**In Vivo Validation of the Release Rate and Palatability of Remoxipride-Modified Release Suspension**

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Remoxipride, a D₂-dopamine receptor antagonist, is well tolerated and completely absorbed after oral administration. Because of its extremely bitter taste, an oral palatable suspension was developed by using a taste-masking microencapsulation. The bioavailability of remoxipride was investigated in two studies in healthy volunteers after administration of a 100-mg dose in suspension. The first study used a capsule as reference, and the second study a plain solution. Taste assessment was carried out in the second study. The extent of bioavailability was the same when comparing the oral suspension to a capsule and to a plain solution. However, the rate of absorption is delayed, and $T_{\text{max}}$ was 3.0 hr after the suspension, 1.0 hr after the oral solution, and 1.6 hr after the capsule. The release rate in vitro from the suspension was determined by applying the USP-paddle method. By using numerical convolution and deconvolution, the release rates in vivo and in vitro were shown to be similar when using water with 0.5% sodium laurel sulfate as dissolution liquid. The taste-masked oral suspension is suitable for full-scale production, with good control of the encapsulation process and of the preparation of a suspension.

**KEY WORDS:** remoxipride; modified release; suspension; bioavailability; convolution; deconvolution; dissolution.

**INTRODUCTION**

Remoxipride, a new antipsychotic drug, is a potent and selective dopamine D₂ receptor antagonist. Thus, remoxipride has the potential to separate the benefits of control from the burden of side effects, such as extrapyramidal symptoms, and sedation, which is a problem for other neuroleptic drugs. Remoxipride has been administered to more than 1500 patients in controlled clinical studies in doses of 150 to 600 mg daily for 6 weeks or longer and has been shown to have antipsychotic activity and to be well tolerated (1–6).

The pharmacokinetics of remoxipride have been investigated in approximately 300 healthy volunteers after administration of single doses ranging from 0.5 to 140 mg and after repeated oral doses of 20, 70, and 140 mg three times a day. The drug is rapidly absorbed (7,8), with an oral bioavailability of above 90% compared to intravenous administration (9). It is well tolerated in single doses of 100 mg or less (10). Oral medication in tablet or capsule form can be a problem for those patients, particularly the elderly, who have difficulty in swallowing tablets. A solution or suspension formulation can facilitate drug-taking for such patients, thus increasing patient compliance. Because plain aqueous solution has an extremely bitter taste, a taste-masked formulation has been developed. A similar bad taste has been reported to be associated with most major neuroleptic liquid preparations (11). Taste-masking of drugs can be achieved by microencapsulation or related techniques (12–14), and it is required for improving patient compliance for certain groups of patients. The aim of the present study was to determine the rate and extent of bioavailability of microencapsulated remoxipride in suspensions with different in vitro characteristics and to establish specification limits of the in vitro release rate when considering the product manufactured both in small-scale and in large-scale production.

**MATERIALS AND METHODS**

**Dosage Forms**

*Remoxipride Capsules, 100 mg.* Remoxipride HCl monohydrate was mixed with lactose and granulated with polyvidone in water. The granulate was dried and lubricated with magnesium stearate before filling into hard gelatin capsules, No. 1.

*Remoxipride Oral Solution, 50 mg/mL.* Remoxipride HCl monohydrate was dissolved in water and no other additives were added.

*Remoxipride Oral Suspension, 25 mg/mL.* Remoxipride HCl monohydrate is freely soluble in water. In order to develop a palatable liquid formulation, a two-step manufacturing procedure has been developed. Step 1 is microencapsulation of remoxipride in wax and step 2 is preparation of the suspension. The microencapsulation procedure is performed in a spray-chilling apparatus where remoxipride is melted in wax at about 85°C. The melted substance is then applied through a tube connected to a rotating, vaned disk, forming droplets which, after solidification in cool air, are collected as microspheres in the bottom of the apparatus. The diameter of the microspheres is 150 μm (15).

In order to achieve a suspension of the remoxipride microspheres which prevents the drug from immediate dissolution, the microspheres are then suspended in a tasteless oily vehicle and thickened to give a proper viscosity. Sweetener and flavors are also added. The suspension had a viscosity of about 100 mPAs, which maintains a homogeneous suspension for several days after shaking the bottle. The suspensions were produced at different scales (Table I). The bottles used for each volunteer in the bioavailability studies contained manually weighed microspheres and vehicle in order to get an exact dose of 100 mg remoxipride in 4 mL of suspension.

**In Vitro Methods**

*Remoxipride Capsules, 100 mg.* The in vitro dissolution of remoxipride from capsules was performed by using the paddle method (USP XXII, 500 mL water at 37°C, 50 rpm).
Table 1. Batch Sizes of Remoxipride Oral Suspension, 25 mg/mL, Manufactured

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Study</th>
<th>Microsphere (g)</th>
<th>Suspension (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspension A</td>
<td>1</td>
<td>300 g, 40% (w/w)</td>
<td>3</td>
</tr>
<tr>
<td>Suspension B&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2</td>
<td>20 kg, 40% (w/w)</td>
<td>1200</td>
</tr>
<tr>
<td>Suspension C&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2</td>
<td>20 kg, 30% (w/w)</td>
<td>1200</td>
</tr>
<tr>
<td>Suspension D&lt;sup&gt;c&lt;/sup&gt;</td>
<td>—</td>
<td>20 kg, 40% (w/w)</td>
<td>1200</td>
</tr>
<tr>
<td>Suspension E&lt;sup&gt;c&lt;/sup&gt;</td>
<td>—</td>
<td>20 kg, 40% (w/w)</td>
<td>1200</td>
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</tbody>
</table>

<sup>a</sup> Payload of remoxipride in wax.

<sup>b</sup> Final filling in laboratory scale.

<sup>c</sup> Production.

Remoxipride Oral Suspension, 25 mg/mL. The same paddle method was used (USP XXII, 500 mL water, pH 7.1, phosphate buffer pH 4.1, or simulated gastric fluid without pepsin, pH 1.2, at 37°C and at 150 rpm). The suspension was added to the dissolution beaker after starting the paddle. Samples were withdrawn and analyzed by HPLC. The method had been optimized based on practical aspects, emulsifying capability, variability, and reproducibility. Accordingly the influence of agitation, volume of suspension fluid, volume of added suspension, and surfactant have been studied. The following surfactants have been tested: sodium lauryl sulfate (SLS), cetrimide, DOSS, ethanol, Myrij 45, and Tween 80. Figure 1 describes the influence of the amount of surfactant added to the dissolution fluid. The in vitro dissolution of the formulation studied are shown in Table II.

Design of the Studies

Two separate bioavailability studies were performed, one at the Department of Psychiatry at Huddinge University Hospital, Huddinge, Sweden (Study 1), and the other at the Royal Infirmary, Edinburgh, Scotland (Study 2). They were approved by the Ethics Committee at Huddinge Hospital and the Lothian Health Board Ethics Committee, respectively. All participants were fully informed both in writing and verbally about the purpose, investigational events, and possible risks involved with the studies. The volunteers were of both sexes and were healthy according to medical history, physical examination, blood and urine analysis, and ECG.

The studies were comparative, randomized, and crossover. Each volunteer was given a single dose of 100 mg remoxipride as one of three formulations. A washout period of at least 1 week elapsed between each treatment. After an overnight fast of minimum 8 hr and 150 mL tap water, given at least 1 hr prior to drug administration, the volunteers were given one of the formulations in the morning with 150 mL water. They continued fasting for a further 3 hr. A standardized lunch was served after the 3-hr sample. Further, a small meal and dinner were served 7 and 10 hr after drug administration, respectively. Venous blood samples (5 mL) were obtained from a cannula inserted in an antecubital vein or by

![Fig. 1. Experimental plasma concentration of remoxipride versus time (mean; SD; n = 15) after 100 mg remoxipride in the modified release suspension A (Study 1). The curves are hypothetical levels derived by use of numerical convolution and the seven in vitro dissolution time functions, I(t), shown in the inset.](image-url)