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Nevirapine-polycaprolactone crystalline inclusion complex as a potential long-acting injectable solid form

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ABSTRACT

Nevirapine (NVP) is recommended by WHO as the antiretroviral treatment to prevent HIV passing from mother to child. However, the once-daily oral administration results in poor patient compliance, and a long-acting injectable form of NVP is desirable. Using single-crystal X-ray diffraction and other characterization methods, we demonstrated NVP can form crystalline inclusion complex (IC) with the biodegradable hydrophobic poly(ε-caprolactone) (PCL), and investigated the potential of the NVP-PCL IC microparticles as a long-acting injectable solid form. Compared with pure NVP crystals and NVP/polylactide microparticles, the NVP-PCL IC crystals showed significantly decreased solubility and slower dissolution rate, making it more suitable to be developed to achieve sustained-release profiles. In addition, the NVP-PCL IC microparticles with an average diameter below 10 μm can be conveniently prepared by spray drying and are found to be easily injectable through a 25G needle. These results demonstrated the possibility of using drug-polymer IC microparticles as long-acting injectable forms, providing a new approach to design sustained-release drug products.

1. Introduction

Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) are serious global health and social problems. As one of the three major transmission pathways of HIV, mother-to-child transmission (MTCT) accounts for over 90% of new HIV infections among children (De Cock et al., 2000). With effective antiretroviral treatment and other interventions, the likelihood of HIV passing from mother to child can be reduced from 15–45% to below 5% (De Cock et al., 2000; World Health Organization, 2010). Therefore, World Health Organization (WHO) guidelines recommend once-daily oral administration of 6–10 mg nevirapine (NVP), a non-nucleoside reverse transcriptase inhibitor (Merluzzi et al., 1990; Guay et al., 1999), to babies born to HIV-infected mothers from birth till 4–6 weeks (World Health Organization, 2010; Schouten et al., 2011). The long-term and frequent dosing for babies results in poor compliance which impedes the successful implementation of the WHO guideline, especially in the developing world with limited health resources (Kruse et al., 1991; Schieber and Maeda, 1999; Claxton et al., 2001). Therefore, like the cases of many antiviral therapies, it is desirable to develop a long-acting dosage form of NVP to reduce the administration frequency, improve the patient compliance and consequently maximize the therapeutic effect.

So far, there are few attempts in the literature to develop a sustained release form of NVP. Chen et al. developed a rod-shaped subcutaneous NVP implant, in which NVP was mixed with poly(vinyl alcohol) (PVA), compressed into rods of 2.0 or 4.5 mm in diameter, and then inserted into a silicone tube (Chen et al., 2005). The implants showed more-or-less linear release profiles *in vitro*, and in a rat study, one 4.5 mm implant (length and dose of the implant were not specified in their publication) was shown to achieve a steady plasma NVP concentration of 35–45 ng/mL for about 14 weeks. However, these implants had a relatively large size in diameter (more than 2.0 or 4.5 mm) and used non-biodegradable PVA and silicones, therefore surgeries were needed both for the implantation and removal, which makes it inappropriate for babies. In contrast to implants, subcutaneously injectable suspension is much less invasive and expected to be a better choice. Cortez et al. prepared large NVP particles coated with poly(D,L-lactide). The median diameters of the final particles and the polymer coating layer thickness were 239 and 2 μm, respectively (Cortez et al., 2015). Though the *in vitro* study demonstrated sustained release for up to 75 days, the particle size was too large and had to be injected through 18G needles. However, smaller drug particles is difficult to coat (Saleh et al., 2003), and more importantly, the drug loading will decrease significantly if the same polymer coating thickness need to be maintained. Therefore, an unmet clinical need still remains for the high drug loading, long-acting, and mini-invasively injectable form of NVP (Scheme 1).

In general, the long-acting effect of injectable drug particles can be

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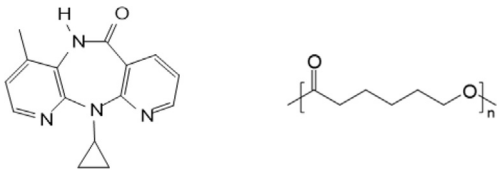

Scheme 1. The chemical structures of nevirapine and poly(ε-caprolactone).

achieved when either the drug itself has a low dissolution rate or the drug is encapsulated into a slowly-degrading polymer matrix such as poly(lactide-co-glycolide) (PLGA) microparticles (Okada, 1997; Hoffman, 2008; Schwendeman et al., 2014; Hutchinson and Furr, 1990; Remenar, 2014a,b). For those slowly-dissolving drug particles, the dissolution rate can be calculated using the Noyes-Whitney equation (Noyes and Whitney, 1897), and the time needed for its dissolution, which also represents the duration of the drug release, is proportional to the initial crystal particle size r_0, and inversely proportional to the drug solubility c_s. Since the particle size should be kept as small as possible in order to be injectable through minimally invasive needles, the sustained release of drugs is usually realized by decreasing drug solubility of the parent drug either through chemical conjugation (e.g., paliperidone palmitate in *Invega Trinza*®) or salt formation with hydrophobic counterions (e.g., olanzapinium pamoate in *Zyprexa® Relprevv™*). The aqueous solubility of NVP Form I and its hemi-hydrate crystal is ~80 μg/mL (Chen et al., 2015) and ~60 μg/mL (Stieger et al., 2009), respectively, which are too high and unsuitable for long-term sustained release (for comparison, the solubility values of olanzapine and olanzapinium pamoate are 43 and 3 μg/mL, respectively (Thakuria and Nangia, 2011; Chue and Chue, 2012)). As discussed before, the duration of the drug release from a crystal is inversely proportional to its solubility, it would be interesting to identify alternative solid forms of NVP with lower solubility. In this study, we developed crystalline particles of NVP-polycaprolactone (PCL) inclusion complex (IC), and proposed it as such a candidate solid form for long-acting injectable NVP.

Drug-polymer crystalline inclusion complex (IC) is a relatively less-explored pharmaceutical solid form, where the drug molecules form a well-ordered host framework with parallel and isolated channels, and linear polymer chains can reside in such channels as guests (Zhong et al., 2014; Yang et al., 2016; Zhong et al., 2016; Yang et al., 2017; Sun, 2006; Remenar, 2014a,b; Nakai et al., 1981; Higuchi and Lach, 1954; Izumikawa and Kambe, 1985). Recently, we demonstrated when using hydrophobic polymers (e.g., PCL) as the guest, the solubility and also the dissolution rate of drug-PCL ICs were significantly lower than those of the drug crystals themselves (Zhong et al., 2017), which provides a new approach to design long-acting injectables. In the current study, we report that nevirapine indeed forms IC crystals with PCL, and injectable IC microparticles can be easily prepared via spray drying. The structure, stability, injectability and *in vitro* dissolution behavior of NVP-PCL IC microparticles were characterized in detail. The results showed the IC form has a much lower solubility than NVP itself, suggesting its potential to be used as long-acting injectable solid form.

2. Experimental

2.1. Materials

Nevirapine (NVP) was purchased from Adamas-beta; poly(ε-caprolactone) (PCL, *M*n 10,000 Da) and PCL oligomer (PCLdiol530, *M*n 530 Da) were purchased from Sigma-Aldrich; poly(L-lactide) (PLLA, *M*n 10,000 Da) was purchased from KRD Co., Ltd. (China); phosphate buffered saline tables (PBS) was purchased from Amresco; hexane, chloroform and carbon tetrachloride (CCl_4) were purchased from Beijing Chemical Works. All reagents were of analytical grade and used as received.

2.2. Sample preparation

2.2.1. NVP-PCL IC microparticles

2 g NVP and 2 g PCL were dissolved in 40 mL chloroform, and the solution was fed into a Yamato ADL311S spray dryer at a speed of 2 mL/min. The inlet and outlet temperatures were 75 and 45 °C respectively, and the air flow rate was 0.1 m^3/min. The obtained sample was collected and stored in a vacuum oven at room temperature before use. To remove the excess PCL in the spray dried samples and to obtain microparticles of NVP-PCL IC, 300 mg spray dried samples were rinsed in 5 mL CCl_4 with a stirring rate of 1200 rpm for 30 min. After rinsing, the solids were collected by filtration and dried in a vacuum oven overnight at room temperature.

2.2.2. NVP hemi-ethyl acetate solvate (NVP-EtOAc)

Ethyl acetate solvate of NVP was prepared following the method in literature (Chadha et al., 2013) to investigate its structural similarity with NVP-PCL IC. 50 mg NVP was added into 5 mL ethyl acetate, and the suspension was heated to a few degrees below the boiling point of ethyl acetate with continuous stirring until all the NVP solid was dissolved. The hot, saturated solution was then allowed to crystallize at room temperature. The obtained crystals were collected by filtration and stored in a vacuum oven overnight at room temperature.

2.2.3. NVP-PCL IC single crystal

5 g NVP and 5 g PCLdiol530 were dissolved in 70 mL chloroform to obtain a concentrated solution of NVP. NVP-PCLdiol530 IC single crystals of diffraction quality were grown by slow vapor diffusion of n-hexane into the concentrated chloroform solution. Colorless crystals obtained were rinsed by CCl_4 and then collected by filtration. The solid was dried in a vacuum oven overnight at room temperature before diffraction measurements and structural analysis.

2.2.4. NVP microparticles

3 g NVP was dissolved in 30 mL chloroform, and the solution was spray dried under the same conditions as used in the preparation of NVP-PCL IC microparticles. The obtained powder was stored in a vacuum oven overnight at room temperature before use.

2.2.5. NVP/PLLA microparticles

2 g NVP and 0.9 g PLLA (equal to the drug/polymer weight ratio in NVP-PCL IC, see below) were dissolved in 30 mL chloroform, and the solution was spray dried under the same conditions as described above. The obtained powder was stored in a vacuum oven for 24 h at 50 °C to remove the residual solvent.

2.2.6. NVP-PCL IC via melt crystallization

Samples for the *in situ* dissolution observation were prepared via melt crystallization. First, 0.5 g NVP and 0.5 g PCL were milled manually with an agate mortar and pestle for 2 min to obtain a physical mixture of these two compounds. Then, suitable amounts of the obtained mixture were melted at 250 °C for 2 min on a glass slide covered with a piece of polyimide film, and then cooled to 60 °C, followed by annealing at this temperature for 4 h. Excess PCL was removed by rinsing the samples with CCl_4 at room temperature to obtain pure NVP-PCL IC.

2.3. Solubility and dissolution profile study

The PBS solution used in the following study had pH of 7.4 and contained 137 mM NaCl, 2.7 mM KCl and 10 mM phosphate buffer. The equilibrium solubilities of NVP crystal and NVP-PCL IC were tested in PBS solution at room temperature as follows. Excess amounts of NVP