Development of implants for sustained release of rotigotine
to achieve CDS for the treatment of PD

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ABSTRACT SUMMARY
Rotigotine was formulated as extended-release implants in this study to achieve CDS for the treatment of PD. The rotigotine-PLGA implants were prepared in two types: hot-melt extrusion implant (HMEI) and in situ forming implant (ISFI). In vivo study of rotigotine HMEI on rats showed a 40-day sustained release with a lag phase which indicated a good potential in clinic application. And ISFI displayed only a 10-day release with high initial burst release.

INTRODUCTION
Levodopa induced dyskinesias (LID) is a common and troublesome motor complication faced with chronic levodopa therapy in Parkinson’s disease (PD) [1]. Substantial evidence has indicated a relationship between non-physiological or pulsatile stimulation of striatal dopamine receptors and LID in PD. Therefore, continuous dopaminergic stimulation (CDS) has become the focus of the treatment strategy for PD which can prevent the development of dyskinesia and received considerable attention for treatment of PD. However, the currently available CDS treatment options, such as duodenal infusion of L-DOPA (Duodopa®) and rotigotine transdermal delivery system (Neupro®), are associated with disadvantages of poor compliance, high cost or varied efficacy [2]. It is crucial to develop a more convenient and practical means to achieve CDS for the treatment of PD. Rotigotine is a non-ergoline agonist of dopamine D3/D2/D1 receptors for the therapy of PD [3]. The present study was designed to prepare a long-acting injection of rotigotine-PLGA implants to provide an alternative of CDS drug delivery.

EXPERIMENTAL METHODS
The extrusion process was performed with a HAAKE MiniCTW co-rotating twin-screw extruder. Rotigotine and polymer powder blends were manually fed into the preheated barrel. The operating temperature was maintained at 60-105°C and the residence time of the materials in the extruder was approximately 0-10 min. Then a 1 mm cylindrical die was used. The produced extrudate was rod-shaped and about 1 mm in diameter.

The polymer solutions were prepared by dissolving PLGA in appropriate amounts of DMSO in a vial under intermittent vortexing at room temperature. Designed portion of rotigotine were added to be dissolved just before the in vitro and in vivo experiment.

The drug loading of implants was determined by HPLC and the in vitro release was carried out according to orbital shaking bath method. Three replicates of each implant type in separate vials of phosphate-buffered saline on a shaker (37°C, 50 rpm). Samples of 8mL were withdrawn at intervals and replaced with fresh media. The samples were analyzed by HPLC. The external and internal morphology of implants was characterized by the optical microscopic observation and SEM morphology study.

Pharmacokinetics evaluation was carried out on rats. A dose of 10 mg/kg rotigotine of HMEI or ISFI was administered subcutaneously. Blood sample were collected pre-dose and at post-dose time points. The samples obtained were immediately centrifuged at 3000 rpm and the plasma was stored at −20°C before analyzed by HPLC-MS/MS.

RESULTS AND DISCUSSION
The in vitro release of rotigotine HMEI prepared from PLGA 5050 2A, 5050 4A, 7525 2A and 7525 5A displayed different release profiles, varying with lactide to glycolide ratio (polymer composition) and the molecular weight of polymer. Rotigotine HMEI prepared from 7525 5A displayed a longer release of about 40 days and presented a much dense internal structure.

The pharmacokinetics of rotigotine HMEI prepared from 7525 5A on rat was investigated (Fig. 1). It showed a 10-day lag phase followed by 40-day sustained release. And the plasma concentration of rotigotine reached $C_{\text{max}}$ of 1.09 ± 0.31 ng/mL on 23rd day.

While rotigotine ISFI prepared from 7525 5A (Fig. 2) only exerted a sustained-release of rotigotine for 10 days with high initial burst release due to the hydrophilicity of rotigotine and the alveolate internal structure of matrix.

Further investigation was needed to modify the lag phase existed in the rotigotine HMEI release profiles by adding low molecular PLGA or hydrophilic substance, such as PEG.

**CONCLUSION**

The current report enabled rotigotine-PLGA implant prepared by hot-melt extrusion to be a potential approach to providing long-term delivery of rotigotine. It could supply a convenient and practical alternative to achieve CDS in the long-term treatment of PD.

**REFERENCES**


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