Preparation and in vitro release of isoperidone gastroretentive tablets

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ABSTRACT SUMMARY
A series of formulations of isoperidone (isoperidone hydrochloric acid salt) gastroretentive tablets were designed with different in vitro release behaviors to improve the oral bioavailability of the isoperidone, a prodrug of paliperidone.

INTRODUCTION
Paliperidone was an atypical antipsychotic drug, launched by JNJ under the trade name of Invega® for the treatment of schizophrenia in 2006, which was also an active metabolite of risperidone. However, the oral bioavailability of Invega® in human was only 28%. To improve the poor availability, we synthesized a series of potential prodrugs of paliperidone that had good absorption and could rapidly metabolized into paliperidone after oral administration. On the basis of the initial studies, we optimized isoperidone hydrochloric acid (Fig.1), one of the prodrugs, to research and development the oral gastroretentive tablets.

EXPERIMENTAL METHODS
The formulation consisted of isoperidone, Hydroxy propyl methyl cellulose (HPMC) (K4M, K100, Colorcon), Spray Dried Lactose (DMV SuperTab 11SD), Sodium Bicarbonate, Citric Acid, Croscarmellose Sodium, Magnesium Stearate. Isoperidone, Sodium Bicarbonate and Citric Acid were milled, respectively, and passed through 80 meshes. All ingredients were mixed according to the formulations (shown in Tab.1) by sieving manually. The tablets were prepared by the mixed powder or dry granulation method.

The release of isoperidone from the tablets was studied using the USP dissolution apparatus II (Rotating paddle). The dissolution test was performed using 500 ml of 0.01 N HCl. The temperature was maintained at 37±0.5 °C. The rotation speed was 50 rpm. Five milliliters was withdrawn at predetermined time intervals. The medium was replenished with 5 ml of fresh dissolution medium each time. The samples were filtered through a 0.45 μm and were analyzed by HPLC.

RESULTS AND DISCUSSION
All the formulations shown in Tab.1 had good floating characteristics which could be seen from in vitro dissolution study. The in vitro...
release profiles were shown in Fig.2. 10% NaHCO₃ was the only gas generating agent in Formulation Powder-1 (P-1). The tablets P-1 had a small initial release in 0.5h but had a relatively high release speed afterwards. The percentage of NaHCO₃ and Citric Acid were lower in P-2. However, the addition of Croscarmellose Sodium ensured P-2 good floating characteristics and release profile. P-3 had similar release profile to P-1 because of high proportion of low viscosity HPMC and high proportion of NaHCO₃ and Citric Acid.

Dry granulation method was also tried in our studies. Formulation Granulation-1 (G-1) had the same formulation with P-2, while the release behavior of G-1 was totally different from that of P-2. It release faster as the tablets would disintegrate into several small piece during dissolution. We could achieve perfect zero order kinetic release profile by adjust the proportion of ingredients in the formulation, such as G-2 or G-3.

**CONCLUSION**

We successfully prepared Isoperidone Hydrochloric Acid gastroretentive tablets. They had good in vitro release behaviors and floating capacities.

**REFERENCES**

2. Joao F. Pinto, Site-specific drug delivery systems within the gastro-intestinal tract: From the mouth to the colon, Int. J. Pharm. 395 (2010) 44 – 52

![Fig.2 In vitro release profiles of isoperidone gastroretentive tablets (mean±S.D., n=6)](image)

**Tab.1 Formulations of Isoperidone gastroretentive tablets**

<table>
<thead>
<tr>
<th></th>
<th>Isoperidone</th>
<th>HPMC K4M</th>
<th>HPMC K100</th>
<th>Lactose</th>
<th>NaHCO₃</th>
<th>Citric Acid</th>
<th>Croscarmellose Sodium</th>
<th>Magnesium Stearate</th>
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<td>57</td>
<td>10</td>
<td>—</td>
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<td>5</td>
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<tr>
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<td>29.4</td>
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*Unit: %.