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Mucosal Dosage Form of Lidocaine for Toothache using Hydroxypropyl Cellulose and Carbopol^{1,2)}

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In the present study, as a continuation of the previous work on a new mucosal dosage form for insulin using hydroxypropyl cellulose-H (HPC) and Carbopol-934 (CP), we attempted to develop a dosage form containing a local anesthetic for toothache, using lidocaine as a model drug in HPC and CP as the peripheral base.

The dissolution profile of lidocaine was investigated with various mixing ratios of freeze-dried HPC/CP (FD-HPC/CP) to lidocaine in the core base, and the absorption when this dosage form was applied to the human gingiva was also studied. It was found that the rate in the dissolution test was delayed with increase in the amount of FD-HPC/CP in the core base and that the absorption of lidocaine was about 30% after 1 hour and then increased by about 10% of the initial amount per hour for 4 hours in preparations containing 5 and 10 mg of FD-HPC/CP.

Keywords—lidocaine; mucosal dosage form; hydroxypropyl cellulose-H; Carbopol-934; human gingiva; toothache; local anesthetics

At present, commercial medicines for toothache are provided in the form of lotions, viscous liquids or ointments which are applied with a piece of cotton. However, they do not provide sustained action, and also act on other parts of the oral cavity.

In the present study, as a continuation of the previous work on a new mucosal dosage form for insulin using hydroxypropyl cellulose-H (HPC) and Carbopol-934 (CP),³⁾ we attempted to develop a dosage form of local anesthetic for toothache containing lidocaine as a model drug. We anticipated that the dosage form might stick to the human gingiva, afford prolonged action and not stimulate other parts of the oral cavity.

In order to prepare a dosage form containing a small amount of lidocaine, freeze-dried HPC/CP (FD-HPC/CP) was used in the core.

Experimental

Materials—Hydroxypropyl cellulose-H (HPC), Carbopol-934 (CP), magnesium stearate (Mg-St) and brilliant blue FCF (B.B.FCF) used were commercial products. Lidocaine was supplied by Fujisawa Pharmaceutical Ind., Ltd.

Preparation of the Mucosal Dosage Form of Lidocaine—A schematic illustration of the mucosal dosage form of lidocaine and its formula are shown in Fig. 1 and Table I, respectively. It was prepared as follows. First, lidocaine and FD-HPC/CP were mixed sufficiently and compressed into a cylindrical form of 6 mm diameter and about 1 mm thickness, which afforded the core. The core was covered with the peripheral base consisting of 100 mg of a physical mixture of HPC and CP (PM-HPC/CP), and compressed directly to make a tablet of 10 mm diameter under 200 kg/cm² for 30 s in a Shimadzu evacuable die and hydraulic press designed to produce KBr tablets for infrared spectroscopy. Finally, it was covered again with 50 mg of physical mixture of FD-HPC/CP and Mg-St (1:1) and compressed in the same way as above to make the cap layer shown in Fig. 1.

The procedure for the preparation of FD-HPC/CP used as the core base is shown in Fig. 2. Product that passed through a 200 mesh sieve was used for the investigation.

Dissolution Test of B.B.FCF from FD-HPC/CP and PM-HPC/CP—Tablets containing 150 mg of FD-HPC/CP or PM-HPC/CP, with 10.00 mg of B.B.FCF as a marker, which had been compressed directly under 200 kg/cm² for 30 s, were tested in purified water at 37 ± 0.2°C at 100 rpm using the dissolution apparatus of Takahashi *et al.*⁴⁾ The concentration of B.B.FCF was determined at 628 nm using a Hitachi 124 spectrophotometer.

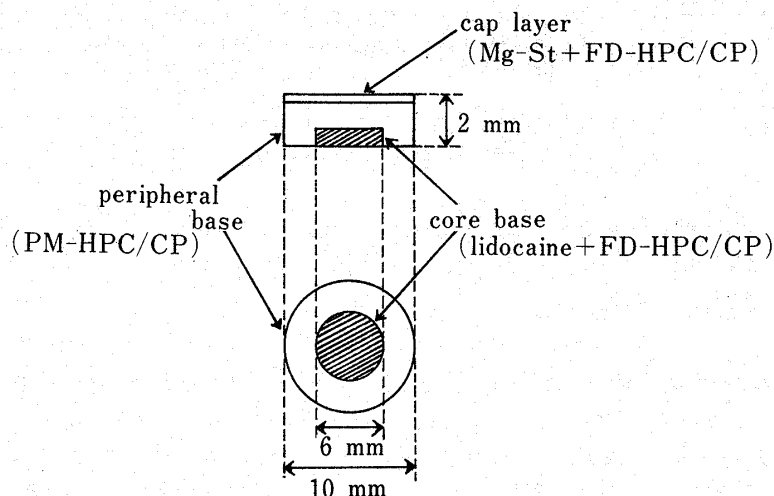


Fig. 1. Schematic Illustration of the Mucosal Dosage Form of Lidocaine

TABLE I. Formula of the Mucosal Dosage Form of Lidocaine

Core Base	{ Lidocaine	5 mg
	{ FD-HPC/CP	x mg ^{a)}
Peripheral Base	PM-HPC/CP	100 mg
Cap Layer	Mg-St + FD-HPC/CP	50 mg

a) x : 5, 10, 15, 20, 30 mg in dissolution test, 5, 10, 20 mg in absorption test.

In Vitro Dissolution of Lidocaine from the Mucosal Dosage Form—The dissolution profile of lidocaine was investigated with various mixing ratios of FD-HPC/CP to lidocaine in the core base, as shown in Table I. The dissolution apparatus used is shown in Fig. 3; it contained 50 ml of chloroform at $27 \pm 0.5^\circ\text{C}$, as the test solution.

In Vivo Absorption of Lidocaine from the Human Gingiva—*In vivo* absorption tests were carried out with reference to the methods reported by Kiddie *et al.*⁵⁾ and Beckett *et al.*⁶⁾ The tablets were applied to the gingiva of each of three male volunteers for 1/6, 1/2, 1, 2, 3, 4, and 6 h, at different spaces, *i.e.*, one tablet per run. It was confirmed by a preliminary experiment that the order and position of application were of no significance. The percentage (%) of lidocaine absorbed was calculated from the amount remaining in the dosage form after removing it completely from the gingiva. The absorption profile of lidocaine was investigated at the same mixing ratios of FD-HPC/CP to lidocaine as in the case of the dissolution test.

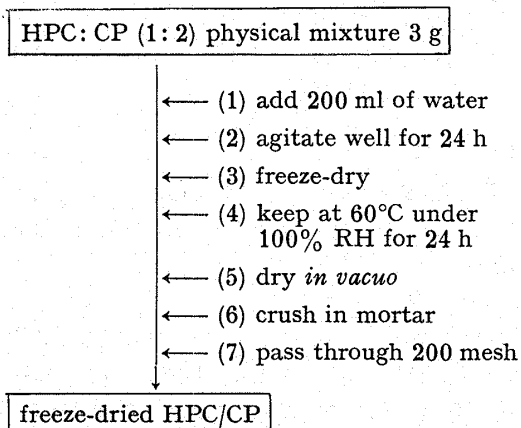


Fig. 2. Preparation of Freeze-dried HPC/CP (FD-HPC/CP)

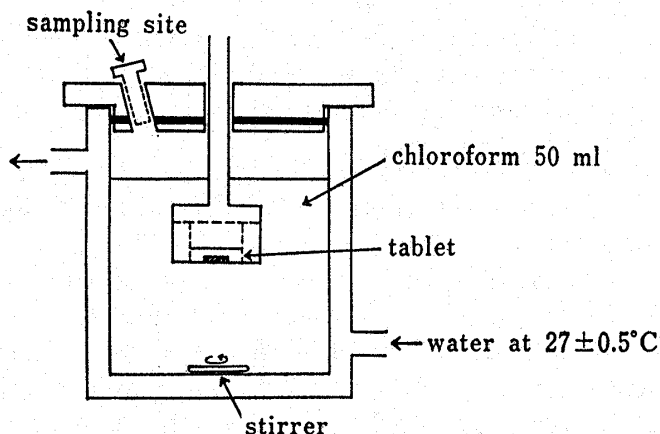


Fig. 3. Schematic Illustration of the Dissolution Test Apparatus

Determination of Lidocaine in *in Vitro* Dissolution and *in Vivo* Absorption Tests—Lidocaine in the dissolution and absorption tests was determined by a gas chromatographic method using *n*-tetracosane as an internal standard. A Shimadzu GC-7A gas chromatograph equipped with a flame-ionization detector and a column packed with 3% silicone OV-17 on Chromosorb WAW DMCS was used.

Results and Discussion

Preparation of the Mucosal Dosage Form of Lidocaine

This dosage form (Fig. 1) was smaller than the previous one for insulin,³⁾ and could be easily applied to the human gingiva.

The lower layer of the tablet was provided in order to make the tablet stick tightly only to the human gingiva and not to the oral mucosa. The tablet behaved as expected in this respect; it did not stick to the oral mucosa due to the Mg-St in the cap layer.

Generally, CP is sticky and develops a static charge, so it is not easy to mix a small amount of drugs with CP alone. This problem was solved by using FD-HPC/CP in this study and the core of the dosage form was prepared easily. However, when the tablets of FD-HPC/CP

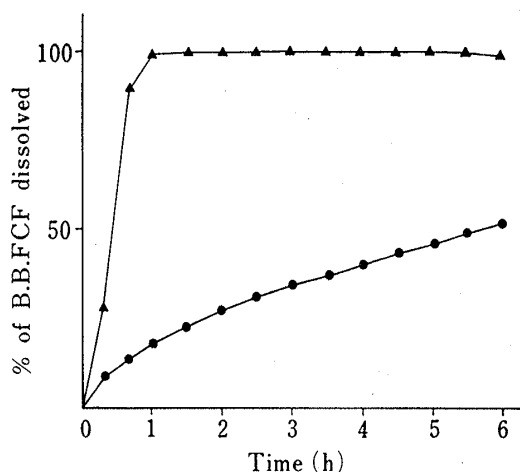


Fig. 4. Effect of FD-HPC/CP on the Dissolution of B.B. FCF

—▲—: freeze-dried, —●—: physical mixture.

and of PM-HPC/CP were applied to the human gingiva, the former was obviously less sticky than the latter, and it was also clear that the rate of gelation of FD-HPC/CP was faster than that of PM-HPC/CP (Fig. 4). An explanation for this phenomenon may be that the viscosity of the gel layer is decreased because of the dispersion of CP in small particles by freeze-drying. The viscosities of FD-HPC/CP and PM-HPC/CP were 4 cps and 2200 cps, respectively, under the conditions used in the previous report.³⁾ Thus PM-HPC/CP was considered to be suitable as the peripheral base.

Lidocaine, a lipophilic drug, is absorbed rapidly from the oral mucosa, in contrast to insulin, a hydrophilic polymer.³⁾ Thus, FD-HPC/CP was used as the core base in order to obtain rapid absorption and the prolonged action.

In Vitro Dissolution of Lidocaine from the Mucosal Dosage Form

The gelation of FD-HPC/CP in the core base must occur for the absorption of lidocaine to be possible. In the *in vitro* test, there was no significance between the preparations containing 5 and 10 mg of FD-HPC/CP, as shown in Fig. 5. However, the dissolution of lidocaine was delayed as the amount of FD-HPC/CP in the core base increased. Therefore, it was assumed that the dissolution rate could be controlled in the oral cavity.

In Vivo Absorption of Lidocaine from the Human Gingiva

The absorption profiles of lidocaine after application of dosage forms to the human gingiva with various mixing ratios of FD-HPC/CP to lidocaine are shown in Fig. 6. There was no significant difference between the preparations containing 5 and 10 mg of FD-HPC/CP, as observed in the case of the dissolution test.

Kiddie *et al.*⁵⁾ reported that the absorption of lidocaine by the oral mucosa was 10.5% at pH 5 and 25.6% at pH 6 in 5 min. Moreover, Beckett *et al.*⁶⁾ reported that the absorption of lidocaine increased with increase in the pH of the solution of lidocaine, though the amount absorbed was lower than that found by Kiddie *et al.* Accordingly, the absorption of lidocaine was related closely to the pH on the oral mucosa. When PM-HPC/CP was dissolved at

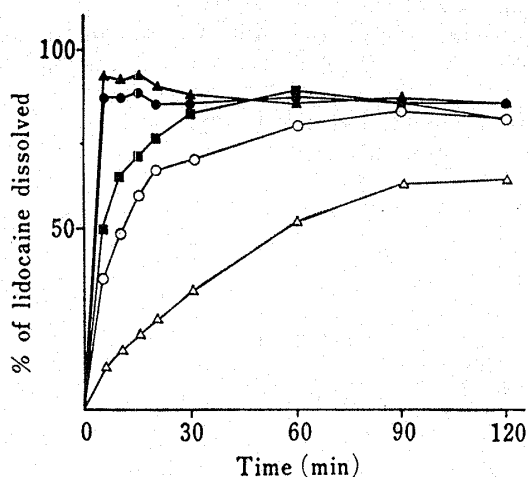


Fig. 5. Dissolution Profile of Lidocaine at Various Contents of FD-HPC/CP

—●—: 5 mg, —▲—: 10 mg, —■—: 15 mg,
—○—: 20 mg, —△—: 30 mg.

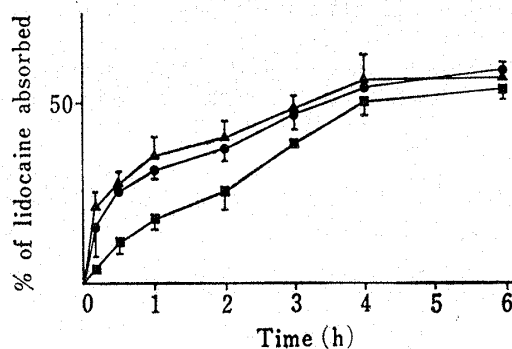


Fig. 6. Absorption Profile of Lidocaine from the Human Gingiva

—▲—: 5 mg, —●—: 10 mg, —■—: 20 mg.
(Each point represents the mean \pm S.E. of 3 determinations.)

1% in 1/15 M phosphate buffer (pH 7.40), the final pH changed from 7.40 to 5.80. Therefore, when this dosage form is expected to be in contact with saliva of about pH 6.2–7.6, the value of pH on the oral mucosa may be considered to be about 5 to 6 due to the acidity of the CP gel layer. Therefore, the present result that about 15 to 20% of lidocaine was absorbed after 10 min is broadly consistent with the above reports. That is to say, it was assumed that the absorption of lidocaine from the preparations of 5 and 10 mg of FD-HPC/CP occurred promptly. It was expected that the absorption of lidocaine might increase with the addition of additives which could increase the pH on the oral mucosa.

Regarding the relationship between the amount of absorbed and the application period, it was found that the absorption was about 30% after 1 hour and then increased by about 10% of the initial amount per hour for 4 hours in the preparations of 5 and 10 mg of FD-HPC/CP. At 20 mg of FD-HPC/CP, the absorption rate was delayed, as was observed in the dissolution test.

In this dosage form, though FD-HPC/CP was used as the core base, it was assumed that lidocaine did not diffuse to the oral cavity through the gel layer of peripheral base, in contrast to the case of insulin,⁹⁾ because the amount of lidocaine absorbed was small in the period from 4 hours to 6 hours.

From the results described above, the present dosage form may be expected to afford a long-acting anesthetic action for the treatment of toothache, beginning immediately after the application and lasting for about 4 hours without anesthetizing other parts of the oral cavity.

However, lidocaine used as a model drug in this study is not exceptionally effective for toothache, and thus if a more effective drug such as dibucaine is used, the clinical utility of this dosage form might be enhanced.

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References and Notes

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