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Loading efficiency of stavudine on polybutylcyanoacrylate and methylmethacrylate-sulfopropylmethacrylate copolymer nanoparticles

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Abstract

Loading efficiency (LE) of stavudine (D4T), a human immunodeficiency antiretroviral agent, on the external surfaces of polybutylcyanoacrylate (PBCA) and methylmethacrylate-sulfopropylmethacrylate (MMA-SPM) was investigated. The experimental results indicate that the larger the polymeric nanoparticles (NPs), the smaller LE of D4T on the two kinds of biomaterials. Freeze drying of the two NPs, however, yields an increase in particle size and an increase in LE of D4T, in general. Preservation of the two D4T-loaded NPs through cold storage at 4 °C over 6 weeks leads to an increase in particle size and a decrease in LE of D4T. LE of D4T on both of the two NPs decreases with a variation in pH value from pH 7.2 of loading medium. LE of D4T on MMA-SPM NPs is larger than that on PBCA NPs at pH 7.4; and for the case of variation in pH value of loading medium from pH 7.2, the extent of decrease in LE of D4T for MMA-SPM NPs is higher than that on PBCA NPs. These outcomes imply that for oral administration, D4T-loaded MMA-SPM NPs may be more advantageous than D4T-loaded PBCA NPs, and D4T-loaded PBCA NPs may be more favorable than D4T-loaded MMA-SPM NPs for intravenous injection.

Keywords: Stavudine (D4T); Nanoparticle; Drug loading; Lyophilization; Cold storage

1. Introduction

The essential material characteristics of an ideal drug carrier include (1) biocompatibility and bioacceptability of the carrier and its degradation products, (2) ability to be loaded with effective dosage, (3) acceptable stability during preservation, (4) satisfactory drug-release rate from the drug-loaded composite, (5) suitable for regular clinical administration, and (6)

Abbreviations: D4T, stavudine; HIV, human immunodeficiency virus; LE, loading efficiency (%); MMA-SPM, methylmethacrylate-sulfopropylmethacrylate; NP, nanoparticle; NRTI, nucleoside reverse transcriptase inhibitor; PBCA, polybutylcyanoacrylate; PDI, polydispersity index; SPM, sulfopropylmethacrylate

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Nomenclature

D_{av}	average particle diameter (nm)
MW_{na}	number-averaged molecular weight (Da)
pH_m	medium pH value for the minimum D_{av}
t	synthesis time (h)
t_c	characteristic t for dramatic increase in D_{av} (h)
w	stirring rate (rpm)

economically feasible for manufacture. Since the average diameter of human microvessels is between 5 and 10 μm, a drug carrier with diameter less than 1 μm can be considered as a candidate for the application to intravenous injection. For drug delivery into the central nervous system, an increase in osmotic pressure can be aggressive and may bring other substances into brain, although tight junction may be opened by high osmotic pressure to efficiently increase drug permeability across blood-brain barrier (Kreuter, 2001). On the other hand, carrier-mediated systems, which may alter body drug distribution without severe intervention in the structure of tight junction, would be an excellent technique for brain-targeting delivery (Kumar, 2000). Colloidal drug carrier, one of the carrier-mediated systems, was already employed in controlled drug release with the advantages of high stability, slow drug-release rate and appropriate sustainability after administration (Govender et al., 1999; Schmidt and Bodmeier, 1999). Drugs can be incorporated with or bound to colloidal drug carriers, such as polymeric nanoparticles (NPs). For instance, azidothymidine (AZT), the first nucleoside reverse transcriptase inhibitor (NRTI) for clinical treatment of the patients infected by human immunodeficiency virus (HIV), was loaded on nanosized polyhexylcyanoacrylate (PHCA), an acrylic acid derivative, rendering an increase in its concentration in rat brains (Löbenberg et al., 1998). For in vitro tissue culture of human macrophages, which belong to cells of reticuloendothelial system, not only AZT-loaded NPs may sustain full antiviral activity (Bender et al., 1994) but also the antiviral activity of saquinavir (SQV), a protease inhibitor for the therapy of acquired immunodeficiency syndrome (AIDS), can be enhanced ten-fold by binding SQV on NPs (Bender et al., 1996).

Biocompatible polybutylcyanoacrylate (PBCA), also belonging to one of the acrylic acid derivatives, can be rapidly biodegraded and completely eliminated from body over a few days (Hillery et al., 1996). The main mechanism for PBCA degradation is the cleavage of ester side bonds and transformation of the polymers into water-soluble polymeric acids, which can be finally removed by urinary excretion. The low cytotoxicity of PBCA NPs was demonstrated by the fact that, for rat cerebrum microvascular endothelial cells, the cell viability was almost not influenced under the dosage of 10 μg/ml, and 20% reduction in the cell viability under the high dosage of 100 μg/ml was observed (Courveur et al., 1986). Hence, PBCA NPs can be a general carrier-mediated system for drug delivery. On the other hand, hydrophobicity of acrylic acid derivatives often results in less adsorption affinity to hydrophilic drugs (Hoffmann et al., 1997). Charged methylmethacrylate-sulfopropylmethacrylate (MMA-SPM) NPs may overcome this difficulty. Through application to the loading of muscarinnic agonist arecaidine propargyl ester (APE), MMA-SPM NPs were shown to be superior to other NP carriers (Langer et al., 1997b). Moreover, without any macroscopic irritation and inflammation, the administration of APE-loaded MMA-SPM NPs leaded to considerable improvement in miotic response after topical administration to the eyes of rabbits (Langer et al., 1997a). These suggest that MMA-SPM NPs can be a suitable carrier system for hydrophilic or even charged drugs.

Stavudine (D4T) is one of the most essential NTRIs for AIDS treatment with its oral bioavailability over 80%. In clinical study, D4T can appreciably increase CD4 cell counts and reduce mean serum p24 antigen levels and infectious HIV titers (Riddler et al., 1995). However, the duration of the above responses is inadequate. Furthermore, D4T is slightly hydrophilic with its $\log D_{oct} = -0.84$, where D_{oct} is the distribution coefficient between octanol and phosphate buffered saline (PBS). Thus, it is worth to investigate and compare the loading behavior of D4T on PBCA or MMA-SPM NP carriers. This is performed in the present study. Also, variation in particle diameters of the above two biodegradable NPs as a function of experimental conditions like synthesis time, stirring rate and relative content of SPM in copolymer were discussed. In particular,