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Sustained release of risperidone from biodegradable microspheres prepared by *in-situ* suspension-evaporation process

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ABSTRACT

Risperidone-loaded poly (D,L-lactide-co-glycolide) (PLGA) microspheres were prepared with a suspension-evaporation process with an aqueous suspension containing an *in situ*-formed aluminum hydroxide inorganic gel (SEP-AL process) and evaluated for encapsulation efficiency, particle size, surface morphology, glass transition temperature, *in vitro* drug release profile, and *in vivo* behavior. The SEP-AL microspheres were compared with conventional oil-in-water (O/W) emulsion solvent evaporation method using polyvinylalcohol (PVA) as an emulsifier (CP-PVA process). The microspheres were spherical in shape. DSC measurements showed that risperidone crystallinity was greatly reduced due to the homogeneous distribution of risperidone in PLGA microspheres. *In vitro* drug release profile from the microspheres showed a sigmoidal pattern of negligible initial burst up to 24 h and minimal release (time-lag) for 7 days. After the lag phase, slow release took a place up to 25 days and then rapid release occurred sharply for 1 week. *In vivo* rat pharmacokinetic profile from the microspheres showed very low blood concentration level at the initial phase (up to 24 h) followed by the latent phase up to 21 days. At the 3rd week, main phase started and the blood concentration of the drug increased up to the 5th week, and then gradually decreased. The risperidone-loaded PLGA microspheres produced by SEP-AL process showed excellent controlled release characteristics for the effective treatment of schizophrenia patients.

1. Introduction

Risperidone is a benzisoxazole derivative which targets the serotonin type 2 (5-HT2), dopamine D2 and alpha1-adrenergic receptors (Amann et al., 2010; Mathot et al., 2006; Tandon and Jibson, 2003; Yerragunta et al., 2015). The oral and injectable long-acting dosage forms of risperidone are presently available for clinical practices. However, the depot formulations have found significant advantages over oral dosage forms owing to: (1) less frequent administration, *e.g.* the patient can receive an intramuscular injection every two weeks instead of oral tablets or capsules a few times daily; (2) fewer side-effects and reduced medical workload; (3) improved patient compliance and more predictable absorption (Manchanda et al., 2013). Those long-acting depot dosage forms offer the full therapeutic potential of maintenance medication. A commercial product of risperidone-loaded microspheres is an intramuscular injection administered once every two weeks, marketed as Risperdal Consta™ by Johnson & Johnson Corp., USA. The release of Risperdal Consta™ shows a sigmoidal profile, exhibiting a slight initial burst (≤3.5%) followed by a lag period of approximate three weeks and then a two-week period of fast release (Eerdekens et al., 2004; Knox and Stimmel, 2004).

Risperdal Consta™ is formulated by solvent-extraction method, which is very complex and time-consuming processes composing of microsphere formation, solidification process, intermediate drying process, ethanol washing process, and complete final drying process to render an initial lag phase and a substantially sigmoidal release profile (Johnson & Johnson Pharmaceutical research & development, 2011; Lyons et al., 2002; Ramstack et al., 2003).

Additionally, conventional solvent evaporation method usually shows an initial burst and a substantially linear release profile.

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Therefore, it is difficult to achieve an initial lag phase and a substantially sigmoidal release profile as Risperdal Consta™ exhibits. If excessive amount of risperidone-loaded microspheres are exposed to patient at initial phase, it can cause serious side effects. Therefore, below 1% of AUC is required at 24 h (Lyons et al., 2002).

To overcome very complex and time-consuming processes of Risperdal Consta™ mentioned above and to achieve an initial lag phase as well as a substantially sigmoidal release profile, a simple manufacturing process was newly designed and investigated.

A suspension-evaporation technique producing drug-containing biodegradable microspheres has been developed (Kim, 2009, 2011). The suspension-evaporation technique uses an aqueous suspension medium consisting of *in situ*-formed, gelatinous inorganic gel. Unlike polyvinyl alcohol (PVA) used for common emulsion-evaporation processes, *in situ*-formed, gelatinous inorganic gel does not have any emulsifying ability and acts as a suspending agent (Kim, 2009, 2011; Markovic et al., 2004; Santos et al., 2004).

In the present study, risperidone-loaded PLGA microspheres were prepared by the suspension-evaporation process with an aqueous suspension containing an *in situ*-formed aluminum hydroxide inorganic gel (SEP-AL process). The prepared risperidone-loaded PLGA microspheres were characterized for encapsulation efficiency, particle size, surface morphology, *in vitro* drug release profile and *in vivo* rat PK profile, and compared with the microspheres by conventional oil-in-water (O/W) emulsion solvent evaporation method (CP-PVA process).

2. Materials and methods

2.1. Materials

Risperidone was purchased from Aurobindo (India). PLGA (Resomer 756S) polymer was purchased from Evonik (Germany). Aluminum chloride ($AlCl_3$), sodium hydroxide (NaOH), and PVA (88% hydrolyzed, molecular weight 30,000–70,000) were purchased from Sigma Chemical Co. (USA). All other chemicals were obtained commercially as analytical grade reagents.

2.2. Preparation of the risperidone-loaded PLGA microspheres

2.2.1. Suspension-evaporation process using in situ-formed aluminum hydroxide inorganic gel (SEP-AL process)

The risperidone-loaded PLGA microsphere was prepared by a novel suspension-evaporation process with an aqueous suspension containing an *in situ*-formed aluminum hydroxide inorganic gel (Fig. 1,Table 2) (Kim, 2009, 2011).

Risperidone (375 mg) and PLGA (750 mg) were dissolved in dichloromethane. Aluminum hydroxide gel was formed *in situ* in water as shown (Markovic et al., 2004; Santos et al., 2004):

$$AlCl_3 + 3NaOH = Al(OH)_3\ (\text{precipitation}) + 3NaCl \quad (1)$$

The drug/polymer solution was dispersed into the aqueous suspension medium (800 ml) consisting of *in situ*-formed aluminum hydroxide inorganic gel. The dispersion was initially homogenized by a high-shear mixer for 10 s. The solvent was then evaporated by stirring at 600 rpm at 25 °C for 15 h. Then concentrated HCl was added to the suspension to dissolve the suspending medium as shown:

$$Al(OH)_3\ (\text{precipitation}) + 3HCl = AlCl_3 + 3H_2O \quad (2)$$

Solidified microspheres were recovered by filtration and washed three times with distilled water before being dried in vacuum at 25 °C. Fig. 1 shows the schematic process using *in situ*-formed aluminum hydroxide inorganic gel to produce the risperidone-loaded PLGA microspheres.

2.2.2. Conventional oil-in-water (O/W) emulsion solvent evaporation method using PVA as an emulsifier (CP-PVA process)

In CP-PVA process, all other experimental conditions were the same as in the SEP-AL process except PVA as an emulsifier. Briefly, risperidone (375 mg) and PLGA (750 mg) were dissolved in dichloromethane. The drug/polymer solution was dispersed into 800 ml of 4% (w/v) PVA aqueous medium. The dispersion was initially homogenized by a high-shear mixer for 10 s. The solvent was then evaporated by stirring at 600 rpm at 25 °C for 15 h. Solidified microspheres were recovered by filtration and washed three times with distilled water before being dried in vacuum at 25 °C.

2.3. Particle size analysis

Particle size of the microspheres was measured by a laser diffraction analyzer (Helos, Sympatec Gmbh, Germany) equipped with a RODOS vibrating trough disperser.

2.4. Residual aluminum content analysis

Residual aluminum content in the microspheres was measured using Inductively Coupled Plasma (ICP, Thermo X series II, aluminum as standard material).

2.5. Residual dichloromethane analysis

Residual dichloromethane analysis in the microspheres was carried out through a headspace gas chromatographic technique

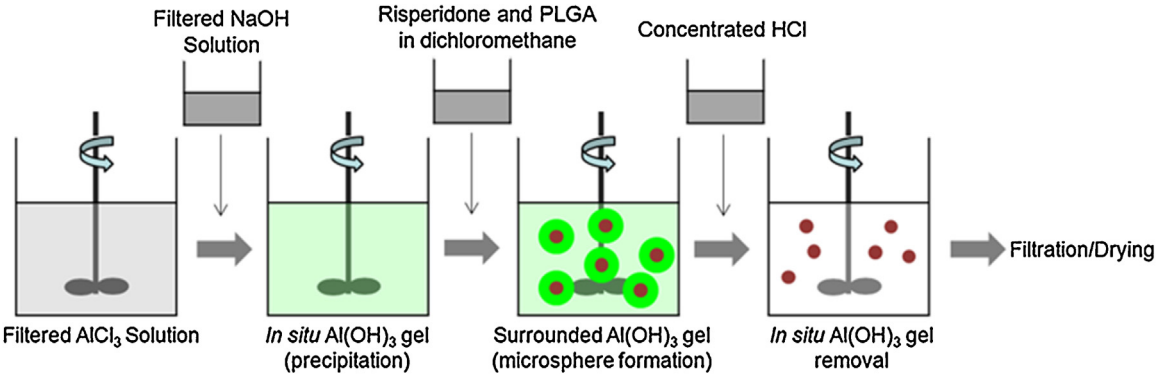

Fig. 1. Suspension-evaporation process to prepare the risperidone-loaded PLGA microspheres.