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Novel self-assembling nanogels: Stability and lyophilisation studies

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Abstract

The stability of new supramolecular nanoassemblies (nanogels), based on the association of a hydrophobically modified dextran (MD) and a β-cyclodextrin polymer (pβCD), has been studied by two complementary methods: (i) size measurements and (ii) turbidity experiments using a Turbiscan optical analyser. Nanogels of about 120–150 nm were obtained whatever the concentration of the two polymer solutions. At low concentrations, the suspensions presented little mean diameter variations upon storage. However, the concentrated ones tended to destabilize and their mean diameter increased upon time. Size measurements and Turbiscan investigations have demonstrated that destabilization in the MD–pβCD nanogel suspension was only due to particle aggregation and/or fusion, as no sedimentation or creaming occurred. The destabilization of MD–pβCD suspensions led to the formation of a highly viscous phase, as a final state. Moreover, the two methods have shown that aggregation and/or fusion phenomena were more pronounced in the concentrated MD–pβCD suspensions than in the diluted ones. The stability of MD–pβCD suspensions could be improved by their storage at 4 °C. Finally, freeze-drying was found to be a convenient method for the long-time storage of MD–pβCD nanoassemblies.

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1. Introduction

In the past few decades, submicronic polymeric particles have attracted considerable attention as potential drug delivery devices for the controlled release of active molecules and targeting (Brannon-Peppas, 1995; Couvreur et al., 1995; Soppimath et al., 2001; Hans and Lowman, 2002).

However, the preparation methods of these systems are often complex and require the use of potentially toxic surfactants and organic solvents in order to solubilize the commonly used (co)polymers such as polyesters (polylactide, poly(lactide-co-glycolide), polycaprolactone), polyanhydrides or polycyanoacrylates, which are insoluble in water (Verrecchia et al., 1995; Bitz and Doelker, 1996; Lin et al., 1999; Birnbaum et al., 2000; Jeon et al., 2000). Therefore, expensive techniques must be employed to remove completely the solvents and surfactants at the end of the preparation process. Nevertheless, solvent and surfactant traces may persist and constitute a drawback for the medical applications of these polymeric systems.

Recently, to overcome these inconveniences, new self-assembling nanogels (NG) were developed by mixing an aqueous solution of a β-cyclodextrin polymer, here designated pβCD with an aqueous solution of a hydrophobically modified polysaccharide, dextran grafted with alkyl moieties, designated MD (Gref et al., 2006). The alkyl moieties in C12 were found to form inclusion complexes with cyclodextrins (CDs), leaving also free CDs accessible for the inclusion of active molecules (Fig. 1).

It was demonstrated that stable nanoassemblies could be obtained only in a very narrow range of experimental conditions and that the main parameters governing stability were the dextran substitution yield ≥ 4%; pβCD M\text{w}>10^6\text{g/mol} and weight ratio MD/pβCD=1.

As the stability of these new nanodevices is a crucial point, the aim of this paper was to set up a methodology to investigate it. Two complementary methods were chosen. On one hand,