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Nanotechnology-based systems for the treatment and prevention of HIV/AIDS☆

José das Neves [a], Mansoor M. Amiji [b], Maria Fernanda Bahia [a], Bruno Sarmento [a,*]

[a] Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Porto, Rua Aníbal Cunha, 164, 4050-047, Porto, Portugal
[b] Department of Pharmaceutical Sciences, School of Pharmacy, Northeastern University, 110 Mugar Life Sciences Building, Boston, MA 02115, USA

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ABSTRACT

The HIV/AIDS pandemic is an increasing global burden with devastating health-related and socioeconomic effects. The widespread use of antiretroviral therapy has dramatically improved life quality and expectancy of infected individuals, but limitations of currently available drug regimens and dosage forms, alongside with the extraordinary adapting capacity of the virus, have impaired further success. Alongside, circumventing the escalating number of new infections can only be attained with effective and practical preventative strategies. Recent advances in the field of drug delivery are providing evidence that engineered nanosystems may contribute importantly for the enhancement of current antiretroviral therapy. Additionally, groundwork is also being carried out in the field nanotechnology-based systems for developing preventative solutions for HIV transmission. This manuscript reviews recent advances in the field of nanotechnology-based systems for the treatment and prevention of HIV/AIDS. Particular attention is given to antiretroviral drug targeting to HIV reservoirs and the usefulness of nanosystems for developing topical microbicides and vaccines.

Contents

Abbreviations: AcLDL, acetylated low-density lipoprotein; AF, amniotic fluid; AF/BP, amniotic fluid/blood plasma concentration ration (determined at birth); AIDS, acquired immune deficiency syndrome; $AUC_{0-24\ h}$, area under the curve (0–24 h); b.i.d., twice daily; BBB, blood-brain barrier; BCS, biopharmaceutics classification system; BMEC, brain-microvascular endothelial cells; CBP, cord blood plasma; CBP/BP, cord blood plasma/blood plasma concentration ration (determined at birth); CNS, central nervous system; CSF, cerebrospinal fluid; CSF/BP, cerebrospinal fluid/blood plasma concentration ratio; DCs, dendritic cells; DC-SIGN, dendritic cell-specific intercellular adhesion molecule-grabbing non-integrin; EMF, electromagnetic field; FGT/BP, female genital tract/blood plasma concentration ratio; fMLF, *N*-formyl-methionyl-leucyl-phenylalanine; GALT, gut-associated lymphoid tissues; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; HJV, hemagglutinating virus of Japan (Sendai virus); HLA-DR, human leukocyte antigen DR-1; IC_{50}, 50% inhibitory concentration; ID, intradermal; IM, intramuscular; IN, intranasal; IP, intraperitoneal; ISCOM, immunostimulating complex; IVag, intravaginal; LCs, Langerhans cells; LN/BP, lymph node/blood plasma concentration ratio; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; NtRTI, nucleotide reverse transcriptase inhibitors; PEG, poly(ethylene glycol); PEG-PLA, PEGylated-poly(L-lactide); PEI, poly(ethyleneimine); PEO–PCL, poly(ethylene oxide)-modified poly(epsilon-caprolactone); PHCA, polyhexylcyanoacrylate; PIs, protease inhibitors; PLA, poly(L-lactide); PLGA, poly(D,L-lactide-*co*-glycolide); PMBCs, peripheral blood mononuclear cells; PPI, poly(propyleneimine); RANTES, regulated on activation normal T cell expressed and secreted chemokine; RES, reticulo-endothelial system; RTIs, reverse transcriptase inhibitors; SC, subcutaneous; SHIV, simian human immunodeficiency virus; SIV, simian immunodeficiency virus; SLNs, solid lipid nanoparticles; Sm/BP, semen/blood plasma concentration ratio; t.i.d., three times a day; $t_{1/2}$, plasma half-life; TAT peptide, HIV-1 trans-activating transcriptor peptide; Th1, type 1 T helper cells; Th2, type 2 T helper cells.

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* Corresponding author. Tel.: +351 222 078 949; fax: +351 222 003 977.
E-mail address: bruno.sarmento@ff.up.pt (B. Sarmento).

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1. Introduction

In the last quarter of a century human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) became an increasing global health, social, and economical concern. By 2007, it was estimated that the total number of people infected by HIV accounted for around 33 million, while another 25 million more have already died since the first reported cases in 1981 [1]. Whereas the infection has a worldwide distribution, there is clearly a disproportionate impact of HIV/AIDS on sub-Saharan African countries, accounting this region for 67% of all people living with HIV. Other important regions affected by HIV include the Caribbean, Latin America, and South and Southeast Asia. Heterosexual transmission is the most common route of viral entry in these developing nations. This fact is resulting in important socioeconomic, family, and public health burdens that compromise the convergence of these regions with developed countries [2,3]. While the number of infected people is steadily increasing each year, most recent available reports from UNAIDS show a slight decrease in the pandemic since the beginning of the 21st century due to the decrease of new infections (2.7 million in 2007 vs. 3.0 million in 2001) [1]. These figures can be explained by the expanding access to antiretroviral drugs, especially in resource-limited settings, which has not only increased lifespan, but also the quality of life of HIV infected people. Indeed, in the absence of an effective cure, prevention and access to antiretroviral therapy are the best options to affect the HIV pandemic [4]. However, current strategies for providing universal access to prevention and treatment, and their field applicability are not enough, urging the search for new and improved options [1].

Although of undeniable importance, antiretroviral therapy has been limited by several factors, such as its inherent toxicity, insufficient efficacy, and drug resistance. The development and recent approval of innovative or improved drugs has managed to minimize some of this issues but the remarkable ability of HIV to resist the new therapeutic options has limited success. Alongside, inadequate physical–chemical properties of most of these antiretroviral drugs (e.g. poor solubility, permeability, and stability) impair optimal absorption, biodistribution, and sustained antiretroviral effect, thus contributing to poor clinical outcome. In order to solve these problems, several new and improved delivery systems and dosage form have been proposed in the literature [5,6]. Particularly, several nanotechnology-based delivery systems have been developed in order to improve HIV therapy, namely polymeric nanoparticles, solid lipid nanoparticles (SLNs), liposomes, nanoemulsions, dendrimers, and drug conjugates (e.g. with low-density lipoproteins or peptides) [6–10]. Although these wide range of systems share their submicron dimensions (from a few nanometers up to 1 micrometer), they differ in physical–chemical properties, biological behavior, preparation methods, or even characterization methodologies [11–13]. For more detailed information about these features, readers are referred to specialized literature in the field. Contrasting with the time and effort dedicated to the investigation of new treatment options, the interest in nanotechnology-based systems for the prevention of HIV/AIDS has been slim and mainly focused on the development of vaccines and microbicides. Conversely, the field of microbicides in particular has seen recent thrilling progresses, namely because of the advanced state in the development pipeline of VivaGel® (Starpharma Pty Ltd., Australia), a dendrimer-based microbicide gel, which captured the attention of the scientific and medical communities to the potentialities of nanotechnology-based microbicides. Hence, the scope of this manuscript is to review recent developments in nanotechnology-based systems specifically designed and developed for the treatment and prevention of HIV/AIDS, with particular emphasis focused on specific individual examples of significant interest. Further, we discuss new prospects and future directions for advancing in the field. Specific crucial topics in the HIV pharmacotherapy are discussed more briefly (e.g., CNS targeting) as other articles of the present issue address them in more detail.

2. HIV basics

Since the identification of the causative agent of AIDS in 1983, efforts to understand the biology of HIV have been impressing and the acquired knowledge contributed valuably to the development of currently available therapeutic and preventative strategies [14]. Undoubtedly, knowledge of the transmission process and pathogenesis of HIV infection is essential to provide important insights towards the development of new and better treatment options, as well as endow researchers with important opportunities to develop novel preventative measures [15]. Therefore the following section is dedicated to briefly address some of the most important aspects of the biology of HIV related to the development of nanotechnology-based systems for the treatment and prevention of HIV/AIDS.

2.1. The virus

HIV is a lentivirus of the family Retroviridae, mostly known for being the causative agent of AIDS [16]. This virus can be seen as a biological nanostructure (around 100–150 nm), composed by a host-derived membrane, a nucleocapsid and genetic material in the form of RNA containing three structural genes. These genes code for important group-specific antigens (gag gene), essential viral enzymes such as reverse transcriptase, integrase and protease (pol gene), and the two glycoproteins present in the outer viral membrane, gp120 and gp41, which are responsible for recognizing the CD4 receptor and the CCR5 or CXCR4 co-receptors of the host cell membrane, and for virus/cell fusion, respectively (env gene). As a consequence of constant transcription errors, these viral structures present high polymorphism