Oral Mucosal Adhesive Film Containing Local Anesthetics: *In Vitro* and Clinical Evaluation

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Abstract: ***In vitro*** **and** ***in vivo*** **studies were conducted to gauge the effectiveness of a novel oral mucosa adhesive, moderately water-soluble, pliant polymer artificial dentifrice (AD) film containing dibucaine (DC) for relief of pain due to oral erosion. The film was prepared from a hydroxypropyl cellulose-M (HPC-M) ethanol solution containing varying amounts of DC, as well as polyethylene glycol. In the** ***in vitro*** **experiments, the disintegration of HPC-M showed a lag time of about 50 min, a much lower rate than that of drug release, which more or less leveled off after 50 min. Twenty-five percent of the DC was released from the film (0.113 and 0.225 mg/cm^2) after the initial 5 min, which then reached about 80% after 50 min, the time at which the polymer began to break up. In the** ***in vivo*** **study, the local anesthetic effect of the film was evaluated in 23 patients (10 males, 13 females) suffering from the adverse effects of chemotherapy. When applied to the wet surface of the mucosa, the AD film absorbed moisture and showed excellent adhesion. Pain relief in patients lasted 2.2 $\pm$ 0.21 and 4.3 $\pm$ 0.25 h at DC doses of 0.113 and 0.225 mg/cm^2, respectively. These results suggest that the AD film may cover mucositis sites of oral mucosa long enough to allow DC release and bring relief from pain arising from chemotherapy and/or radiotherapy.** © 1998 John Wiley & Sons, Inc. J Biomed Mater Res (Appl Biomater) 43: 313–317, 1998

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INTRODUCTION

Radiotherapy and chemotherapy are the usual modes of treatment for various types of cancer. A typical adverse effect of this cytotoxic treatment is serious aphthae and subsequent erosion on the oral mucosa and tongue. The accompanying pain is almost intolerable and can last for up to 2 weeks. Oral mucosal erosion and mucositis frequently complicate treatment and adversely affect patient comfort, nutrition, speech, and treatment compliance.

The development of an external drug delivery system is currently the subject of considerable interest. Mucosal adhesive systems are envisaged as safe and effective therapeutic means for drug administration in the treatment of aphthae and erosion on the oral mucosa[1,2] and have even been explored for the purpose of bypassing the liver in first-pass metabolism.[3,4] These systems basically consist of adhesive films or matrices comprising water-soluble polymer in which drugs are incorporated.

The extemporaneous preparation of a water-soluble polymer film containing local anesthetics and antibiotics was requested by physicians in our hospital. The film had to be mucosa adhesive, moderately water-soluble, and pliant because it was intended to be applied to highly irritable areas of the oral mucosa and/or tongue. In a preliminary study, we reported the use of a mucosa-soluble adhesive film containing tetracaine in the treatment of two leukemia patients with severe aphthae and subsequent erosion induced by radiation and chemotherapy on the oral mucosa

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No benefit of any kind will be received either directly or indirectly by the authors.

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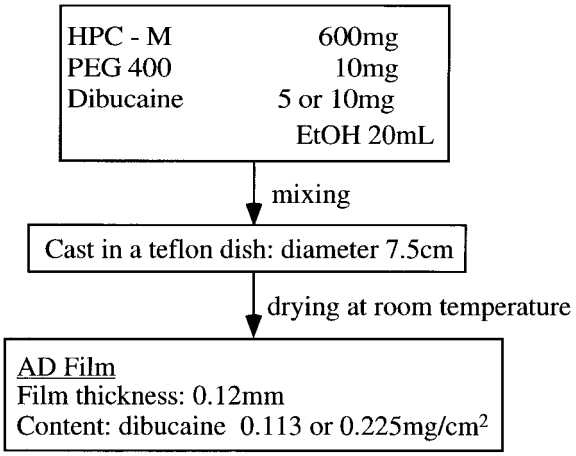

Scheme 1. Preparation of the AD film.

and tongue.[5] Pain relief continued for 4 to 6 h in the patients receiving the film, allowing them to sleep.

The objective of this study was to evaluate the effect of local anesthetic on pain in patients with severe oral erosion induced by chemotherapy after application of artificial dentifrice (AD) film containing dibucaine (DC) to oral mucosa.

In the *in vitro* experiment, the release rate of DC from the AD film and the disintegration rate of the polymer were compared, because the effectiveness of this form of treatment can be compromised if the latter is not substantially less than the former.

MATERIALS AND METHODS

In Vitro Study

Hydroxypropyl cellulose-M (HPC-M; JP grade, Nippon Soda Co., Tokyo), polyethylene glycol 400 (PEG 400; Wako Pure Chemical Co., Osaka), and DC (Sigma Chemical Co., St. Louis) were used. A nonwoven collagen sheet (MEIPAC, 0.1-mm thickness; Meiji Confectionery Co., Tokyo), which was used as support for the film, was washed overnight in distilled water. HPC-M (600 mg) was dissolved in ethanol (20 mL) to which DC (5 or 10 mg) and PEG 400 (10 mg) were added and mixed (Scheme 1). The resulting ethanol solution was placed in a level Teflon dish (7.5-cm diameter) and dried overnight under slightly negative pressure in a desiccator. The DC film formed was translucent, 0.12 ± 0.05 mm thick, and pliant even after drying. No precipitate of the drug was detected under polarization microscopy.

Film for the final application was cut into 2-cm squares that were determined to contain 0.113 or 0.225 mg/cm^2 DC each in the 5- and 10-mg samples, respectively, by the following method: several 2-cm squares were soaked in 10 mL of distilled water in a capped vial and shaken at room temperature for 1 h until the film was completely dissolved in the water. The concentration of DC dissolved in the media was assayed by high-performance liquid chromatography (HPLC; LC-9A system, Shimadzu Corp., Kyoto) under the following conditions: Deverosil ODSN-5 reversed-phase column (Shimadzu Corp.); phosphoric acid (0.001%)-acetonitrile (60:40) eluent; 1.2 mL/min flow rate; detection, UV at 240 nm. The recoveries of DC from the films ranged from 95 to 105%; the coefficients of variation were <5%.

Although several apparatuses have been used to evaluate *in vitro* drug release behavior,[6,7] for the most part the only consideration has been the release rate of the drug incorporated while disintegration of the polymeric matrix due to contact with water has been ignored. No suitable device has been found so far for the measurement of drug release from a water-soluble matrix, making it difficult to perform a quantitative study of drug release. Therefore, we designed a diffusion cell to measure not only the release rate of an incorporated drug but also the disintegration rate of the matrix (Fig. 1). The diffusion cell, fabricated entirely of acrylic resin, had three components: a top cover, a ring-type sheet-fixing device, and a double-jacketed chamber for temperature control. The cell was vertically divided into two compartments by a collagen sheet. The sheet was pushed down and fixed by the ring device, which was carefully machined to fit in the part of the cell and treated so that only the central dotted portion remained permeable. The magnetic stirring bar (30 × 8 mm) was driven by a constant-rate adjustable stirrer (Aimex AS-2T, Tokyo Seisakusho Co., Tokyo) positioned directly beneath the apparatus. The sampling port, which was an ordinary rub-

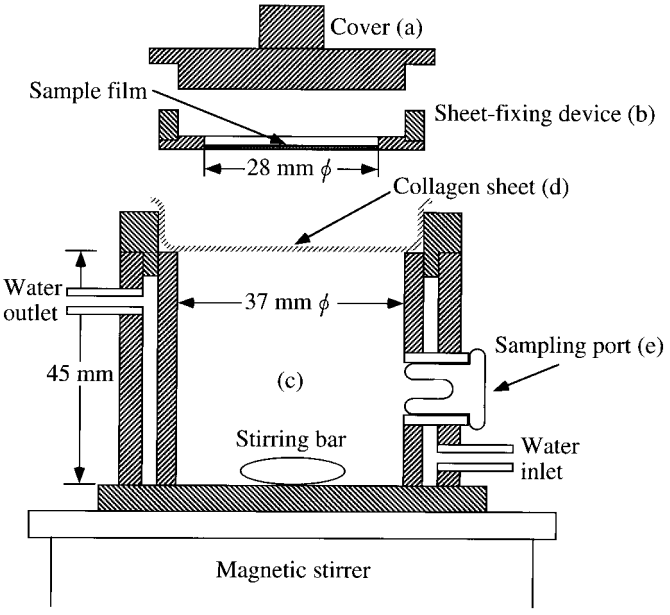

Figure 1. Diffusion cell for testing drug release from a water-soluble film and polymer disintegration.

ber stopper from an injection vial, was installed on the side of the lower chamber. The rubber stopper made possible repeated sampling of 10 to 20 μL for HPLC assay over time.

The diffusion cell (capacity 47.9 mL) was first filled with buffer solution (pH 7.0) until it reached slightly above the top level of the chamber on which the collagen sheet was placed so that it was wetted by solution and pushed down by the ring-type device, leaving no air bubbles in the chamber. Excess solution on the sheet was decanted and blotted; at the same time, it was assured that the surface of the wet sheet remained smooth. The film was cut to a diameter of 28 mm and was placed directly onto the collagen sheet. Water maintained at 37 °C circulated through the jacketed cell from a water bath at a constant controlled rate. An aliquot (10–20 μL) was withdrawn with a microsyringe through the rubber sampling port at appropriate intervals. The same volume of the solution withdrawn was returned to the chamber at each sampling. The released drug and disintegrated HPC-M were assayed by HPLC.

The amount of disintegrated HPC-M was determined by a Shimadzu RID-6A differential refractive index detector under the following conditions: column, Shodex OHpak KB-804 (Shimadzu Corp.); $NaNO_3$ (0.1 *M*) solution eluent; 0.5 mL/min flow rate.

The clinical application of AD films containing local anesthetics requires that the latter remain stable for long periods. Because high temperature is a critical factor in promoting drug degradation, we decided to measure the temperature conditions necessary for the preservation of films. DC films were prepared by the procedure described above and followed for 84 days under different storage conditions at 40 °, 50 °, and 60 °C.

Clinical Study

A two-part clinical study was conducted. All subjects granted informed consent per a protocol approved by the Nagoya University Ethics Committee on Human Research.

In the first part of the study, 10 healthy volunteers (five males and five females) were selected to evaluate the analgesic effects of the AD film after oral mucosal application. A single 0.9-mg DC film was applied to the right buccal mucosa and a drug-free film to the left buccal mucosa. Using a questionnaire, subjects evaluated the effectiveness of the films in terms of time until onset of numbness and numbness duration time.

The second part of the study utilized 23 patients (10 males, 13 females) with malignant tumors who were receiving chemotherapy treatment. AD film was applied to patients with mucositis presenting as erythema or a blister membrane; in all patients the diameter of the mucositis

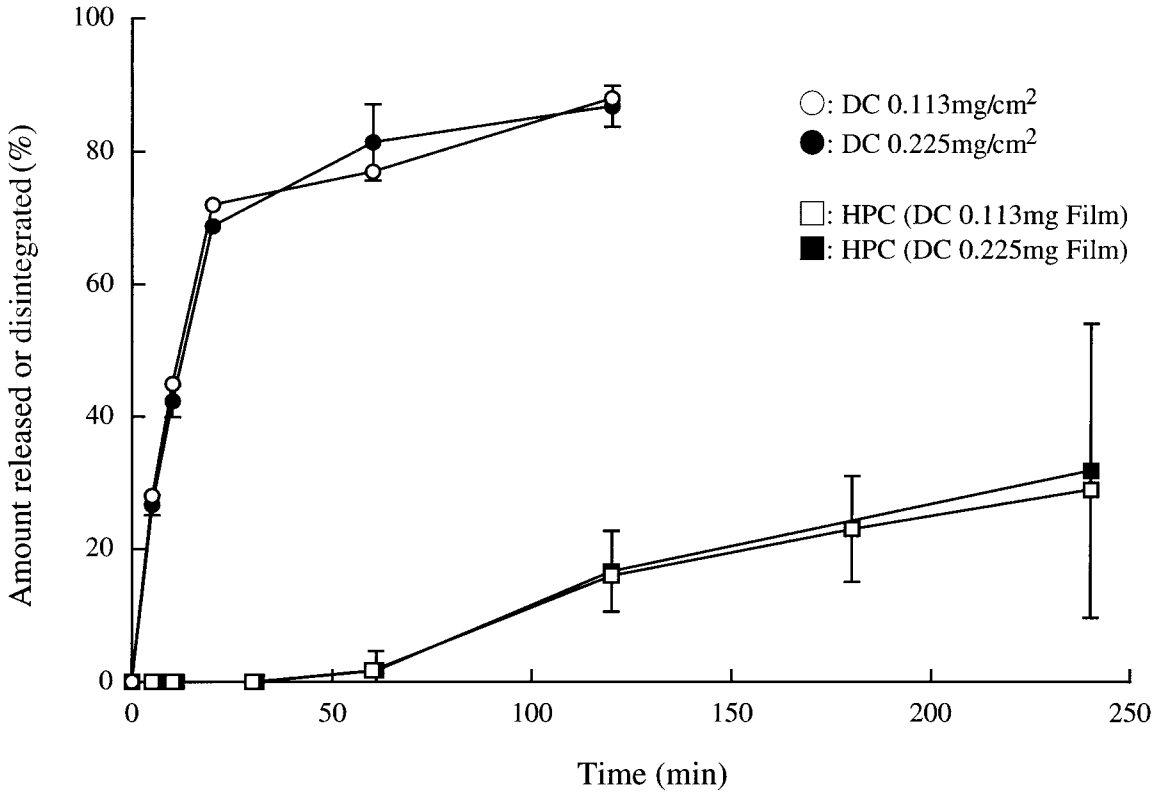

Figure 2. Release rates of dibucaine and HPC-M polymers from the AD films across a collagen sheet (mean ± SD, n = 5); bulk phase, pH 7.0 phosphate buffer (47.9 mL, 37 °C); agitation, 50 rpm.

TABLE I. Percentage of Dibucaine Remaining in AD Films after 84-Days Storage at Various Temperatures

Original Drug Concn (mg/cm^2/film)	Remaining (%)		
	40 °C	50 °C	60 °C
0.113	97.5 ± 0.3	97.2 ± 0.1	96.5 ± 0.2
0.225	98.9 ± 0.2	98.2 ± 0.3	97.2 ± 0.2

Values represent mean ± SD; $n = 5$ for each sample group.

was <20 mm and there was only mild contact pain. Patients were divided into two groups: 11 patients (five males, six females) receiving the 0.113-mg DC film and 12 patients (five males, seven females) receiving the 0.225-mg DC film. Evaluation was expressed in terms of pain-free onset time and pain-free duration time.

RESULTS

In Vitro Study

Figure 2 shows cumulative percentages of DC released from films and amount of disintegrated HPC-M. DC (0.113 and 0.225 mg/cm^2) was rapidly released from films incubated in buffer solution without appreciable lag time. Twenty-five percent of DC was released from the film by 5 min; the proportion reached approximately 80% after 50 min, at which time the polymer had still not disintegrated.

Disintegration of HPC-M showed a lag time of about 50 min and proceeded much longer than drug release, which reached a more or less constant rate of release after 50 min.

Table I shows the results of stability tests for DC in the AD films at three different temperatures (40°, 50°, and 60 °C). The DC in the films was stable for up to 84 days at any temperatures examined.

Clinical Study

When the film was applied to the wet surface of the oral mucosa in all subjects, it swelled and demonstrated excellent adhesion.

Table II shows the clinical evaluation of AD films by healthy volunteers. Mean numbness onset time was 3.3 ± 1.1 min, and numbness duration was 1.6 + 0.14 h for doses of 0.225 mg/cm^2 applied to the right buccal mucosa. No analgesic effect was noted for the drug-free film applied to the left buccal mucosa.

TABLE II. Anesthetic Effects of AD Films Applied to Oral Mucosa in Healthy Volunteers

Drug Concn	n	Numbness	
		Onset Time (min)	Duration (h)
0.225	10	3.3 ± 1.1	1.6 ± 0.14
0	10	No affect	No affect

Values are mean ± SD.

TABLE III. Analgesic Affects of AD Films in Patients with Oral Mucositis

Drug Concn (mg/cm^3)	Patient		Pain Free	
	Sex	Age (years)	Onset Time (min)	Duration (h)
0.113	F	38	<5	2.5
	F	35	<5	2.0
	F	30	<5	3.0
	F	29	<5	1.5
	F	42	<5	1.5
	F	46	<5	3.0
	M	29	<5	2.5
	M	66	<5	2.0
	M	48	<5	3.0
	M	58	<5	2.0
	M	47	<5	1.0
			2.2 ± 0.21[a]	
0.225	F	48	<5	4.0
	F	42	<5	5.0
	F	34	<5	5.5
	F	28	<5	4.0
	F	41	<5	3.0
	F	55	<5	4.0
	F	51	<5	3.5
	M	52	<5	4.5
	M	56	<5	5.0
	M	61	<5	4.0
	M	62	<5	3.0
	M	57	<5	5.5
			4.3 ± 0.25[a]	

[a] Mean ± SD.

Table III shows the clinical evaluation of AD films in patients with oral mucositis. Pain-free onset time was <5 min in all patients, irrespective of DC dose. Pain-free duration time was 2.2 ± 0.21 and 4.3 ± 0.25 h for DC doses of 0.113 and 0.225 mg/cm^2, respectively. Three of the 23 patients reported strange sensations in the mouth at the time of application of the film. No serious or unexpected adverse experiences were observed during or after application in any patient.

The data obtained in the 84 days of accelerated stability studies at temperatures up to 60 °C suggest that our DC–HPC-M film formulations should have a shelf life of at least 2 years.[8]

DISCUSSION

It is important for patients with oral erosion that the pain-free onset time be as short as possible and thus that the

release rate of the drug from the film be as high as possible. The release rate of a drug incorporated into a water-soluble polymeric matrix is closely related to the penetration rate of the water into that matrix. The interpretation of this release behavior is complex due to a variety of factors associated with the disintegration of the matrix; these generally include the penetration of water into the matrix, swelling of the polymer structure, and the start of disintegration after a maximal point of swelling is reached. To simplify such a complex system, it may be beneficial to keep the matrix as thin as possible.[9] The films examined in this study were about 0.1 mm thick, which also made them sufficiently pliant for easy application to oral lesions. The AD film seemed to swell rapidly because its surface appeared to become thoroughly wetted within 30 to 50 s of placing it on the collagen sheet. As a consequence, the drug incorporated into the film seemed to dissolve and released into the buffer solution *in vitro* and into saliva *in vivo* at a rapid rate.

The results of the first part of our clinical study showed that AD films, but not drug-free films, had analgesic effects. Pain relief in all patients began in <5 min. The results of the clinical evaluation are in good agreement with the rapid release behavior of DC in the *in vitro* study in which about 25% of the DC was released in the initial 5 min without appreciable lag time. Pain-free duration time in patients appeared to depend on the quantity of drug in the films. Furthermore, the disintegration rate of the film was much slower than drug release, which may thus be expected to protect the oral mucosa while relieving pain.

These results suggest that an AD film containing DC may be a useful means for providing relief of the pain associated with oral mucositis induced by chemotherapy and/or radiotherapy. The advantages of this material are that it provides rapid pain-free onset time and the polymer matrix covers the affected area over a sustained period. Further studies are needed to confirm the efficacy of this approach in effecting lasting pain-free duration for various degrees of oral mucositis.

REFERENCES

1. Yamasaki, K.; Shibata, Y.; Imai, S.; Tani, Y.; Shibasaki, Y.; Fukuhara, T. Clinical application of prostaglandin E1 (PGE1) upon orthodontic tooth movement. Am. J. Orthodontol. 85:508–518; 1984.
2. Leveque, F. G.; Parzuchowski, J. B.; Farinacci, G. C., et al. Clinical evaluation of MGI 209, an anesthetic, film forming agent for relief from painful oral ulcers associated with chemotherapy. J. Clin. Oncol. 10:1963–1968; 1992.
3. Danjo, K.; Kitamura, Y.; Miyagawa, Y.; Otsuka, A. Release of isosorbite dinitrate from polymer film dosage forms and absorption of this drug through the oral mucosa of rats. Chem. Pharm. Bull. 42:2126–2130; 1994.
4. Guo, J. H.; Cooklock, K. M. The effects of backing materials and multilayered systems on the characteristics of bioadhesive buccal patches. J. Pharm. Pharmacol. 48:255–257; 1995.
5. Yotsuyanagi, T.; Yamamura, K.; Akao, Y. Mucosa-adhesive film containing local analgesic. Lancet 14:613; 1985.
6. Danjo, K.; Higuchi, F.; Otsuka, A. Release of lidocaine from polymer film dosage forms. Chem. Pharm. Bull. 43:1759–1763; 1995.
7. Aguiar, A. J.; Weiner, M. A. Percutaneous absorption studies of chloramphenicol solution. J. Pharm. Sci. 58:210–215; 1969.
8. Martin, A.; Swarbrick, J.; Cammarata, A., Eds. Physical Pharmacy, 3rd edition. Philadelphia, PA: Lea & Febiger; 1983:391–394.
9. Martin, A.; Swarbrick, J.; Cammarata, A., Eds. Physical Pharmacy, 3rd edition. Philadelphia, PA: Lea & Febiger; 1983:412–418.