# Preparation and characterization of sustained-released ropinirole tablet for the effective treatment of Parkinson's Disease

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## Introduction

- Parkinson's disease(PD) is a progressive neuro-degenerative disease characterized typically by motor features of tremor, rigidity, and bradykinesia due to the depletion of dopaminergic nigrostriatal neurons[1]. It is the second common neuro-degenerative disease after Alzheimer's disease [2, 3], PD results in a significant decline in quality of life.

- Ropinirole acts as a D2, D3, and D4 dopamine receptor agonist of the non-ergoline class of medications with highest affinity for D2. It stimulates striatal dopamine receptors alleviating the dopamine deficiency that characterizes PD.
The formulation of ropinirole is approved for use as monotherapy in the treatment of early-stage PD.
The common side effects reported were nausea, dizziness, and somnolence, typically ranging from 10 % to 20 %. It was reported that the side effects might be related closely to the rapid increase in blood drug concentration and the extent of depth between the peak and trough in the drug concentration.

- Sustained release dosage form can provide potential advantages including maintaining more consistent pharmacological activity, improved tolerability, greater compliance from once-a-day administration and easy dose titration.

## Objectives

- The purpose of this study was to develop the optimal monolith matrix system containing Ropinirole HCl showing sustained drug release profiles for 24 hours equivalent to the reference product (triple-layer structured Requip PD™ tablet) and superior chemical stability of ropinirole HCl.

## Methods

- Active pharmaceutical ingredient
  - Ropinirole HCl (Alembic pharmaceuticals)
  - Particle size: D90(108㎛), D50(32㎛), D10(2.5㎛)

- Hydrophobic release controller
  - Hydrogenated castor oil (Freund)

- Hydrophilic release controller
  - Carbomer (Lubrizol)
  - Hypromellose (90SH100,000SR, Shin-Etsu)
  - Hypromellose (60SH50, Shin-Etsu)

- Reference product
  - Requip PD™ tablet 2mg (GSK)

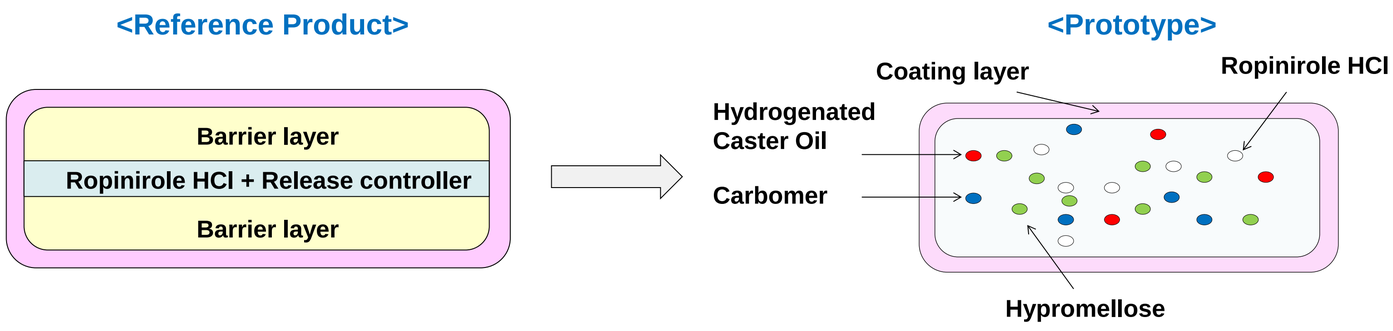
- Manufacturing processes of prototypes comprised wet granulation using a high shear mixer, posterior mixing, tablet compressing and film coating.

- Drug release tests were conducted according to USP Apparatus 2 at a paddle speed of 50 rpm in 900 mL of pH 1.2, 4.0 and 6.8 buffers with as a reference product.

- Stability test was performed under the stressed condition of 60℃ and the amount of impurity was evaluated in comparison with the reference product.

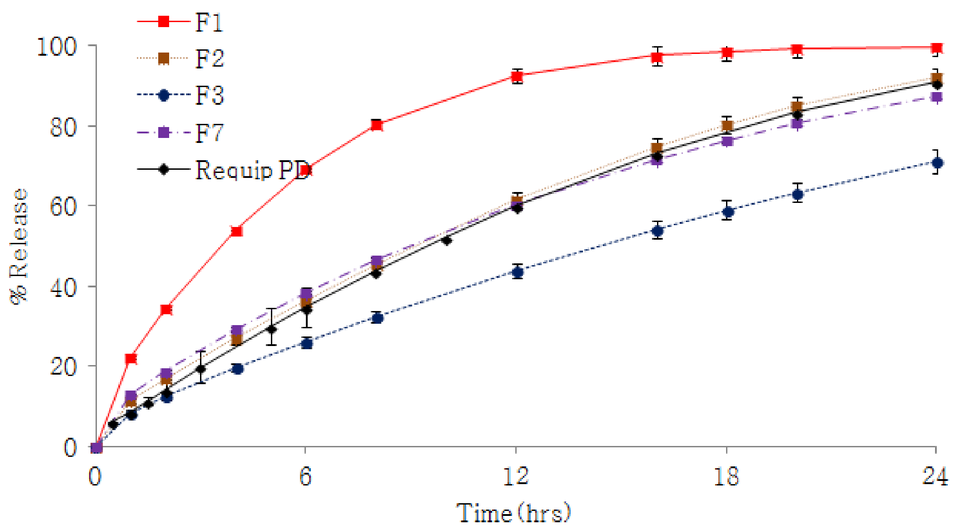
## Results

### Formulation concept of the tablets




| Prototypes | Ropinirole : Hydrophobic controller | Hydrophobic : Hydrophilic controller |
|---|---|---|
| F1 | 1 : 10 | 1 : 3.25 |
| F2 | 1 : 20 | 1 : 3.25 |
| F3 | 1 : 30 | 1 : 3.25 |
| F7 | 1 : 19 | 1 : 3.90 |

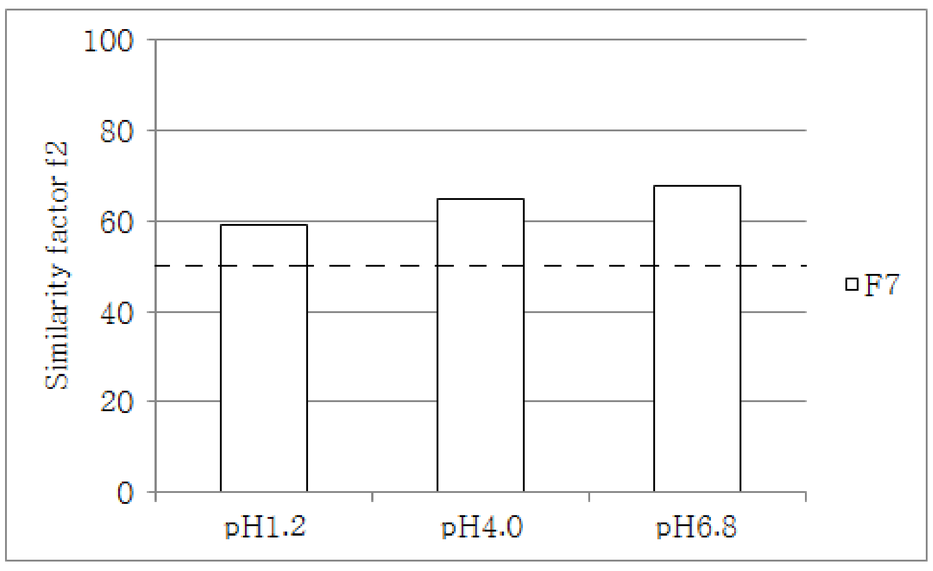
### Comparative Dissolution profiles of prototypes and reference product




* Formulation F1 - F7 tablets and Requip PD™ of dissolution profile; USP Apparatus 2 at a paddle speed of 50 rpm in 900 mL of pH 6.8 buffer

- Hydrophobic controller played an important role in drug release profile.
(Optimal ratio = 1 : 20)

- Balanced ratio of hydrophobic and hydrophilic controller led to 24-hours sustained release profile.




Similarity factor f2 calculated with dissolution data of final formulation (F7) and Requip PD™ tablet.

- Dissolution profiles of F7 prototype showed acceptable similarity with the reference product in media at the pH range of 1.2 ~ 6.8.

- Calculation of the f2 similarity factor was performed using following equation.

$$f_2 = 50 \times \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{j=1}^{n}|R_j - T_j|^2\right]^{-0.5} \times 100\right\}$$

### Comparative Stability test of prototype and reference product

| Total impurity | Requip PD™ | F7 |
|---|---|---|
| initial | 0.54 % | 0.35 % |
| 1 week | 0.78 % | 0.38 % |
| 2 weeks | 1.10 % | 0.39 % |
| 2 months | 1.36 % | 0.66 % |

* Stability test of tablet at stress condition (60 ℃)

- Prototype showed superior stability to the reference product at the point of the amount of impurity under the stressed condition.
(Δ2M-Initial : 0.31% vs 0.82%)

## Conclusions

- Sustained released (SR) prototypes containing Ropinirole HCl were successfully manufactured using simple and conventional processes.
- Prototypes including well-balanced drug/hydrophobic controller and hydrophilic/hydrophobic controller showed equivalent dissolution profiles and superior stability to the reference product.

* Reference
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