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Research paper

Preparation of a fast dissolving oral thin film containing dexamethasone: A possible application to antiemesis during cancer chemotherapy

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ABSTRACT

We prepared fast dissolving oral thin film that contains dexamethasone and base materials, including microcrystalline cellulose, polyethylene glycol, hydroxypropylmethyl cellulose, polysorbate 80 and low-substituted hydroxypropyl cellulose. This preparation showed excellent uniformity and stability, when stored at 40 °C and 75% in humidity for up to 24 weeks. The film was disintegrated within 15 s after immersion into distilled water. The dissolution test showed that approximately 90% of dexamethasone was dissolved within 5 min. Subsequently, pharmacokinetic properties of dexamethasone were compared in rats with oral administration of 4 mg dexamethasone suspension or topical application of the film preparation containing 4 mg dexamethasone to the oral cavity. Pharmacokinetic parameters were similar between the two groups in which C_{max} (h), T_{max} (μg/mL), AUC (μg/mL/h) and half-life (h) were 12.7 ± 6.6 (mean ± SD, N = 10), 3.4 ± 1.4, 93.6 ± 37.8 and 1.66 ± 0.07, respectively, for oral suspension and 13.3 ± 4.0, 3.2 ± 1.0, 98.0 ± 22.3 and 1.65 ± 0.06, respectively, for film preparation. These findings suggest that the fast dissolving oral thin film containing dexamethasone is likely to become one of choices of dexamethasone preparations for antiemesis during cancer chemotherapy.

1. Introduction

The fast dissolving oral film preparation is a new drug delivery technique to provide medicines to patients with obstacles in swallowing or under emetic condition during cancer chemotherapy. The morbidity and mortality of cancer have been increasing and thus the number of patients who receive cancer chemotherapy has been elevated in the recent years. However, a number of patients who undertook cancer chemotherapy complain of side effects associated with anticancer drugs. Among them, nausea and vomiting are one of the most frequent side effects. Nausea and vomiting induced by emetogenic anticancer drugs include acute and delayed events, in which acute emesis occurs within a day of chemotherapy, while delayed event appears after 24 h and persists for several days [1–8]. According to the guidelines for prevention of cancer chemotherapy-induced emesis documented by Multinational Association of Supportive Care in Cancer (MASCC) [9], American Society of Clinical Oncology (ASCO) [10], and National Comprehensive Cancer Network (NCCN) [7], 5-HT_3 receptor antagonist, dexamethasone and/or neurokinin NK_1 receptor antagonist aprepitant are recommended to use in combination before chemotherapy for prevention of acute emesis, and dexamethasone alone or in combination with aprepitant is encouraged to administer orally for prophylaxis of the delayed emesis induced by high to moderate risk of emetogenic anticancer drugs. On the other hand, disturbance in eating and swallowing associated with oral mucositis is often encountered in patients with head and neck cancer who underwent combination of chemotherapy and radiotherapy [11–14]. Therefore, the antiemetic oral medicines are inconvenient to use in such patients.

Oral disintegrating tablets [15,16] and oral jerry preparations [17] have been developed for patients with dysphagia or aphagia. The jerry preparations have an advantage of taking without choke and are useful for elderly patients but are bulky in many cases,

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while oral disintegrating tablets are readily disintegrated but the disintegrated materials are insoluble and remain until swallowing. On the other hand, edible thin oral film preparations have been used as oral care products [18,19]. These preparations easily dissolve in saliva, thereby requiring no water to take. Therefore, the oral disintegrating thin film preparation appears to be useful for patients with eating and swallowing disturbance.

In the present study, we developed a fast-disintegrating oral thin film containing dexamethasone. The content uniformity and stability were tested. We also investigated the pharmacokinetic characteristics in rats with topical application of the film preparation to the oral cavity.

2. Materials and methods

2.1. Materials

Dexamethasone and ethyl-*p*-hydroxybenzoate were obtained from Nacalai Tesque (Kyoto, Japan). Microcrystalline cellulose (Asahikasei Co. Ltd., Tokyo, Japan), polyethylene glycol (Sanyo Chemical Industries, Ltd., Kyoto), polysorbate 80 (Nichiyu Co., Ltd., Tokyo), 5% low-substituted hydroxypropyl cellulose (L-HPC) and hydroxypropylmethyl cellulose (hypromellose) (Shin-Etsu Chemical Co., Ltd., Tokyo) were used as film base materials.

2.2. Preparation of oral film

The constituents of the basic materials were microcrystalline cellulose (57%), polyethylene glycol (15%), hypromellose (7.4%), polysorbate 80 (5.4%) and 5% L-HPC (1.3%). The bases of the film preparation were mixed and fragrance ingredients were included, then the mixture was coated onto plastic film to prepare thin film, then dried by heating. The resultant film was cut into the four-square of 2 cm × 2 cm in size, in which 4 mg dexamethasone was included.

2.3. Uniformity of dosage units of the preparation

The uniformity of dosage units of the oral film preparation was tested using 20 preparations, and the content of dexamethasone was determined by HPLC with spectrometric detection. The acceptance value (*AV*) of the preparation is less than 15%, according to the JP15. *AV* for JP15 was calculated according to the following equation:

$$AV = |M - X| + ks, \quad (1)$$

where M is label claim (100%), X is the average (%) of individual contents, k is the acceptability constant (2.2), s is the standard deviation.

In USP27, the contents of major component in the preparation should be within a range between 85% and 115%, and the relative standard deviation should be less than or equal to 6.0%.

2.4. Sample preparation

A piece of oral film containing 4 mg dexamethasone was dissolved in 100 mL of 50% methanol solution. One-milliliter aliquot of the solution was transferred to a polypropylene tube and 1 mL of ethyl-*p*-hydroxybenzoate (40 μg/mL) was added as the internal standard. Then, mobile phase was added to the mixture and the volume was adjusted exactly to 10 mL.

2.5. Stability test

A piece of film preparation was stored in an aluminum package at 25 °C with 50–60% humidity (normal condition) or at 40 °C with 75% humidity (accelerated condition) for 4–24 weeks, then the content of dexamethasone was determined. In addition, the film sample was subjected to the dissolution test.

2.6. Dissolution test

The dissolution test was performed according to the JP15 paddle method using the paddle apparatus (NTR-6000, Toyama Sangyo Co., Ltd., Osaka, Japan). Test solution was 900 mL of phosphate solution (pH 1.2) at 37 ± 0.5 °C with a rotation rate of 50 rpm. Ten-milliliter aliquot of samples was taken from 2 min to 60 min with autosampler (PAS-615, Toyama Sangyo Co., Ltd.) and the same volume of fresh test solution was replenished. One-milliliter aliquot of samples was taken in a polyethylene tube and the same volume of the internal standard solution (4 μg/mL) was added, and 50-μL aliquot of the mixture was injected onto HPLC to determine the concentration of dexamethasone.

2.7. Determination of pharmacokinetic parameters in rats

Seven-week-old male Sprague–Dawley rats were used in the present experiment. The animals were housed in a room maintained on a 12-h light/dark cycle at 23 ± 2 °C with free access to food and water. The experimental procedures were approved by the Committee for the Care and Use of Laboratory Animals at the Gifu Pharmaceutical University. Under light ether anesthesia, rats were orally given with 4 mg of dexamethasone suspension in a volume of 0.5 mL or topically applied with the film (2 cm × 2 cm) containing 4 mg of dexamethasone to the oral cavity. The film was cut into two pieces (1 cm × 2 cm) and applied to the inner cheeks bilaterally. Blood specimens were taken (every 0.25 mL) in a heparinized glass capillary tube from the tail vein at 15 min, 30 min, 1 h, 2 h, 3 h, 6 h, 12 h, 24 h and 48 h after drug administration. After centrifugation at 10,000 rpm for 5 min, plasma was taken in a polyethylene tube and stored at −70 °C until assay. The concentration of dexamethasone was determined by HPLC with spectrometric detection using ethyl-*p*-hydroxybenzoate as the internal standard. The HPLC system was LC-VP system (Shimazdu Co. Ltd, Kyoto) with the reversed-phase ODS separation column (Symmetry C18, 4.6 × 250 mm, Nihon Waters, Tokyo). The mobile phase was a mixture of 0.01 M potassium phosphate buffer (pH 7.0) and acetonitrile (55:45% v/v) and delivered at a flow rate of 1.0 mL/min. A 50-μL aliquot of sample was injected directly onto HPLC and dexamethasone was detected from the absorbance of OD at 240 nm.

2.8. Validation of analysis

The calibration curve for dexamethasone was plotted in triplicate using eight different concentrations of rat serum spiked with 0.1, 0.25, 0.5, 1, 5, 10, 25 and 50 μg/mL of dexamethasone.

2.9. Statistical analysis

Data were expressed as the mean ± SD. In the stability test and dissolution study, data were analyzed and statistically compared by Dunnett's test. Data on the pharmacokinetic parameters were compared between two groups and statistically evaluated by *t*-test.

3. Results and discussion

3.1. Uniformity of dosage units of oral film preparation

The average of dexamethasone content in 20 preparations was 3.97 ± 0.16 mg and the values were ranging from 93.4% to 106.2%. The relative standard deviation was 4.4%. Thus, the preparation met the criteria of USP27 content uniformity. Moreover, *AV* was 11.8%, a value that was within the limit (15%) of uniformity of dosage units for JP15.

3.2. Stability

When the oral film preparation was stored in an aluminum package under normal condition or in a chamber controlled at 40 °C and 75% in humidity for 4–24 weeks, no apparent changes in the dexamethasone content, form or color of preparations were observed. The contents of dexamethasone were fairly stable ranging from 92.4% to 102.7% during 24 weeks after storage at 25 °C and 50–60% humidity (normal condition), or from 98.0% to 103.4% during the same periods after storage at 40 °C and 75% humidity (accelerated condition) (Fig. 1).

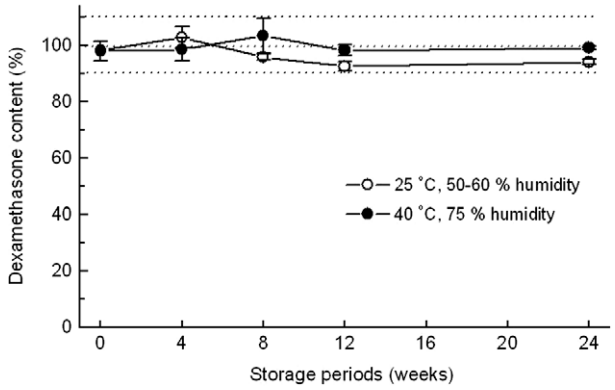

Fig. 1. Stability of the fast dissolving oral film containing dexamethasone after storage under normal condition (A) or accelerated condition (B) for up to 24 weeks. Each film was wrapped in an aluminum package and stored at 25 °C with 50–60% humidity (normal condition) or at 40 °C with 75% humidity (accelerated condition). Each column represents the mean ± SD of 10 experiments. Data were statistically analyzed by Dunnett's test.

3.3. Dissolution of film preparation

Disintegration of film was checked by immersion of the film into distilled water and the time to disintegrate was 12.5 ± 1.3 s (mean ± SD, $N = 6$). On the other hand, the dissolution test was performed using pH 1.2 phosphate buffer solution since dexamethasone is more stable in a slightly acidic pH condition. As shown in Fig. 2, a rapid dissolution of the film preparation was observed by the dissolution test, in which approximately 90% of dexamethasone dissolved within 5 min. Notably, the dissolution profile was similar among preparations stored for 0–24 weeks in aluminum packages. Chambin et al. [20] have shown that addition of microcrystalline cellulose to the tablet increases dissolution rate, although the compound itself is not soluble in water, while addition of hydroxypropylmethyl cellulose reveals the steady dissolution. Therefore, the rapid dissolution of the present film preparation may be due to the inclusion of high amounts of microcrystalline cellulose in the preparation (more than 50%).

3.4. Comparison of pharmacokinetic parameters between oral solution and oral film in rats

Fig. 3 shows the time course of changes in dexamethasone concentrations in rat plasma after oral administration of dexamethasone suspension or topical application of the fast-disintegrating film to the oral cavity. The pattern of changes in plasma concentrations was similar between the two groups. The pharmacokinetic parameters such as T_{max}, C_{max}, $AUC_{(\infty)}$, Ke, $t_{1/2}$, Cl_{tot} and steady-state Vd were thus comparable between the two groups (Table 1).

The present fast-disintegrating film met the criteria of *AV* in the dosage uniformity test for JP15 and USP27. The content of dexamethasone was stable for at least 24 weeks after preparation, even stored at 40 °C and 75% humidity. The film also showed a rapid disintegration and dissolution profile of dexamethasone. In rats, plasma concentration of dexamethasone increased after topical application of the film preparation to the oral cavity, in which the peak appeared at 3.4 h with a C_{max} value of 12.66 mg/mL and area under curve of 93.64 mg/mL/h. Similar pharmacokinetic parameters were obtained from rats with oral administration of dexamethasone suspension. One of the advantages of oral film preparation is the ease to intake without water. The base materials used in the present film preparation have been applied to oral care products and food additives, thus the safety of the materials was certified. Thus, the present film containing dexamethasone can

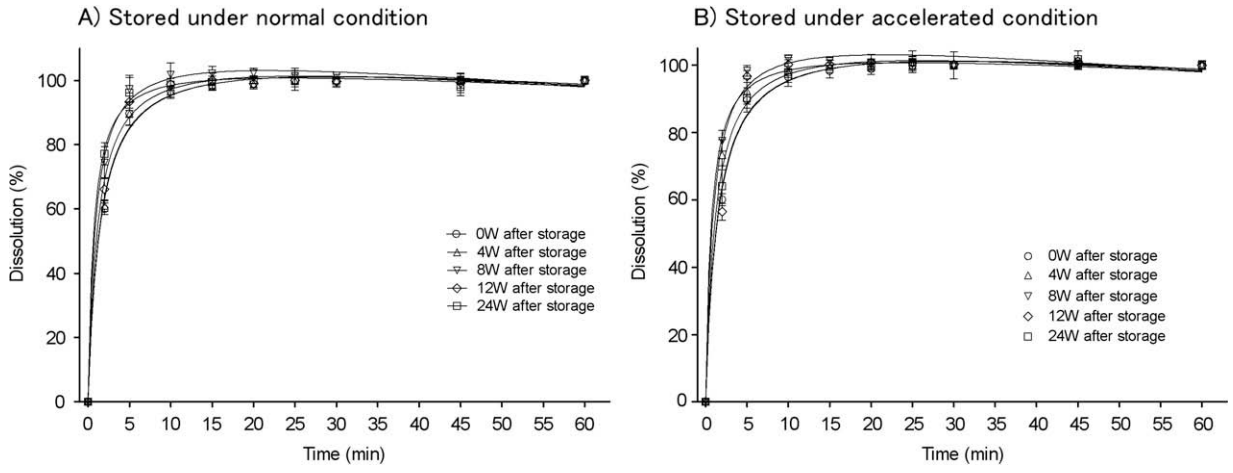

Fig. 2. Dissolution profile of dexamethasone-containing film stored for up to 24 weeks under normal (A) and accelerated conditions (B). Each film was wrapped in an aluminum package and stored at 25 °C with 50–60% humidity (normal condition) or at 40 °C with 75% humidity (accelerated condition). Each point represents the mean ± SD of six experiments. Data were statistically analyzed by Dunnett's test.

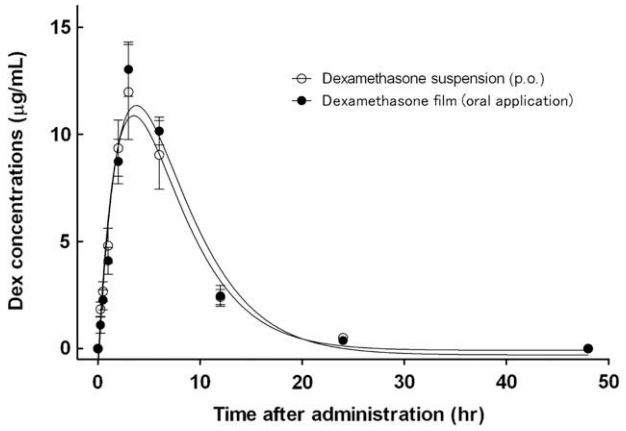

Fig. 3. Comparison of time course changes in plasma concentration of dexamethasone administered with oral film or suspension in rats. Rats were lightly anesthetized with ethyl ether and dexamethasone was administered orally with solution or ingested with oral film preparation at a dose of 5 mg. Each point represents the mean ± SD of 10 animals.

Table 1
Comparison of pharmacokinetic parameters of dexamethasone between oral film and oral suspension in rats.

	Oral film (N = 10)	Solution (N = 10)	P values
T_{max} (h)	3.20 ± 1.03	3.40 ± 1.43	0.724
C_{max} (μg/mL)	13.33 ± 3.97	12.66 ± 6.61	0.785
$AUC_{(\infty)}$ (μg/mL/h)	98.01 ± 22.28	93.64 ± 37.75	0.756
ke (h^{-1})	0.42 ± 0.01	0.42 ± 0.02	0.713
$T_{1/2}$ (h)	1.65 ± 0.06	1.66 ± 0.07	0.696
Cl_{tot} (L/h)	0.05 ± 0.01	0.06 ± 0.02	0.410
Vd_{ss} (L)	0.37 ± 0.12	0.44 ± 0.20	0.344

T_{max} and C_{max} were determined from individual real value. Each value represents the mean ± SD.

be applicable to patients with difficulties in oral intake, particularly to patients who need antiemetic therapy during cancer chemotherapy. On the other hand, oral steroid film may sometimes cause several side effects such as irritation of the oral mucosa, hoarseness, bacterial or fungal infections. To minimize the risk of such side effects in clinical setting, patients are sure to rinse thoroughly or gargle after taking the present dexamethasone-containing oral film.

Several lines of evidence have shown that stimulation of 5-HT_3 receptors is implicated in the etiology of chemotherapy-induced acute emesis: serotonin release from intestinal enterochromaffin cells, as evidenced by the increase in urine and plasma levels of 5-hydroxyindole acetic acid, a major metabolite of serotonin, is elevated after high doses of cisplatin [21], several 5-HT_3 receptor antagonists are effective for prophylaxis of acute but not delayed emesis induced by high- or moderate-emetogenic anticancer drugs [21,22]. On the other hand, glucocorticoids such as dexamethasone is effective for prevention of acute as well as delayed emesis in patients who received a high dose of cisplatin [23,24]. Moreover, dexamethasone causes a more marked antiemetic effect against acute and delayed emesis, when used in combination with the 5-HT_3 receptor antagonist [4,25]. Although the precise mechanisms underlying the antiemetic action of dexamethasone remain to be clarified, Malik et al. [26] have shown in rats that cisplatin increased, while dexamethasone decreased, acylated form of ghrelin, an endogenous orexigenic peptide that stimulates gastric motility in plasma, suggesting a possible involvement of ghrelin modulation in the antiemetic action of dexamethasone. Several clinical practice guidelines for antiemesis during cancer chemotherapy have recommended the use of dexamethasone on days 1–4 of chemotherapy. For outpatients, oral preparation of dexamethasone is usually prescribed but is hard to use for patients with difficulties in intake due to emetic symptoms or oral inflammation. In this regards, the present fast dissolving oral film seems to be potentially useful for such patients.

4. Conclusion

We prepared for the first time a fast dissolving oral thin film containing dexamethasone. The preparation revealed excellent uniformity and stability of dexamethasone and rapidly disintegrated in water. There were no significant differences in pharmacokinetic parameters obtained from rats with oral administration of dexamethasone suspension and those with topical application of the film to the oral cavity. Therefore, the present fast-disintegrating oral film containing dexamethasone is considered to be potentially useful for cancer patients with disturbance in eating and swallowing who receive radiotherapy and/or high- to moderate-emetogenic anticancer drugs.

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