Buccal tablets of ritodrine (RD) hydrochloride (HCl), called RD-HCl, were prepared using the direct compression method with alginate (AL), lactose (LC), magnesium stearate (ST), and microcrystalline cellulose (MC) as excipients. The tablets were evaluated based on hardness, and tablets weighing 80 mg and with hardness of greater than 30 N were chosen as appropriate ones. As a result, tablets composed of RD-HCl (4 mg)/LC (38.5 mg)/ST (0.5 mg)/MC (37 mg) and RD-HCl (4 mg)/AL (7 mg)/LC (28.5 mg)/ST (0.5 mg)/MC (37 mg), called D9 and D10, respectively, were selected. These tablets were further evaluated based on in vitro dissolution and in vivo absorption studies in rats. D9 rapidly released RD, achieved an effective plasma concentration from 15 min to 7 h after its buccal administration, and did not exceed the toxic plasma level of 80 ng/mL. D10 gradually released RD, and maintained an effective concentration from 1 h to 7 h after its buccal administration, without exceeding the toxic plasma level. The absorption was more prolonged in D10 than D9. Their in vivo release was considered to be caused gradually from the amount of RD remaining in the oral cavity at 7 h, in particular D10. The superior retention of D10 in plasma and oral cavity appeared to be related to its higher mucoadhesive properties. Although these results were obtained using rats, they suggest that the chosen tablets should have adequate characteristics from the viewpoints of plasma levels.

Key words  ritodrine; buccal tablet formulation; hardness; in vitro dissolution; in vivo absorption

Ritodrine (RD) hydrochloride (HCl), called RD-HCl, is essential in the treatment of premature labor or imminent abortion, which have been shown to increase the risk of damage to newborn infants. Respiratory complications associated with preterm birth can lead to obstructive lung diseases in the later life. RD, a β2-adrenergic agonist, induces relaxation of the uterine smooth muscle, and is selected as a first-line drug in the treatment of premature labor. Although RD is known to exhibit highly specific β2-adrenergic actions, its β1-adrenergic function still exists to some extent. Therefore, the side effects associated with an increase in the plasma concentration of RD, such as an elevated heart rate and chest pain, must be carefully monitored.

RD is generally intravenously infused or orally ingested. Also, it is rapidly administered into the systemic circulation via intravenous infusion in urgent cases, such as to inhibit preterm labor. The plasma concentration of RD was recently shown to be closely associated with the suppression of preterm labor. Furthermore, it had to be maintained above a minimal effective concentration in order to preserve the pregnant state. Although intravenous infusions can maintain effective plasma concentrations of RD, patients are confined to bed rest through the infusion period, which may reduce their QOL. Once the prevention of premature labor is achieved under certain dosing conditions, the administration of RD can be converted from its intravenous infusion to oral ingestion, which is markedly better for the QOL of patients.

The oral dosage form of RD is a commercially available tablet. Since the tablet can be easily taken and is highly acceptable due to the low burden on patients, its administration can be continued for a long period of time. However, the bioavailability of the oral RD formulation is known to be very low, namely, approximately 30% or less, and its plasma half-life of RD is also relatively short at 1–2 h; therefore, the drug has to be taken orally at least 3 times per day.

The disadvantages associated with both the intravenous infusion and tablet formulation of RD, as described above, need to be improved. Oral mucosal absorption has recently attracted attention because it is easy for drug dosing, allows the first-pass effect in the intestine or liver to be avoided, and enables relatively fast absorption and maintains prolonged systemic levels. Thus, we previously attempted buccal administration as a novel administration route and found that the bioavailability and maintenance of plasma concentrations of RD were superior with buccal administration than with oral dosing. Relatively rapid absorption was also attained with the buccal administration of RD. We developed buccal tablets of RD-HCl for easier handling, tablets with good hardness and fast drug release were produced using alginate (AL), lactose (LC), magnesium stearate (ST), and microcrystalline cellulose (MC) as excipients. MC was found to be crucial for providing good hardness and achieving rapid drug release. However, a detailed formulation study was not performed in our previous study. Therefore, tablet formulations with AL/LC/ST/MC or LC/ST/MC as excipients were herein investigated in detail from the viewpoints of tablet size, hardness, drug release, and the maintenance of plasma concentrations.

MATERIALS AND METHODS

Materials  RD-HCl, phosphoric acid, urethane, sodium alginate of 80–120 cP grade (AL: 80–120 mPa·s for 10 g/L at 20°C), and ST were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). LC of JP16 grade was supplied by Miyazawa Yakuhin Co., Ltd. (Tokyo, Japan). Avicel PH301, purchased from Asahi Kasei Corp. (Tokyo, Japan), was used as MC. All other chemicals used were reagent grade.

Animals  Male Wistar rats (7 weeks old, 200–210 g) were
were kept at 23°C by Oriental Yeast Co., Ltd. (Tokyo, Japan) with water added. Rats were kept on the MF breeding diet supplied by Tokyo Laboratory Animal Science Co., Ltd., purchased. Rats were fixed to the glass plate with glue and the one flat side of the tablet was placed into a cylinder, and then compressed at 2 kN for 30 s. After the removal of the pressure, the tablets were placed into the cylinder, and compressed at 2 kN for 30 s. The drug content per tablet was investigated as follows (n=3). A tablet was placed in 10 mL of the JP16 2nd fluid, that is, 0.05 M phosphate buffer of pH 6.8, and incubated by horizontal shaking at 60 strokes per min at 37°C for 24 h. The resultant solution or suspension was stirred vigorously with a vortex mixer. After centrifugation of the sample, the supernatant was diluted adequately using the 2nd fluid, and analyzed fluorometrically with a FP-777 spectrofluorometer (Jasco Corp., Tokyo, Japan) at an excitation wavelength of 278 nm and emission wavelength of 306 nm. The absolute calibration curve method was used to determine RD concentrations at which a linear calibration was obtained, 0.1–12 µg/mL/mL (R^2=0.999).

**In Vitro Dissolution Studies** Dissolution studies were conducted on the chosen tablets. Drug release profiles were investigated by the JP16 paddle method using an NTR-3000 dissolution tester (Toyama Sangyo Co., Ltd., Osaka, Japan). JP 2nd fluid (400 mL) was used as a test medium at 37°C, and the paddle was rotated at 50 rpm at a position 2.5 cm from the bottom of the container. After a tablet was placed in the medium, aliquot samples (4 mL each) were withdrawn at the appropriate time points; fresh JP 2nd fluid (4 mL) was added after each sampling. The clear supernatant of the sample was measured fluorometrically in the same manner described above.

**In Vitro Mucoadhesion Studies** The mucoadhesive properties of tablets D9 and D10 were investigated in vitro. After the rats were sacrificed by excessive anesthesia with ether inhalation, their oral mucosa tissue (approximately 1 cm in length×1 cm in width×1 mm in thickness) was taken from the buccal mucosa around the bottom lip. The mucoadhesion of the tablet was examined based on the method by Agarwal et al. The opposite side of the mucosal membrane was fixed to the glass plate with glue, and the one flat side of the tablet was also fixed to the glass plate with glue. The glass plate with the mucosal membrane fixed to the table so that the mucosal surface was set upward. After 50 µL of saline was dropped on the mucosal membrane, the tablet surface was set to the downward direction, and brought into contact with the mucosal membrane, and 0.49 N was added to the tablet/membrane composite for 30 s. After the removal of the pressure, the tablet holder was lifted with the increase in force at 0.06 N/min. The force immediately before the tablet was detached from the mucosal membrane was determined as mucoadhesive strength.

**In Vivo Absorption Studies** Bucal absorption was examined for the chosen tablets. After rats were anesthetized by an i.p. injection of 1.2 mL of a 25% (w/v) urethane solution in saline, they were fixed on their backs. A sample (0.3 mL)
of blood was collected prior to the administration of tablets. After one tablet had been placed on the right cheek mucosa of the rat, 0.1 mL saline was placed on the mucosa near the bottom of the inserted tablet, and the tablet was gently pressed against the mucosal surface at the administered site. Blood samples (0.3 mL) were withdrawn via the jugular vein at the appropriate time points. Plasma was obtained by centrifuging blood samples at 1400×g for 5 min. Plasma (0.1 mL) was mixed with 0.1 mL of 1 M carbonate buffer (pH 9.5) and stirred vigorously. A total of 0.5 mL ethyl acetate was then added, shaken vigorously, and centrifuged at 1500×g for 10 min. The resultant organic phase (0.3 mL) was collected, and the solvent was evaporated under nitrogen gas. The residue was dissolved in 0.1 mL of the HPLC mobile phase. Forty microliters of the solution was injected onto the HPLC column to determine the RD concentration.

Seven hours after the buccal administration of RD, the whole tablet residue in the oral cavity was collected using a small spatula, and transferred into a glass tube. Saline was added to the residue to adjust the volume to 8 mL. A portion (0.4 mL) was collected after vigorous shaking. It was treated in a similar manner to the plasma sample. The volume ratio of sample/1 M carbonate buffer/ethyl acetate at 1/1/5 (v/v) was used in the extraction. The organic phase (0.5 mL) was obtained after centrifugation of the operated mixture, and dried under nitrogen gas. The residue was dissolved in the mobile phase (0.5 mL), diluted appropriately, and the final sample (40 µL) was injected onto the HPLC column. The amount of RD in the residue in the oral cavity was calculated from the RD concentration.

HPLC Assay A HPLC assay of RD was performed at room temperature using a Shimadzu LC-6AD pump equipped with a Shimadzu RF-10AXL fluorescence detector and a Shimadzu C-R7A chromatopac. A YMC Pack ODS-AM column (6 mm inner diameter ×150 mm length; YMC Co., Ltd., Kyoto, Japan) was used as an analytical column. A mixture of 0.05% phosphoric acid and acetonitrile (5:1, v/v) was used as the mobile phase. Detection was performed with the fluorescent detector set at excitation and emission wavelengths of 278 nm and 306 nm, respectively. The concentration of RD was determined by the absolute calibration curve method.

Statistical Analysis The unpaired t-test was used for statistical analyses, and a significant difference was set as p<0.05.

RESULTS AND DISCUSSION

Tablet Formulations and Hardness As reported previously, 21) although AL/LC tablets could be formed adequately by the direct compression method, their hardness was insufficient. The addition of MC improved the strength of tablets. The addition of MC also provided tablets with disintegration properties, thereby enhancing drug dissolution. Although the addition of MC to AL/LC tablets enhanced tablet characteristics such as hardness and drug release, these effects had not been investigated in detail. The weight of these tablets, approximately 120 mg, was also slightly large; therefore, a smaller tablet size was desirable.

In the present study, first, the effects of MC on tablet strength were examined in the absence of RD. The influence of adding MC was investigated by comparing the 5 formulations. Tablets of a size that was easy to place on the oral mucosa were considered desirable for buccal dosing. Thus, the weight of tablets was set at 76 mg, which was achieved by reducing the amount of AL while increasing that of MC. Tablet hardness of greater than 30 N was generally required to prevent it from breaking with normal handling. As shown in Table 1, a larger amount of MC was needed than LC to achieve this hardness. ND8 and ND9 were found to be acceptable.

RD-containing tablets (Dn) were subsequently produced by referring to the above estimation of the relationship between the formulation and hardness of tablets with no RD, and the hardness of the obtained tablets was then investigated. The addition of MC influenced tablet hardness in a similar manner to that of tablets with no RD. D1 and the bottom 6 formulations in Table 2 were prepared with a tablet weight of 80 mg. In D1 vs. D5 and D7 vs. D8, 0.5 mg of ST appeared to increase tablet hardness more than 1 mg of ST. A comparison of D8, D9, and D10 revealed elevations in tablet hardness with increases in the amount of MC. When the tablet hardness was compared between D5 and D6, or D8 and D9, the increase in the MC amount was observed to raise the tablet hardness. MC appeared to contribute to the increase in tablet strength, while AL did not seem to work on the elevation of tablet harness. In fact, as reported previously, 21) tablets, made using AL as a major component, showed low tablet strength. D9 tablets could be formed well even in the absence of AL, and this was attributed to the good binding ability of MC. Since hardness greater than 30 N was required for tablet strength, D9 and D10 were selected as tablets with a weight of 80 mg, thereby fulfilling the requirements.

In Vitro Characteristics of Chosen Tablets The physical characteristics of the chosen tablets, D9 and D10, were investigated in detail. The amount of RD contained in these tablets needed to be determined in order to exactly calculate the ratio of RD released. The physical features of these tablets are shown in Table 3. The tablet weight indicated nearly 99% of the whole amount was recovered. From the content of RD in each tablet, approximately 95% of the drug added was recovered, which indicated that approximately 5% was lost in the tableting process. This might be related to the fact that RD tended to attach to the metal or glass surface. In the drug release test, the mean content was used as 100% in the calculation of release percentage. These physical features were considered to be sufficient from the viewpoint of recovery ratios.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Tablet weight (mg)</th>
<th>Tablet thickness (mm)</th>
<th>Drug content (mg)</th>
<th>Mucoadhesive strength (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D9</td>
<td>78.95±0.28</td>
<td>1.12±0.02</td>
<td>3.80±0.02</td>
<td>0.012±0.001</td>
</tr>
<tr>
<td>D10</td>
<td>78.98±0.17</td>
<td>1.12±0.01</td>
<td>3.82±0.01</td>
<td>0.035±0.024</td>
</tr>
</tbody>
</table>

a) Mean±S.D. (n=3). b) Mean±S.D. (n=6).
In vitro release was investigated using the JP16 2nd fluid. The release profiles of D9 and D10 were obtained, as shown in Fig. 1. D9 disintegrated quickly within 10 min, resulting in the rapid release of RD. The mean release percentage from D9 was 76% at 20 min and 83% at 40 min. The release hardly increased after 40 min, which was assumed as follows: 1) the main reason was considered to be because the drug would still remain in the disintegrated tablet to a small extent, not released completely. 2) The other reason, considered to be minor, was that small loss of RD might happen in the carry and store in the glass bottle because RD tend to attach to the surrounding surface of glass or metal as stated above. On the other hand, D10 swelled in the first stage and took more than 1 h to disintegrate completely. RD was released gradually, with 63% being released 1 h after the start of the test. At 2 h, the average release reached approximately 76% for D10 (data not shown in Fig. 1). These release features demonstrated that D9 was useful for fast drug absorption due to the quick release of RD, while D10 was more suitable for prolonged drug absorption because of the gradual release of RD.

The tablets D9 and D10 were investigated for their mucoadhesive properties. The mucoadhesive strength is shown in Table 3. The strength of D10 tended to be greater than that of D9. Although D9 absorbed water quickly from the membrane surface, the tablet wet surface did not become viscous, and disintegrated rapidly. After the mucoadhesion test, the tablet surface was not sticky. On the other hand, the wet surface of D10 was viscous, and the surface after the mucoadhesion test showed sticky characteristics. As AL is known as a bioadhesive polymer, it was considered to contribute importantly to mucoadhesive properties of D10.

In Vivo Evaluation of Chosen Tablets

Plasma RD concentrations were monitored for 7 h after the buccal administration of D9 and D10. When these tablets were placed on the buccal mucosa, difficulties were encountered when fixing it to the site. Therefore, a small volume of saline (0.1 mL) was added around the placement site. However, D9 did not adhere well to the buccal mucosa. Since AL, which has a mucoadhesive function, was not contained in D9 tablets, these tablets could not be fixed well to the mucosa. D9 quickly became wet, disintegrated within 30 min of its buccal administration, and the resultant powder dispersed gradually over the oral cavity. On the other hand, D10 was fixed well to the buccal mucosa following the addition of saline at the tablet placement site due to mucoadhesive characteristics of AL. D10 became wet, swelled, and remained at the administration site to a large extent even after 2 h.

Plasma concentration–time profiles were obtained for RD after the buccal administration of D9 or D10, as shown in Fig. 2. For D9 tablets, the drug was rapidly absorbed. The mean plasma concentration of RD was 19 ng/mL at 15 min, which was higher than the minimal effective RD concentration of 15 ng/mL, though this level was the concentration for humans. The plasma concentration of RD increased gradually until 2 h,

![Fig. 1. Release Profiles of RD from Chosen Tablets, D9 and D10](image1)

![Fig. 2. Plasma Concentration–Time Profiles after Buccal Administration of Chosen Tablets, D9 and D10](image2)

Regarding intravenous data, the observed (▲; mean±S.E. (n=4)) and calculated (---) values are plotted. D9: Mean±S.E. (n=3), D10: Mean±S.E. (n=4). The dashed-dotted line shows the level of 15 ng/mL.
and was then slowly eliminated. The plasma concentration of RD was still higher than the minimal effective level after 7 h. Thus, D9 maintained an effective concentration of RD from 15 min to 7 h after its buccal administration. The plasma concentration of RD obtained following the buccal administration of D10 was lower than the minimal effective level in the initial periods, 15 and 30 min, but the level reached a concentration of greater than 15 ng/mL after 1 h. The RD concentration increased until 4 h, and then with the intravenous infusion of RD, the calculated plasma concentration–time curve after the intravenous (i.v.) administration, respectively. D10 was expected to maintain the RD concentration for a much more prolonged period than D9. In addition, the plasma concentration varied more widely with D10 than D9. As D9 disintegrated more simply in vivo than D10, D9 was considered to exhibit less variability in the in vivo release, leading to less variation of the plasma concentration. The variation in plasma concentration regarding D10 might indicate that the dose of RD should be increased in order to ensure the plasma level of more than 15 ng/mL. The plasma concentration–time curve after the intravenous (i.v.) administration of RD (1 mg/kg), as reported previously, was superimposed onto the results obtained for D9 and D10 (Fig. 2). The plasma concentration of RD was greater than 180 ng/mL 5 min after its i.v. administration, and decreased rapidly to less than 15 ng/mL after 4 h. An RD concentration of greater than 80 ng/mL had been reported to cause toxic side effects, such as an elevated heart rate, chest pain, and shortness of breath, whereas less than 15 ng/mL may not be able to maintain the pregnancy. Therefore, although the i.v. administration of RD achieved the highest exposure, it was considered to be inadequate from the viewpoints of toxic side effects and efficacy.

Pharmacokinetic parameters were calculated based on each profile, and the results obtained are shown in Table 4, in which the area under the curve (AUC), mean residence time (MRT), and variance of residence time (VRT) were calculated for 0–7 h using the data observed based on the trapezoidal rule with the program MULTI. In order to compare profiles with the intravenous infusion of RD, the calculated plasma concentration–time profile after its i.v. administration at 1 mg/kg, reported previously, was described in Fig. 2 with a dotted line.

\[ C_{\text{calc, iv}}(t) = 132.6 \exp(-0.667t) + 107.7 \exp(-0.567t) \]

in which \( C_{\text{calc, iv}}(t) \) was the calculated concentration (ng/mL) at time \( t \) (h). Since Eq. 1 was well fitted to the mean observed profile, it was used to calculate the AUC for 0–7 h after the i.v. administration of RD at 1 mg/kg.

The \( C_{\text{max}} \) values of both D9 and D10 indicated that plasma concentrations were maintained below toxic levels, while the MRT and VRT values showed that absorption was more prolonged than the intravenous infusion. The \( T_{\text{max}} \) value was significantly larger in D10 than in D9 \((p<0.05)\), while the MRT value was slightly larger in D10 than in D9 \((p>0.05)\). Therefore, the absorption of D10 was more prolonged than that of D9, which was attributed to differences in tablet characteristics. Namely, mucoadhesive properties were observed for D10, but not for D9. D9 released RD rapidly, whereas D10 gradually released RD (Fig. 1). These physical and biological features were considered to be associated with the greater \( T_{\text{max}} \) and MRT values of D10. Absolute bioavailability (B.A.) values were calculated using the following equation.

\[ \text{B.A.} (%) = 100 \times \frac{\text{AUC(buccal)}}{[20 \times \text{AUC(i.v.)}]} \]

in which \( \text{AUC(buccal)} \) and \( \text{AUC(i.v.)} \) represented the AUC values of buccal (20 mg/kg) and i.v. (1 mg/kg) administrations, respectively. The \( \text{AUC(i.v.)} \) value for 0–7 h was 206.2 ng·h/mL from Eq. 1. As the present results were calculated for the data from 0–7 h, the B.A. values of D9 and D10 were considerably low (Table 4). The B.A. values of D9 and D10 from 0–∞ were assumed to be larger by the following estimation based on the mono-exponential extrapolation of the plasma profiles. Namely, when the mono-exponential extrapolation to the infinite time was conducted, and then the mean \( \text{AUC(0–∞)} \) values in D9 and D10 were estimated, they were calculated as 956 and 1272 ng·h/mL, respectively. The i.v. mean \( \text{AUC(0–∞)} \) value was calculated as 210 ng·h/mL. Although these values were calculated by simple extrapolation, the B.A. values from 0–∞ were estimated to be 14 and 30% for D9 and D10, respectively. On the other hand, the previous paper indicated that the intragastric B.A. value from 0–∞ was estimated to be approximately 4%. The longer monitoring would give a more exact bioavailability for each formulation.

The wet powder products remaining in the oral cavity 7 h after the buccal administration of D9 and D10 were recovered. The amounts of RD in the remaining products are shown in Fig. 3. The mean amount of RD remaining was very low, at less than 1%, for D9, while it was approximately 22% for D10; however, this difference was not significant due to the large variations noted for D10. These results were considered to be attributed to the physical and biological features of each tablet. D9 disintegrated quickly, rapidly released RD, and did not adhere to the mucosa, resulting in RD diffusing almost completely over the oral mucosa. Therefore, RD was considered hardly to be recovered from the remaining powder of D9. D10 was mucoadhesive and remained around the administration site to a fairly large extent even after its disintegration. AL suppressed powder diffusion because of its viscous characteristics and sticky to the mucosa even after the collapse of the tablet. Thus, RD was considered to remain to a certain extent

<table>
<thead>
<tr>
<th>Formulation</th>
<th>( C_{\text{max}} ) (ng/mL)</th>
<th>( T_{\text{max}} ) (ng/mL)</th>
<th>( AUC(0–7h) ) (ng·h/mL)</th>
<th>( MRT(0–7h) ) (h)</th>
<th>( VRT(0–7h) ) (h²)</th>
<th>B.A. (0–7h) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D9</td>
<td>27.1±0.64</td>
<td>1.7±0.3</td>
<td>137±15.7</td>
<td>3.3±0.3</td>
<td>4.3±0.1</td>
<td>3.5</td>
</tr>
<tr>
<td>D10</td>
<td>30.9±13.7</td>
<td>4.8±0.8</td>
<td>153.6±79.2</td>
<td>4.2±0.3</td>
<td>4.1±0.3</td>
<td>3.7</td>
</tr>
</tbody>
</table>

\( AUC, MRT, VRT \) and B.A. were calculated for 0–7 h by the trapezoidal rule based on the data in Fig. 2. B.A. was calculated using Eq. 2, in which the \( AUC(\text{i.v.}) \) value was 206.2 (ng·h/mL). The results are expressed as the mean±S.E. \((n=3 \text{ for D9, 4 for D10).} \) *: \( p<0.05 \) vs. D9.

Vol. 38, No. 6 (2015) 923

**Table 4. Pharmacokinetic Parameters of Chosen Tablets, D9 and D10**

1. The \( C_{\text{max}} \) values of both D9 and D10 indicated that plasma concentrations were maintained below toxic levels, while the \( MRT \) and \( VRT \) values showed that absorption was more prolonged than the intravenous infusion. The \( T_{\text{max}} \) value was significantly larger in D10 than in D9 \((p<0.05)\), while the \( MRT \) value was slightly larger in D10 than in D9 \((p>0.05)\).

2. Therefore, the absorption of D10 was more prolonged than that of D9, which was attributed to differences in tablet characteristics. Namely, mucoadhesive properties were observed for D10, but not for D9. D9 released RD rapidly, whereas D10 gradually released RD (Fig. 1). These physical and biological features were considered to be associated with the greater \( T_{\text{max}} \) and MRT values of D10. Absolute bioavailability (B.A.) values were calculated using the following equation.

\[ \text{B.A.} (%) = 100 \times \frac{\text{AUC(buccal)}}{[20 \times \text{AUC(i.v.)}]} \]

3. in which \( \text{AUC(buccal)} \) and \( \text{AUC(i.v.)} \) represented the AUC values of buccal (20 mg/kg) and i.v. (1 mg/kg) administrations, respectively. The \( \text{AUC(i.v.)} \) value for 0–7 h was 206.2 ng·h/mL from Eq. 1. As the present results were calculated for the data from 0–7 h, the B.A. values of D9 and D10 were considerably low (Table 4). The B.A. values of D9 and D10 from 0–∞ were assumed to be larger by the following estimation based on the mono-exponential extrapolation of the plasma profiles. Namely, when the mono-exponential extrapolation to the infinite time was conducted, and then the mean \( \text{AUC(0–∞)} \) values in D9 and D10 were estimated, they were calculated as 956 and 1272 ng·h/mL, respectively. The i.v. mean \( \text{AUC(0–∞)} \) value was calculated as 210 ng·h/mL. Although these values were calculated by simple extrapolation, the B.A. values from 0–∞ were estimated to be 14 and 30% for D9 and D10, respectively. On the other hand, the previous paper indicated that the intragastric B.A. value from 0–∞ was estimated to be approximately 4%. The longer monitoring would give a more exact bioavailability for each formulation.

4. The wet powder products remaining in the oral cavity 7 h after the buccal administration of D9 and D10 were recovered. The amounts of RD in the remaining products are shown in Fig. 3. The mean amount of RD remaining was very low, at less than 1%, for D9, while it was approximately 22% for D10; however, this difference was not significant due to the large variations noted for D10. These results were considered to be attributed to the physical and biological features of each tablet. D9 disintegrated quickly, rapidly released RD, and did not adhere to the mucosa, resulting in RD diffusing almost completely over the oral mucosa. Therefore, RD was considered hardly to be recovered from the remaining powder of D9. D10 was mucoadhesive and remained around the administration site to a fairly large extent even after its disintegration. AL suppressed powder diffusion because of its viscous characteristics and sticky to the mucosa even after the collapse of the tablet. Thus, RD was considered to remain to a certain extent.
in the wet powder after the disintegration of D10. Individual
variations in saliva volumes and tablet fixation were related
to the large variations observed in the remaining amounts
of D10. As only the remaining wet powder in the oral cavity
was collected roughly in this experiment, more RD should exist
in the oral cavity. Therefore, Fig. 3 only suggested that in vivo
release should be slower with D10 than D9.

As to the retention of RD in the mucosal tissue, it was es-
timated from the absorption studies in the application of
the cotton ball loaded with RD solution. Cotton ball loaded with RD solution was applied for 1 h and then removed. The
drug concentration at the administration site and in the muco-
sal tissue was measured immediately and 3 h after the removal
of cotton ball. At that time, the drug concentration in the oral
cavity was quickly eliminated extensively 3 h after the
removal of cotton ball (data not shown). On the other hand,
the mucosal concentration did not change so much between
immediately and 3 h after the removal of cotton ball; the
concentration of RD in mucosal tissue was 78 µg/g immediately
after cotton ball removal, and 43 µg/g 3 h after cotton ball
removal. This suggested that the mucosal tissue should act as
a reservoir of RD in the mucosal absorption.

In conclusion, in the present formulation study, two kinds
of tablets, D9 and D10, were chosen as possibly useful buc-
cal tablets. The results of the in vivo study revealed that these
tables achieved effective plasma concentrations of RD over a
long period of time without exceeding toxic levels. D9, which
did not contain AL, showed rapid absorption, but was expected
to be effective for approximately 10 h from the mono-

Conflict of Interest The authors declare no conflict of
interest.

REFERENCES

of ritodrine in blood and plasma by high-performance liquid
chromatography with fluorescence detection. J. Chromatogr. B, 416,
400–408 (1987).

2) Konda A, Ito T, Yoshida H, Toda T, Hayakawa T, Inotsume N.
Pharmacokinetics of ritodrine diastereomers in patients pregnant
(2009).

3) Chye JK, Lim CT, Leong HL, Wong PK. Retinopathy of prematurity
in very low birth weight infants. Ann. Acad. Med. Singapore,

4) Kwinta P, Pietrzyk JJ. Preterm birth and respiratory disease in later

in human plasma by high-performance liquid chromatography
coupled with electrospray ionization tandem mass spectrometry.
(2008).

6) Marzo A, Coa K, Fontana E, Tavazzi S, Bo LD, Ismaili S, Zava D,
Cantoni V, Bertolini A. Pharmacokinetics and pharmacodynamics
of ritodrine hydrochloride administered orally and intramuscularly
to female healthy volunteers. Arzneimittelorschung, 60, 510–518
(2010).

7) Caritis SN, Lin LS, Wong LK. Evaluation of the pharmacodynamics
and pharmacokinetics of ritodrine when administered as a loading
dose. On establishing a potentially useful drug administration
regimen in cases of fetal distress. Am. J. Obstet. Gynecol., 152,

8) Fujimoto S, Akahane M, Tanaka T, Hanatani K. Pharmacokinetics
and materno-fetal influence of ritodrine hydrochloride during the
continuous treatment of threatened premature labor. Nihon Sanka

9) Caritis SN, Lin LS, Toig G, Wong LK. Pharmacodynamics of

10) Caritis SN. A pharmacologic approach to the infusion of ritodrine.

11) Schiff E, Sivan E, Terry S, Dultzky M, Friedman SA, Mashiah
S, Sibai BM. Currently recommended oral regimens for ritodrine
tocolysis result in extremely low plasma levels. Am. J. Obstet. Gyn-

12) Gandar R, de Zoeten LW, van der Schoot JB. Serum level of rito-

13) Essed GG, Struyker Boudier HA, Van Zijl JA. Biopharmaceutical
aspects of ritodrine retard in pregnant women. Arch. Int. Pharma-

14) Dhiman MK, Yedurkar PD, Sawant KK. Buccal bioadhesive de-
leverage system of 5-fluorouracil: optimization and characterization.

15) Semalty A, Semalty M, Naityal U. Formulation and evaluation of
mucoadhesive buccal films of enalapril maleate. Indian J. Pharm.

16) Bray CL, Jain S, Paraghey EB, Myers A, Myers P, MacIntyre P, Rae
A, Goldman M, Alcorn M. A comparison of buccal nitroglycerin
and sublingual nitroglycerin in the prophylaxis and treatment of
exertional (situation-provoked) angina pectoris. Eur. Heart J., 12,

FW, Hooymans PM. Absorption of clonazepam after intranasal and

18) Sakata O, Onishi H, Machida Y. Clonazepam oral droplets for the
treatment of acute epileptic seizures. Drug Dev. Ind. Pharm.,
34, 1376–1380 (2008).

19) Mohamed SP, Muzzammil S, Pramod KT. Preparation of flucon-


