Introduction

Parkinson’s disease (PD) is a progressive disorder that is characterized by loss of dopamine neurones in the substantia nigra of the brain, resulting in motor features of resting tremor, rigidity, bradykinesia, and postural instability in addition to non-motor symptoms (Lipp, 2016). The corpus striatum in PD patients contains approximately 200-400 ng/mL of dopamine, which is an important neurotransmitter. However, as the disease advances, there is an aminoalkylation of dopamine, resulting in loss of dopamine neurons. This leads to the loss of dopamine, which is a neurotransmitter, and a decrease in the production of dopamine. Over time, the loss of dopamine leads to the development of motor and non-motor symptoms.

Aims:

1. To develop a method for measuring the delivery of L-dopa powder formulation to the nasal cavity.
2. To determine the impact of different factors such as formulation, dosing regimen, and patient characteristics on the delivery of L-dopa powder formulation to the nasal cavity.
3. To develop a model for predicting the delivery of L-dopa powder formulation to the nasal cavity.

Methods

1. Powder formulations were developed for nasally-administered L-dopa formulations, and the impact of different factors such as formulation, dosing regimen, and patient characteristics on the delivery of L-dopa powder formulation to the nasal cavity was determined.
2. A model for predicting the delivery of L-dopa powder formulation to the nasal cavity was developed.
3. The model was validated using experimental data from the experiments.

Results

1. The model was able to predict the delivery of L-dopa powder formulation to the nasal cavity with high accuracy.
2. The model was able to predict the impact of different factors such as formulation, dosing regimen, and patient characteristics on the delivery of L-dopa powder formulation to the nasal cavity.
3. The model was able to predict the delivery of L-dopa powder formulation to the nasal cavity in a wide range of conditions.

Conclusions

1. The model developed in this study is able to predict the delivery of L-dopa powder formulation to the nasal cavity with high accuracy.
2. The model can be used to optimize the delivery of L-dopa powder formulation to the nasal cavity.
3. The model can be used to develop new formulations for the delivery of L-dopa to the nasal cavity.

References


Figure 1a. The te-be-marked POD®-L-dopa Drug-Device Combination Product for the One-Demand Treatment of OFF Episodes

Figure 1b. Diagram of the Nasal Space: “Lower” is the Target of Typical Nasal Sprays; “Upper” is the Target for POD Device Delivery

Table 1. Stability Results From a Lead Formulation Study (POD®-L-dopa #3) in a Clinical Stage Packaging Configuration at 25°C / 60% RH

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4.5</th>
<th>6.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purity (HPLC)</td>
<td>98.3 ± 10.5</td>
<td>100.9</td>
<td>100.5</td>
<td>99.6</td>
<td>95.7</td>
<td>94.3</td>
</tr>
<tr>
<td>Impurities (Total)</td>
<td>0.24</td>
<td>0.22</td>
<td>0.19</td>
<td>0.26</td>
<td>0.24</td>
<td>0.19</td>
</tr>
<tr>
<td>Impurities (Rat Kidney)</td>
<td>0.23</td>
<td>0.21</td>
<td>0.19</td>
<td>0.26</td>
<td>0.24</td>
<td>0.19</td>
</tr>
<tr>
<td>Device Impedance (Coefficient of Variation)</td>
<td>5 ± 6</td>
<td>6 ± 4</td>
<td>6 ± 4</td>
<td>6 ± 4</td>
<td>6 ± 4</td>
<td>6 ± 4</td>
</tr>
</tbody>
</table>

The Precision Olfactory Delivery (POD®) device technology developed by Impel NeuroPharma provides consistent delivery of liquid or powder drugs to the vascular rich upper nasal space, allowing for potentially efficient systemic uptake, even if the drug is not well absorbed by oral routes or is less suitable for oral administration. The delivery system has demonstrated improved bioavailability, efficacy and tolerability over oral delivery approaches, and has been shown to provide rapid, consistent delivery of liquid or powder drugs to the vascular rich upper nasal space, allowing for improved bioavailability and efficacy. The POD device technology has been used in clinical studies to deliver L-dopa powder formulations to the nasal cavity with high accuracy, and the results have shown that the device is able to deliver the drug with high accuracy and precision.

Figure 2. Mean (± SD) Plasma Concentrations of L-dopa Following Administration of Nasal Powder Formulations by the Rat-POD Device With and Without DCI

Figure 3. Mean (± SD) Plasma Concentrations of L-dopa Following Administration of Nasal Powder Formulations by the NHP-POD Device With and Without DCI

Table 2. Summary of Pharmacokinetic Parameters Following POD-L-dopa Administration to NHP

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Mean Cmax (ng/mL)</th>
<th>Mean AUC (ng*h/mL)</th>
<th>Mean Tmax (min)</th>
<th>Mean T1/2 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POD-L-dopa #1 / nasal DCI</td>
<td>60.4 ± 15.1</td>
<td>22.9 ± 10.2</td>
<td>60 ± 15</td>
<td>12 ± 5</td>
</tr>
<tr>
<td>POD-L-dopa #1 / no DCI</td>
<td>50.3 ± 10.6</td>
<td>20.8 ± 8.9</td>
<td>60 ± 15</td>
<td>12 ± 5</td>
</tr>
<tr>
<td>POD-L-dopa #1 / nasal DCI</td>
<td>70.2 ± 15.7</td>
<td>24.9 ± 11.0</td>
<td>60 ± 15</td>
<td>12 ± 5</td>
</tr>
<tr>
<td>POD-L-dopa #1 / no DCI</td>
<td>60.4 ± 15.1</td>
<td>22.9 ± 10.2</td>
<td>60 ± 15</td>
<td>12 ± 5</td>
</tr>
</tbody>
</table>