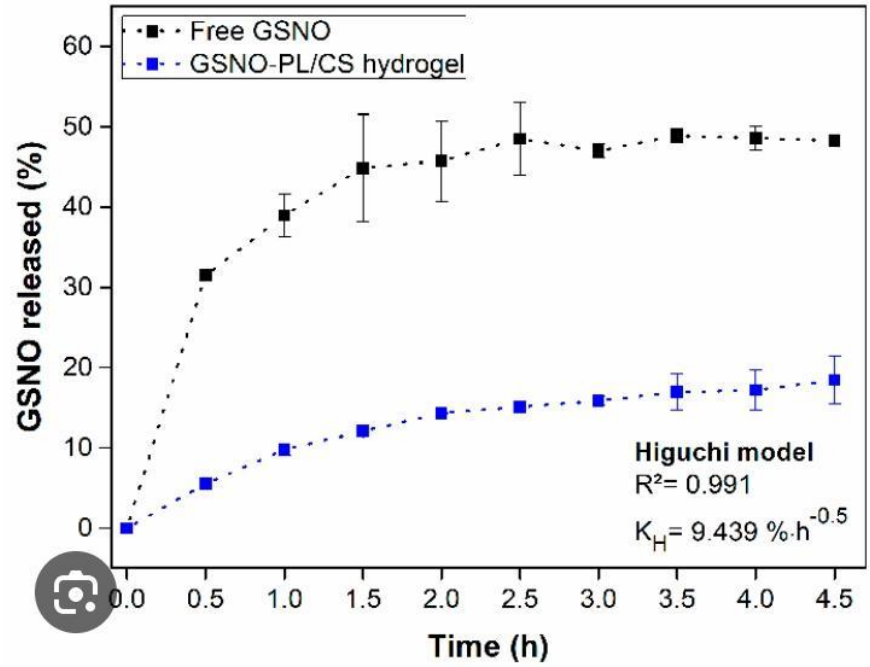
Table 1. Values of minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) for PL/CS and GSNO-PL/CS hydrogels against Pseudomonas aeruginosa (PAR) ATCC 27853, as model microorganism.



Similar to our results, Hetrick et al. showed a treatment composed of nitrosatedproline as an NO donor (PROLI/NO) against PAR. The treatment exhibited a MIC value of 2.5 mg·mL−1 [95]. Seabra et al. demonstrated the antibacterial effects of NO-releasing polyester [10] and NO-releasing-AgNPs towards different gram positive and negative bacteria strains [2]. Barraud et al. studied the effect of NO donor, sodium nitroprusside (SNP), against PAR strains in planktonic and biofilm forms [96]. At concentration of 5 µmol·L−1 of SNP, a decrease of 50% in the CFU of planktonic PAR was observed. In addition, the authors observed that this effect was decreased when the NO treatment was combined with a phosphodiesterases inhibitor. Thus, the possible antibacterial mechanism of NO is related to phosphodiesterases, which contributes to a genetic network that modulates virulence and biofilm formation and dispersion [96].

NO is known to have a potent and wide range of antimicrobial effects against both gram-negative and gram-positive bacteria [60]. The main mechanism by which NO kills bacteria is understood to involve nitrosative stress, which evolves the production of reactive nitrogen/oxygen species. As the antibacterial effect of NO involves multiple pathways, bacteria have, thus far, not been able to develop resistance towards NO [60].

CS is also known to have antibacterial effects [82,88]. The main antibacterial effects caused by CS include: (1) cell penetration and interaction with DNA; (2) CS chelation of metal ions, which leads to the production of toxins, inhibition of enzymatic activity, and finally the cell cycle; and (3) electrostatic interactions between positively charged CS and negatively charged cell membrane [88].

Thus, a biomaterial that combines the antimicrobial activities of CS and NO might be considered a potent antimicrobial agent. In addition, the viscosity of the semi-solid hydrogel matrix allows its topical/dermatological applications, increasing the contact time and, therefore, the interaction of the formulation with application target sites. In this sense, the NO/NO donor can be directly released from the hydrogel matrix. This approach might find important applications in the treatment of skin and soft tissue infections, such as diabetic foot infections, otitis externa and burn wounds.

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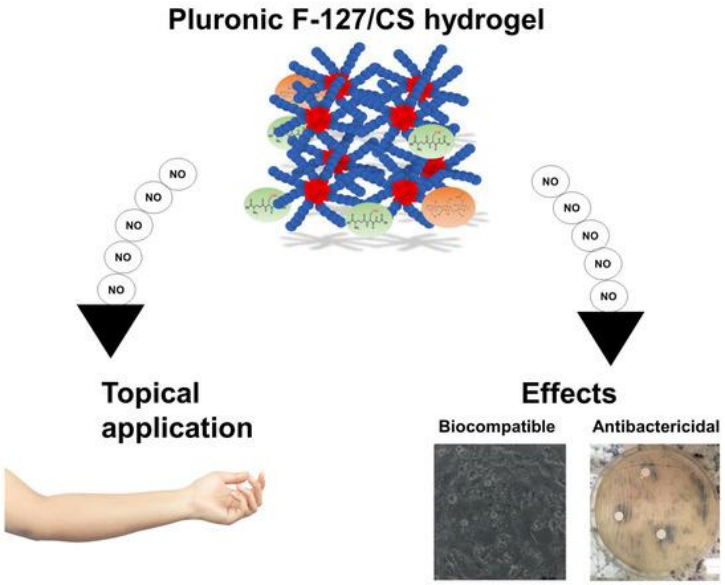

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