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Preparation and evaluation of ritodrine buccal tablets for rational therapeutic use

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ABSTRACT

Ritodrine hydrochloride (RD-HCl) tablets containing alginate (AL) and lactose (LC) with or without microcrystalline cellulose (MC) as excipients were produced as a buccal dosage form. The RD-HCl (2 mg) tablets with AL/LC but no MC swelled and dissolved gradually in the in vitro dissolution test. The tablet showing the fastest dissolution and highest drug release rate, called Tablet A1, was selected as a tablet to show rapid and prolonged absorption. However, in the in vivo buccal absorption test using rats, it could not give a plasma concentration over the human minimal effective level (15 ng/mL). The modified tablet containing AL, LC, MC and RD-HCl (4 mg), named Tablet B/MC, showed better hardness and faster drug release. Tablet B/MC gave a plasma concentration over the human effective level within 15 min, and the plasma concentration was maintained at >15 ng/mL over 4 h. Moreover, the deconvolution analyses demonstrated that a prolonged high absorption rate could be achieved in vivo best with Tablet B/MC. Tablet B/MC improved the pharmacokinetic profile in comparison with Tablet A1 and the solution dosage form. The RD-HCl buccal tablets with AL, LC and MC as excipients are suggested to be possibly useful for the treatment of premature labor.

1. Introduction

Premature labor is one of the important problems in the field of gynecology and obstetrics and is seen fairly frequently in various countries. Recently, it was reported that about 60,000 premature birth events happen per year in Japan. Also, in the U.S.A., yearly births are reported to include approximately 300,000 premature births. Immature infants are subject to damage or disorders of various organs, which might result in dysfunction (Chye et al., 1999; Kwinta and Pietrzyk, 2010). Threatened premature labor is a condition that suggests premature birth. Drugs suppressing myometrial contractions are used for the treatment of these events. Agonists of the β2 adrenergic receptor are useful to stop premature labor and fetal asphyxia during labor. Ritodrine (RD) hydrochloride (RD-HCl) is a first-line drug for the treatment of premature labor because it is highly selective for the suppression of myometrial contractions (Caritis et al., 1991).

Currently, parenteral and tablet dosage forms are commercially available for the use of RD. RD is used as an intravenous infusion in an emergency (Caritis, 1988). Once the relationship between the dosing schedule and the therapeutic effect is found and a patient condition is stabilized, the infusion can be substituted by an oral dosage tablet form (Van Lierde et al., 1984). As immature birth remains an important problem, research has been performed to solve the problem. In particular, research related to the clinical pharmacokinetics of RD has been performed. Plasma levels of RD have been reported to be importantly associated with its efficacy and toxic side effects (Gandar et al., 1980; Caritis et al., 1985; Konda et al., 2009; Marzo et al., 2010). According to Caritis et al. (1983), many patients with serum concentrations of 15 ng/mL or more experienced good inhibition of premature labor. On the other hand, high plasma concentrations of RD are related to toxic side effects such as increase in heart rate and blood glucose, and nausea (Caritis et al., 1983; Fujimoto et al., 1989). Although intravenous infusion is the most appropriate method to control therapeutic efficacy and avoid toxic side effects, long-term intravenous infusion causes pain and restricts movement, resulting in lowered quality of life (QOL). Oral dosing with tablets is the best approach to achieve high patient QOL. However, RD undergoes a considerable first-pass effect in oral administration, leading to low bioavailability (Gandar et al., 1980; Essed et al., 1988; Nishimuta et al., 2005). Moreover, RD is eliminated relatively rapidly from the body in both intravenous injection and oral dosing (Gandar et al., 1980). Therefore, frequent oral dosing is required even when the tablets are taken orally.

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Considering these features of RD itself and its commercial formulations, it is suggested to be important to develop novel administration methods or dosage forms that can improve use and patient QOL. Mucosal delivery has drawn attention as an alternative dosing method because it allows the avoidance of a first-pass effect (Dhiman et al., 2008; Semalty et al., 2010), enables sustained drug supply (Bray et al., 1991; Mohamed et al., 2011), and can achieve systemic absorption fairly rapidly (Schols-Hendriks et al., 1995; Sakata et al., 2011; Bayrak et al., 2011). In a previous paper (Sakata and Onishi, 2013), buccal delivery of RD was examined and evaluated for its usefulness as a novel dosing method. Namely, when RD-HCl saline solution was administered by different routes (intravenous, intragastric and buccal), the plasma concentration–time profiles were compared. Although absolute bioavailability decreased greatly with buccal and intragastric administration as compared with intravenous infusion, the plasma level was achieved at a human therapeutic level with the former two types of administration at 10 mg/kg. In addition, bioavailability and maintenance of plasma concentration more than human effective level tended to be better with buccal dosing than intragastric administration. Thus, it was demonstrated that buccal dosing was superior to intragastric administration to achieve maintenance of the effective plasma level. A solution dosage form is not convenient for actual dosing, because the administration volume has to be adjusted each dosing time, and it is inconvenient to carry the solution dosage form. Also, the stability in the aqueous solution might have to be tested. Recently, dosage forms such as tablets and films have been studied actively because they are easy to handle (Semalty et al., 2010; Bayrak et al., 2011; Asane et al., 2008; Hassan et al., 2010). In particular, tablets are easy to prepare and simple to use. In this study, buccal tablets of RD have been produced and investigated for their effectiveness and usability. The obtained tablets were evaluated in vitro and in vivo.

2. Materials and methods

2.1. Materials

Ritodrine hydrochloride (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 magnesium stearate (MS) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Lactose (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 microcrystalline cellulose (MC). All other chemicals used were of reagent grade.

2.2. Animals

Male Wistar rats (7 weeks old, 200–210 g) were purchased from Tokyo Laboratory Animal Science Co., Ltd., and used for in vivo experiments several days after purchase. The animals were kept on the MF breeding diet supplied by Oriental Yeast Co., Ltd. (Tokyo, Japan) with water ad libitum in a room where the temperature and relative humidity were kept at 23 ± 1 °C and 60 ± 1%, respectively. The light–dark cycle was set at 12 h. The experimental protocol was approved by the Committee on Animal Research of Hoshi University (Tokyo, Japan), and animal experiments were performed according to the Guiding Principles for the Care and Use of Laboratory Animals of Hoshi University.

2.3. Preparation of tablets

Disk-shaped tablets were produced by direct compression using an SSP-10A manual press (Shimadzu Corp., Kyoto, Japan) using an 8 mm flat face punch and die set. First, tablets containing 2 mg RD-HCl, named Tablet Ax (x = 1–6), were prepared by direct compression using AL and LC as a binder and filler, respectively. Compositions of Tablet Ax are given in Table 1; one tablet contained 2 mg RD-HCl, and the weight was set at 80 mg. The powder mixture (0.8 g), containing the components at the ratios shown in Table 1, was stirred with a pestle in a mortar. The powder mixture (80 mg) was weighed, put into the cylinder and compressed at 2 kN for 30 s.

A tablet containing 4 mg RD-HCl (Tablet B) was produced in a similar manner. In addition, a tablet containing 4 mg RD-HCl, to which MC was added further as an excipient, (Tablet B/MC) was produced. Their composition is shown in Table 1.

2.4. Measurement of physical features of tablets

The tablets were weighed, and their thickness was measured using a micrometer. The drug content per tablet was investigated as follows. A tablet was put 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. Then, 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 excitation wavelength of 278 nm and emission wavelength of 306 nm. The absolute calibration curve method was used for the determination of RD concentration, in which linear calibration was obtained, 0.1–12 μg/mL (R^2 = 0.999).

Table 1
Formulations and characteristics of buccal tablets.

Formulation	Composition (mg) per tablet					Tablet characteristics			
	RD (mg)	AL (mg)	LC (mg)	MC (mg)	ST (mg)	Weight[a] (mg)	Thickness[b] (mm)	Drug content[a] (mg)	Hardness[a] (N)
A1	2	10	67	–	1	78.9 ± 0.2	1.12 ± 0.02	1.97 ± 0.01	10.6 ± 2.5
A2	2	20	57	–	1	78.8 ± 0.1	1.14 ± 0.01	2.00 ± 0.02	2.8 ± 0.7
A3	2	30	47	–	1	79.0 ± 0.2	1.15 ± 0.01	1.92 ± 0.02	3.9 ± 1.0
A4	2	40	37	–	1	79.6 ± 0.1	1.14 ± 0.02	1.92 ± 0.02	2.6 ± 0.6
A5	2	50	27	–	1	79.8 ± 0.0	1.16 ± 0.01	1.83 ± 0.05	1.3 ± 0.3
A6	2	60	17	–	1	80.0 ± 0.1	1.17 ± 0.02	1.82 ± 0.01	0.8 ± 0.3
B	4	7	48	–	1	58.6 ± 0.1	0.88 ± 0.03	3.77 ± 0.1	6.9 ± 2.5
B/MC	4	7	48	60	1	117.8 ± 0.2	1.67 ± 0.01	3.73 ± 0.03	54.0 ± 2.7

RD: ritodrine hydrochloride, AL: sodium alginate, LC: lactose, MC: microcrystalline cellulose, ST: magnesium stearate.
[a] The results are expressed as the mean ± S.D. (n = 3).
[b] The results are expressed as the mean ± S.D. (n = 6).