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Material characterisation

^{1}H NMR relaxometry and X-ray study of PCL/nevirapine hybrids

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ABSTRACT

Polycaprolactone (PCL) hybrids containing layered silicates, silica and dioxide titanium were developed and used as matrixes for the incorporation of nevirapine. These systems were characterized by X-ray diffraction (XRD) and proton nuclear magnetic resonance (NMR) relaxometry. The XRD showed that the PCL crystallization is hindered with higher amounts of nevirapine and that the drug has an amorphous distribution in the PCL matrix. The NMR showed that the hybrids present three distinct environments: crystallites, rigid-amorphous and flexible-amorphous regions, with three distinct spin-lattice relaxation times, T_{11}, T_{12}, T_{13}. The proton relaxometry showed that the PCL chains have more restricted motions in the presence of Viscogel organoclay S7 comparing to TiO_2 and SiO_2. The presence of nevirapine and nanoparticles together decreased the polymer chain mobility, especially in the amorphous regions. Both T_{12} and T_{13} dispersions could be interpreted in terms of power laws T_{12}, $T_{13} \sim \nu^{p}$. In the case of T_{12}, the exponent obtained was around 0.73, which in the frame of the renormalized Rouse model could be associated with a type I mesophase region, indicating some constraint in the amorphous part.

1. Introduction

Nanoscience and nanotechnology have been increasingly used in the development of new products and processes, especially those for biomedical applications. Several studies have reported new nanobiomaterials for modified drug release systems, which have many advantages compared with the isolated polymers or other pharmaceutical excipients [1–3]. Polycaprolactone (PCL) is currently used in controlled drug release systems as well as in other medical applications. It is linear semi-crystalline polyester and is biocompatible and biodegradable, either through hydrolytic or enzymatic cleavage of the macromolecular chains [4–7].

The blending of polymer materials as PCL with inorganic nanoparticles, such as montmorillonite clay, silica and titanium dioxide, can provide new compounds. These nanostructured materials are physically more stable and have other improved properties for pharmaceutical purposes [8–10]. Thus, polymer nanostructured materials are interesting materials for producing modified release systems [2,11].

In this work, the PCL nanostructured materials developed were used as matrices for the incorporation of nevirapine. Nevirapine (Nev) is a non-nucleoside reverse transcriptase inhibitor of human immunodeficiency virus type 1 (HIV-1). It blocks polymerase activity after binding directly to the HIV-1 reverse transcriptase, leading to the disruption of the enzyme's catalytic site [12–14].

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There is a great interest in understanding the molecular dynamics of new materials, especially those intended for application in the pharmaceutical sector. The physical properties depend on the molecular dynamics and influence the final formulation, biological activity, manufacturing process and storage conditions chosen for pharmaceutical systems [15]. One of the best techniques to measure the molecular dynamics of pharmaceutical and polymer systems is proton nuclear magnetic resonance (NMR) relaxometry [16].

Proton NMR relaxometry measures the energy exchange between proton spins of the hydrogen nuclei and the energy exchange between the proton spin system and the surrounding lattice. When the proton spin-lattice relaxation time (T_1) is measured over a broad range of Larmor frequencies ($\nu_L = \gamma B/2\pi$, where B is the external magnetic field and γ is the ^1H gyromagnetic ratio), it is possible to obtain detailed information regarding the molecular dynamics of the system. Spin-lattice relaxation is highly sensitive, not only to local molecular rotations/reorientations but also to translational self-diffusion of molecules because the ^1H spin-lattice relaxation depends on the dipolar spin interactions that can occur between inter or intramolecular spins [17–21].

Due to the low signal-to-noise ratio at low Larmor frequencies, conventional T_1 measurements are limited to frequencies above around 4 MHz. FFC NMR relaxometry has been used to extend the T_1 measurements below the MHz range. Both techniques are currently extensively used in the study of molecular dynamics in polymer melts, polymer networks and liquid crystalline systems. This technique is a convenient tool to detect changes in motions at the molecular level, since it allows the measurement of T_1 in the broad frequency range of 1 kHz–10 MHz, without signal degradation, since the free-induction decay always us to detect at a sufficiently high magnetic field, B, (e.g., ν_L >8 MHz) [22–25]. When measured at different Larmor frequencies, the spin-lattice time can detect molecular motions, with a broad range of correlation times. At MHZ Larmor frequencies, T_1 is mainly determined by individual molecular reorientations and by local molecular translational displacements. Both dynamic processes are usually classified as “fast molecular motions”. To get an insight into the “slow” molecular dynamics in the kilohertz frequency range, FFC has to be applied [26].

In this paper, we report experiments to characterize PCL/nanoparticle/nevirapine hybrids using X-ray diffraction (XRD) and proton nuclear magnetic resonance (NMR) relaxometry. NMR relaxometry measurements were performed to study the mobility of PCL macromolecules and of the drug, helping to make inferences about their confinement level inside the hybrids.

2. Experimental

2.1. Materials

Polycaprolactone (PCL) Mn = 80,000, supplied by Sigma Aldrich, was used as the polymer matrix (Fig. 1). The organoclay Viscogel S7, containing the dimethyl benzyl hydrogenated tallow ammonium group as a modifier, was obtained from Bentec-Laviosa Chimica Mineraria (Italy). This clay is based on montmorillonite, which is a sodium aluminum hydrosilicate, morphologically constituted of alumina octahedrons sandwiched between two layers of silica tetrahedrons. The layer thickness is around 1 nm and the surface area is around 800 m^2/g. Hydrophilic silica oxide particles (SiO_2) were supplied by Evonik (Brazil), named Aerosil® A200. They have a specific surface area of 170 $mg^2\ g^{-1}$ and an average primary particle size of 12 nm. Titanium dioxide particles (TiO_2) were supplied by DuPont (Brazil) and they have a specific surface area of 50 $mg^2\ g^{-1}$ and an average primary particle size of 25 nm. Nevirapine was supplied by Oswaldo Cruz Foundation of Rio de Janeiro (Brazil). Chloroform was purchased from TediaBrazil. All materials were used without further modification.

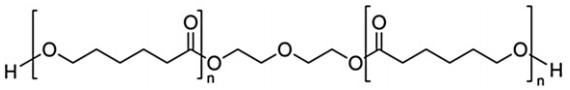

Fig. 1. Structure of PCL.

2.2. Preparation of hybrids

The PCL film was produced using a solvent casting technique. The PCL granules were dissolved in chloroform at room temperature overnight with vigorous stirring to obtain a concentration of 5% w/v. The solution was put into a glass Petri dish, which was covered and placed at room temperature for slow evaporation. The dried film was dried at vacuum for 48 h. The PCL/clay nanostructured materials were also prepared through the solvent casting technique, using $CHCl_3$ as the solvent. The solutions of PCL and organoclay were added in a flat-bottom insulated flask. The flasks with the isolated solutions were sealed and stirred at room temperature for 24 h. After that, the solutions were mixed and left for 24 h under stirring, which was poured into Petri dishes and kept at room temperature. The nanostructured films were dried under vacuum for 48 h and all the samples were stored in desiccators until use. Films with 3% w/w of Viscogel S7 clay were obtained. The same procedure was performed for the titanium and silica dioxide particles, but the final concentration of both particles in each system was 0.25% w/w.

The nevirapine was added to the PCL by dissolving it in a small amount of chloroform and then stirring the solution for 20–30 min before pouring into a glass Petri dish. The amounts of nevirapine in each system were 5%, 10% and 20% w/w in relation to the PCL.

2.3. Characterization techniques

2.3.1. X-ray diffraction

The crystalline structure of the PCL and PCL/nevirapine hybrids were investigated by X-ray diffraction using a Rigaku D/Max 2400 diffractometer, with nickel-filtered CuKα radiation of wavelength 1.54 Å, at room temperature. The 2θ scanning range was varied from 2° to 30°, with