New Spectrophotometric Methods for the Determination of Racecadotril in Bulk Drug and Capsules

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Two simple and sensitive spectrophotometric methods (A and B) for the determination of racecadotril in bulk drugs and pharmaceutical formulations are described. In method A, methanol was used as solvent and shows absorption maximum at 231 nm. In method B, the solvent used was acetonitrile:water in the ratio of 1:3 and shows absorption maximum at 232 nm. The Beer's law range for method A is 25-100 µg/ml and 20-80 µg/ml for method B. When capsules dosage forms were analyzed, the results obtained by the proposed methods are in good agreement with the labeled amounts and the results were validated statistically.

Racecadotril is an effective and safe drug for acute diarrhea in adults and children. Chemically racecadotril is N-[(R,S)-3-acetylmercapto-2-benzylpropanoyl]-glycine benzyl ester1-3 (fig. 1). The Drug Controller General of India approved it as an antidiarrheal in October 20014. It is not yet official in any Pharmacopoeia. A survey of literature revealed that a few HPLC5 methods were reported for the estimation of racecadotril in biological fluids. In the present report, the paper describes two simple, economical and sensitive spectrophotometric methods for the determination of racecadotril in bulk samples and solid dosage forms. In method A, methanol was used as solvent and in method B, acetonitrile:water (1:3) was employed.

Absorbance measurements were made on a Shimadzu-1700 double beam UV/Vis spectrophotometer. All the solvents used for analytical studies of racecadotril were of analytical reagent grade. Pharmaceutical grade of racecadotril was kindly gifted by M/s. Micro Labs, Pondicherry, India. The capsules of racecadotril used for the studies were procured from a local Pharmacy. The solubility of racecadotril was determined in a variety of solvents using essentially a method of Schefter and Higuchi6. From the solubility studies, methanol and acetonitrile:water (1:3) were selected as solvents for UV spectroscopical studies of racecadotril in bulk drug and capsules dosage form. The λmax was determined in methanol and acetonitrile:water (1:3).

In method A, racecadotril (25 mg) was dissolved in methanol and the total volume was brought to 100 ml with

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Fig. 1: Structure of the racecadotril
methanol. It was further diluted to obtain 25-100 µg/ml with methanol. The absorbance was measured at 231 nm against methanol as blank. The calibration curve was plotted in the concentration range of 0.025 to 0.1 mg/ml of racemadotril in methanol. In method B, racemadotril (50 mg) was dissolved in acetonitrile:water (1:3) and the total volume was brought to 100 ml. It was further diluted to obtain 20-80 µg/ml with acetonitrile:water (1:3). The absorbance was measured at 232 nm against reagent as blank. The calibration curve was plotted in the concentration range of 0.02-0.08 mg/ml of racemadotril.

In method A, twenty capsules of each formulation $S_1$ and $S_2$ containing racemadotril were powdered, weighed equivalent to 25 mg of racemadotril and dissolved with 20 ml methanol, vigorously shaken for 20 minutes and filtered through Whatmann filter paper No. 41. Repeated the extraction three times, filtered and made up to 100 ml with methanol. The dilutions were made in the same manner as described under bulk drug. The absorbance measurements were made six times for each formulation. The amount of racemadotril was calculated from the respective calibration curve (method A). In method B, Capsules powder equivalent to 50 mg of racemadotril was weighed and extracted with successive quantities of acetonitrile:water (1:3), filtered through Whatmann filter paper No. 41 and made up to 100 ml with the same solvent. Subsequent dilutions and absorbance were measured as described under procedure for calibration curve. The amount of racemadotril was calculated from the respective calibration curve (Method B). Recovery experiments were performed by adding six different quantity of drug in previously analyzed sample, but with in the limit of Beer’s Law amount. The percentage of drug recovered was calculated by a mathematical relation followed by Sane et al.

The range of linearity for racemadotril was determined in methanol and acetonitrile:water and found to be 25-100 µg/ml and 20-80 µg/ml respectively. Beer’s Law limits, molar absorptivity, Sandell’s sensitivity, slope and intercept of regression analysis using least square method, precision and accuracy of the analysis are summarized in Table 1. The results of pharmaceutical preparations (capsules) containing racemadotril are shown in Table 2. The outcome of recovery studies revealed the method B is more sensitive and accurate than the method A. As an additional check on the accuracy of the methods, recovery experiments were performed by adding known amount of pure drug to pre-analyzed dosage forms. The percentage of drug recovered (99-102%) was good agreement with the added amount and labeled claim. Recovery experiments indicated the absence of interference from commonly encountered pharmaceutical additives and excipients. The proposed methods were validated statistically and found reproducible results. All statistical data proves validity of the proposed methods, which can be applied in industries for routine analysis of this method to analyze racemadotril in bulk drug and Pharmaceutical preparation. These results indicate that the proposed methods are sensitive, accurate, precise and reproducible.

**ACKNOWLEDGEMENTS**

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**TABLE 1: OPTICAL CHARACTERISTICS OF PROPOSED METHODS**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Method A</th>
<th>Method B</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda_{\text{max}}$ (nm)</td>
<td>231</td>
<td>223</td>
</tr>
<tr>
<td>Beers law limit ($\mu$g/ml)</td>
<td>25-100</td>
<td>20-80</td>
</tr>
<tr>
<td>Sandell’s sensitivity* ($\mu$g/cm$^2$/0.001 A.U)</td>
<td>0.087412</td>
<td>0.077519</td>
</tr>
<tr>
<td>Molar extinction coefficient (1 mol$^{-1}$cm$^{-1}$)</td>
<td>4.411×10$^3$</td>
<td>5.282×10$^3$</td>
</tr>
<tr>
<td>Correlation coefficient ($r^2$)</td>
<td>0.999329</td>
<td>0.999623</td>
</tr>
<tr>
<td>Regression equation (y=mx+c)</td>
<td>0.566</td>
<td>0.514</td>
</tr>
<tr>
<td>Slope ($m$)</td>
<td>0.011148</td>
<td>0.01299</td>
</tr>
<tr>
<td>Intercept ($c$)</td>
<td>0.014737</td>
<td>0.007121</td>
</tr>
<tr>
<td>Confidence limit with 0.05 level (95%)</td>
<td>± 0.5800</td>
<td>± 0.3965</td>
</tr>
<tr>
<td>Confidence limit with 0.01 level (90%)</td>
<td>± 0.9096</td>
<td>± 0.6218</td>
</tr>
</tbody>
</table>

*Sandell sensitivity (S) = 10$^{-3}$/A; $S$ = Number of micrograms of the determined per ml of a solution having a cross section of 1 cm$^2$ and absorbance of 0.001 and a = absorbance of 1 mg/ml solution determined in a cuvette with an optical path length of 1 cm.

**TABLE 2: ASSAY AND RECOVERY STUDIES OF RACEMADOTRIL IN CAPSULE DOSAGE FORM**

<table>
<thead>
<tr>
<th>Pharmaceutical formulation $^*$</th>
<th>Labeled amount (mg/capsule)</th>
<th>Amount found in mg* by Method A (mg) (mean±SD)</th>
<th>Method B (mg) (mean±SD)</th>
<th>Percent recovery Method A</th>
<th>Percent recovery Method B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsule – $S_1$</td>
<td>100</td>
<td>100.3±0.1469</td>
<td>99.9±0.077</td>
<td>99.11</td>
<td>100.45</td>
</tr>
<tr>
<td>Capsule – $S_2$</td>
<td>100</td>
<td>100.1±0.2104</td>
<td>100.19±0.0194</td>
<td>99.08</td>
<td>101.65</td>
</tr>
</tbody>
</table>

*Mean of six determinations. $^*$The commercial preparations used were, Capsule – $S_1$ is Redotil, and Capsule– $S_2$ is Cadotril.
The plasma concentration time profiles for nicotine were characterized after a single application of nicotine transdermal system to the upper fore arm of healthy smokers. A 12 cm$^2$ system was applied for 24 h. Blood samples were withdrawn at predetermined time intervals. Plasma nicotine concentrations rose rapidly and achieved a mean $C_{\text{max}}$ value of 14.5 ng/ml. The half life was estimated as 4.78 h and $AUC(0-24)$ 181.0 ng.h/ ml. The nicotine transdermal system was well tolerated. The results indicate that the system has potential usefulness in smoking cessation. The pharmacokinetic profiles of marketed patch system was compared with the developed system. Significant difference was observed in the pharmacokinetic parameters.

Pharmacokinetic Evaluation of a Developed Nicotine Transdermal System

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Nicotine Transdermal Systems (NTS) are widely available in the western countries and significant advances have been made in this field. NTS are reported to be well tolerated in clinical trials because of their ease of use and unobstrusive nature resulting in better patient compliance. NTS have also been reported to reduce daily cigarette use in subjects who are unable to totally abstain from smoking.

Several forms of nicotine replacement therapy are available in the market. However, difference in the amount and pattern of nicotine delivery from patches may confer clinical advantages and disadvantages to individual patch users as cigarette users also vary in the amount and pattern of nicotine obtained from smoking. There are many reviews reporting the pharmacokinetics of nicotine transdermal systems. These reviews report differences between the systems in terms of both amount of nicotine delivered, as well as rate of delivery; however, the data reported were taken from studies of individual systems.

The current study compared the pharmacokinetic profiles of marketed patch system with the developed system. The developed system was loaded with 40 mg of nicotine and bore a rate controlling membrane. The system was designed to deliver nicotine over a 12 cm$^2$ area at a controlled rate of 95 µg/cm$^2$/h.

The study was conducted in six healthy south Indian adult male smokers. The study was open and conducted in age group between 25-40 y and weighing 50-60 kg. Subjects were confirmed to be in good health by physical examination, medical history and routine clinical tests. Exclusion criteria were any illness or medication use and drug or alcohol abuse. Written consent was obtained from each subject. The study was approved by Hospital Ethical Committee.

REFERENCES