Journal of Controlled Release 205 (2015) 190–205

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Delivering nitric oxide with nanoparticles

John F. Quinn [a], Michael R. Whittaker [a], Thomas P. Davis [a,b,*]

[a] ARC Centre of Excellence in Convergent Bio-Nano Science and Technology, Monash Institute of Pharmaceutical Sciences, Monash University (Parkville Campus), 399 Royal Parade, Parkville, Victoria 3152, Australia
[b] Department of Chemistry, University of Warwick, Coventry CV4 7AL, UK

ARTICLE INFO

Article history:
Received 23 October 2014
Received in revised form 30 January 2015
Accepted 4 February 2015
Available online 7 February 2015

Keywords:
Nanoparticle
Nitric oxide
Gasotransmitter
Therapy

ABSTRACT

While best known for its important signalling functions in human physiology, nitric oxide is also of considerable therapeutic interest. As such, nanoparticle-based systems which enable the sustained exogenous delivery of nitric oxide have been the subject of considerable investigation in recent years. Herein we review the various nanoparticle systems that have been used to date for nitric oxide delivery, and explore the array of potential therapeutic applications that have been reported. Specifically, we discuss the modification of sol–gel based silica particles, functionalised metal/metal oxide nanoparticles, polymer-coated metal nanoparticles, dendrimers, micelles and star polymers to impart nitric oxide release capability. We also consider the various areas in which therapeutic applications are envisaged: wound healing, antimicrobial applications, cardiovascular treatments, sexual medicine and cancer treatment. Finally, we discuss possible future directions for this versatile and potentially important technology.

1. Introduction

The gasotransmitters (nitric oxide, carbon monoxide and hydrogen sulphide) are a small family of otherwise gaseous molecules with an important role in intra- and extra-cellular signalling [1]. The role of gaseous molecules in cell signalling was first identified in the 1980s [2], though the term "gasotransmitter" only came into common usage in 2001 [3]. Of the three molecules so far identified, nitric oxide (NO) has been the subject of the most considerable investigation, and has been shown to have a role in many different physiological events [4]. For instance, nitric oxide signalling is important in pain perception [5], sleep control and regulation [6], vasodilation [7], mucus production [8], sphincter contraction and relaxation [9], regulation of erection [10] and the proper functioning of the immune system [11].

Deficiency or overproduction of NO is associated with a number of pathologies. For instance, reduced NO is associated with hypertension in preeclampsia [12] and Prinzmetal's angina [13]. Elevated levels of NO have also been associated with autoimmune diseases such as rheumatoid arthritis [14], systemic lupus erythematosus [15] and multiple sclerosis [16]. High levels of NO are also related to the processes in transplant rejection [17] and in septic shock [18]. Clearly appropriate regulation of NO in the body is important in maintaining good overall health.

In addition to its role in biological signalling processes and in various pathologies, NO has also demonstrated some potential as a therapeutic agent. In particular, exogenous delivery of NO has been demonstrated to have some activity against tumour cells, [19] and to be potentially useful in antimicrobial applications [20]. For instance, exogenous NO has been applied successfully in the dissipation of biofilms [21]. With increased antibiotic resistance becoming a major clinical problem, new antimicrobials which release NO may be of clinical benefit either alone or when applied alongside traditional antibiotics.

As NO is a gaseous radical species, direct delivery, while possible, has significant limitations. Instead, it is generally necessary to deliver NO using a reactive precursor of some description. Although there are a number of different chemistries available, organic nitrates, S-nitrosothiols, metal complexes and N-diazeniumdiolates have received much attention as potential small molecule agents for the delivery of NO in a therapeutic context (see Scheme 1) [22]. One of the principle ways to alter the biodistribution and pharmacokinetic properties of NO donors is to incorporate them into a nanoparticulate form. Friedman and co-workers have previously noted that the most important features of an NO delivery system are that the material should be easily applied, and be capable of delivering NO over a therapeutically meaningful time interval [23]. Issues of cost, storage stability and transportability also need to be considered (it is these issues that render the use of gaseous NO particularly impractical). Herein we review the current state of the art for nitric oxide delivery using nanoparticles, looking at both the preparation of the particles, post assembly modification to incorporate

* Corresponding author at: ARC Centre of Excellence in Convergent Bio-Nano Science and Technology, Monash Institute of Pharmaceutical Sciences, Monash University (Parkville Campus), 399 Royal Parade, Parkville, Victoria 3052, Australia.
E-mail address: Thomas.p.davis@monash.edu (T.P. Davis).

http://dx.doi.org/10.1016/j.jconrel.2015.02.007
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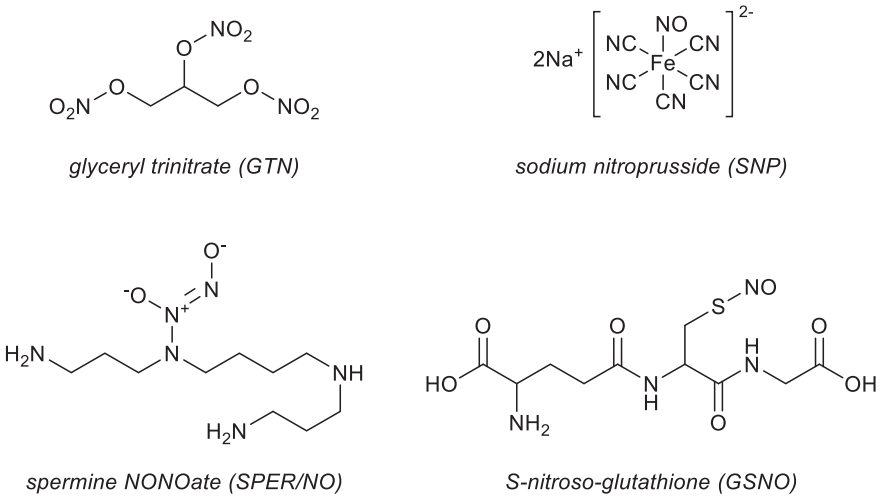
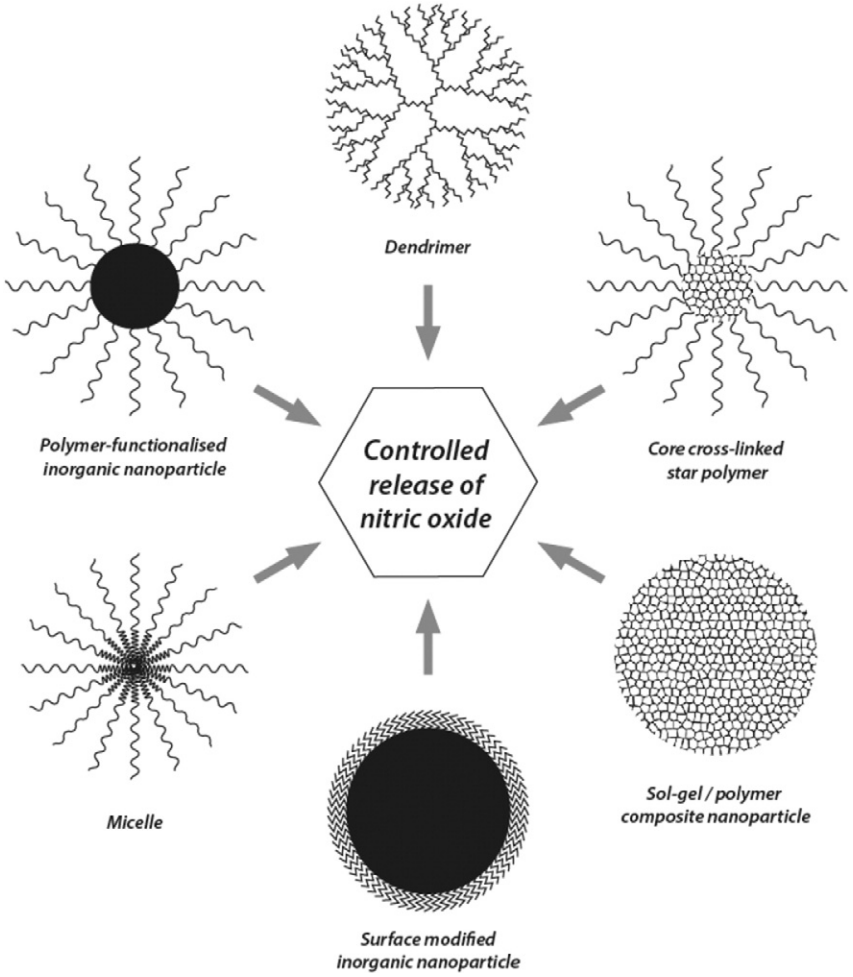


Scheme 1. Common small molecule nitric oxide donors.

the NO delivering moiety, and in vitro and in vivo studies of the particles. We also explore possible future strategies for the preparation of NO delivering nanoparticles, and examine some potential future directions for this important technology.

2. Preparation of NO-releasing nanoparticles

To date, studies have been conducted on a number of different vehicles for the exogenous delivery of NO [24]. These may be broadly



Scheme 2. Main classes of nanomaterials applied in the exogenous delivery of nitric oxide.