International Journal of Pharmaceutics 368 (2009) 98–102

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

In vitro and *in vivo* characteristics of prochlorperazine oral disintegrating film

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ARTICLE INFO

Article history:
Received 22 July 2008
Received in revised form 25 August 2008
Accepted 2 October 2008
Available online 15 October 2008

Keywords:
Oral disintegrating film
Prochlorperazine
Uniformity of dosage units
Dissolution test
Pharmacokinetics

ABSTRACT

Oral disintegrating film containing prochlorperazine, a dopamine D_2 receptor antagonist with anti-emetic property, was newly developed using microcrystalline cellulose, polyethlene glycol and hydroxypropylmethyl cellulose as the base materials. The uniformity of dosage units of the preparation was acceptable according to the criteria of JP15 or USP27. The film showed an excellent stability at least for 8 weeks when stored at 40 °C and 75% in humidity. The dissolution test revealed a rapid disintegration property, in which most of prochlorperazine dissolved within 2 min after insertion into the medium. Subsequently, rats were used to compare pharmacokinetic properties of the film preparation applied topically into the oral cavity with those of oral administration of prochlorperazine solution. None of the parameters, including T_{max}, C_{max}, area under curves, clearance and steady-state distribution volume was significantly different between oral disintegrating film and oral solution. These findings suggest that the present prochlorperazine-containing oral film is potentially useful to control emesis induced by anti-cancer agents or opioid analgesics in patients who limit the oral intake.

1. Introduction

Malignant neoplasm has long been the first leading cause of death in Japan as well as a number of western countries. Moreover, the morbidity of carcinoma is increasing and thus the number of patients who undertake cancer chemotherapy is elevated during recent years. It has been shown that approximately 70% of patients with advanced cancer complain of pain and about half of them have severe symptom that require medication with strong opioid analgesics (Braiteh et al., 2007; Chang et al., 2007). A number of strong opioid analgesic preparations have been developed. Opioid compounds reveal a potent and effective analgesic action but have several adverse reactions, including constipation and nausea/vomiting (Schug et al., 1992; Cherny et al., 2001; McNicol et al., 2003). Nausea and vomiting is known to be elicited in 30–50% of strong opioid analgesic users. Dopamine D_2 receptor antagonists such as prochlorperazine are effective in suppressing opioid analgesic-induced nausea and vomiting (Fiocchi et al., 1982; Foss et al., 1993; Williams and Smith, 1999). Therefore, the prophylactic medication with dopamine D_2 receptor antagonists is recommended for prevention of nausea and vomiting associated with strong opioid analgesics. Moreover, D_2 receptor antagonists are often used for ameliorating chemotherapy-induced nausea and vomiting in patients who experienced uncontrolled emesis regardless of the conventional premedication regimen such as the combination of 5-HT_3 receptor antagonists and dexamethasone (Morran et al., 1979; Nesse et al., 1980; Jenns, 1994; Roila et al., 2004; Kris et al., 2006). However, the emetic symptoms that appeared in such uncontrolled patients often results in dysphagia or difficulty in oral intake. Oral disintegrating tablets (ODT) (Howden, 2004; Carnaby-Mann and Crary, 2005) and oral jerry preparations (Morita, 2003) have been developed for patients with dysphagia or aphagia. Although ODT can be taken with slight or no water and are readily disintegrated, the disintegrated materials are insoluble and remain until swallowing. The jerry preparations have an advantage of taking without choke and are useful for elderly patients but are bulky in many cases.

On the other hand, edible thin film preparations have been used as oral care products for removing bad breath (Wu et al., 2002; Hambleton et al., 2008). These preparations dissolve in saliva, thereby requiring no water to take. Therefore, oral disintegrating film preparations appear to be suitable to apply to patients with dysphagia or aphagia.

In the present study, we developed an oral disintegrating film containing prochlorperazine, and the content uniformity and stability were tested. We also investigated the pharmacokinetic

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doi:10.1016/j.ijpharm.2008.10.002

characteristics of the preparation in rats after topical application to the oral cavity.

2. Materials and methods

2.1. Chemicals

Prochlorperazine maleate was obtained from Shionogi & Co., Ltd. (Osaka, Japan). Microcrystalline cellulose (Asahikasei Co., Ltd., Tokyo, Japan), polyethylene glycol (Sanyo Chemical Industries, Ltd. (Kyoto, Japan), polysorbate 80 (Nichiyu Co., Ltd., Tokyo), 5% low substituted hydroxypropylcellulose (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 are microcrystalline cellulose (57%), polyethylene glycol (15%), hydroxypropylmethyl cellulose (hypromellose) (7.4%), polysorbate 80 (5.4%) and 5% low substituted hydroxypropyl cellulose (L-HPC) (1.3%). As shown in Fig. 1, bases of the film preparation were mixed and fragrance ingredients were included. The mixture was coated onto plastic film to prepare thin film using the coating apparatus originally manufactured by Tsukioka Co., Ltd., then dried by heating. The resultant film with the basic plastic film was cut without severing the plastic film into the foursquare of 1 cm × 1 cm in size, in which 1 mg prochlorperazine maleate was contained, then the film was removed from plastic film. In another set of experiment where pharmacokinetic parameters in rats were measured, oral film that contains 5 mg prochlorperazine maleate in 1 cm^2 of foursquare was prepared. The weight of the film preparation was 11.0 ± 0.3 mg/cm^2 (mean ± S.D., N = 20). The thickness of the film was 100 μm (102–109 μm).

2.3. Uniformity of dosage units of the preparation

The uniformity of dosage units of the oral film preparation was tested using 10 preparations, and the content of prochlorperazine was determined by LC–MS/MS. The acceptance value (AV) of the preparation is less than 15%, according to the JP15. While in USP27, the contents of preparations are between 85% and 115% and the relative standard deviation is less than or equal to 6.0%. AV for JP15 was calculated according to the following equation:

$$AV = |M - X| + ks$$

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

2.3.1. Sample preparation

A piece of oral film containing 1 mg prochlorperazine maleate was dissolved in mobile phase by sonification and the volume was adjusted exactly to 10 mL. A 0.1-mL aliquot of the solution and 0.1 mL aliquot of chlorpromazine hydrochloride solution (0.1 mg/mL), an internal standard, were taken into a polyethylene tube and the total volume was adjusted to 10 mL.

2.4. 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-mL aliquots of samples were taken from 2 min to 120 min with autosampler (PAS-615, Toyama Sangyo Co., Ltd.) and the same volume of fresh test solution was replenished. One-mL aliquot of samples was taken in a polyethylene tube and the same volume of internal standard solution (1 μg/mL chlorpromazine) was added, and the mixture was injected onto HPLC to determine the concentration of prochlorperazine.

2.5. Stability test

A piece of film preparation was stored in an aluminum package in a chamber controlled at 40 °C and 75% in humidity for 4–8 weeks, then the content of prochlorperazine was determined. In addition, the film sample was subjected to the dissolution test.

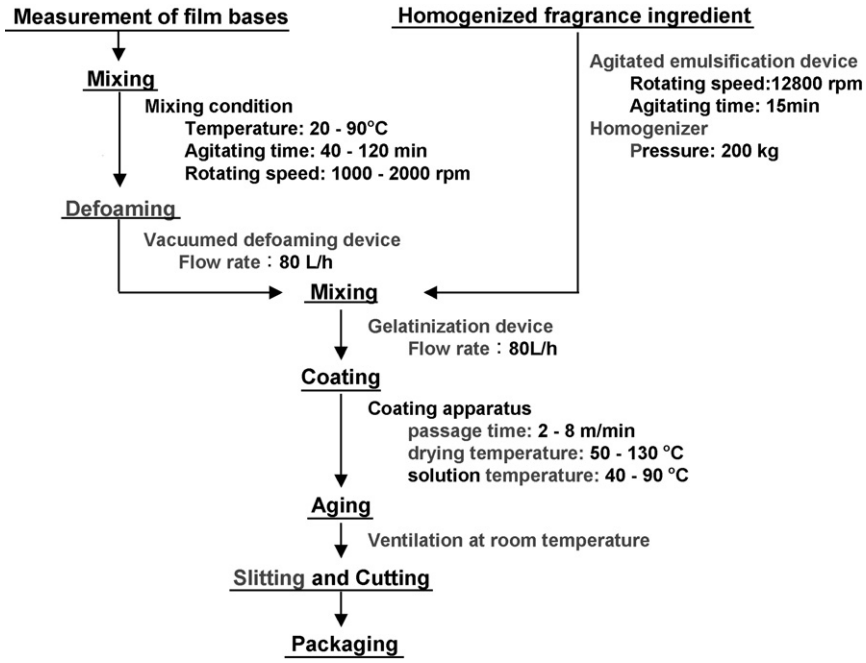

Fig. 1. Procedures for the preparation of oral film (solution casting method).

2.6. Determination of pharmacokinetic parameters in rats

Seven-week-old male Sprague–Dawley rats were used in the present experiment. 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. For topical application of film preparation, 50-μL aliquot of distilled water was dropped into the rat oral cavity under light ether anesthesia, then two halves (1 cm × 0.5 cm) of the film preparation were applied to the buccal cavity bilaterally. After checking disintegration of the film, anesthesia was discontinued. It took up to 1 min for the film to disintegrate, thus the duration of anesthesia was adjusted to 3 min. For oral administration, rats were orally given with 5 mg of prochlorperazine maleate solution containing 5 mg in a volume of 0.5 mL under light ether anesthesia and the anesthesia continued for 3 min. Blood specimens were taken (every 0.25 mL) in a heparinized glass capillary tube from the tail vein at 1 min, 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 prochlorperazine was determined by LC–MS/MS. A moment analysis was performed to obtain pharmacokinetic variables (Michels et al., 2000), including the total area under the first-moment time curve extrapolated to infinity [$AUC_{(\infty)}$], elimination half-life ($t_{1/2}$), total clearance (Cl_{tot}) and the steady-state distribution volume (Vd_{ss}). The C_{max} and T_{max} values were obtained from real values. In addition, 90% confidence intervals (CI) for the ratio of means of pharmacokinetic parameters between the film preparation and oral solution were calculated to evaluate the bioequivalence, according to the guidance for industry regarding bioavailability and bioequivalence studies for orally administered drug products (Food and Drug Administration 2003; http://www.fda.gov/cder/guidance/5356fnl.pdf).

2.7. Determination of prochlorperazine by LC–MS/MS

Prochlorperazine in plasma samples was extracted as follows: a 100-μL aliquot of plasma specimen was taken and 20 μL chlorpromazine solution (200 ng/mL), an internal standard, and 280-μL of 10 mM ammonium acetate were added and subjected to vortex mixing. The mixture was applied to the solid-phase column (Oasis® HLB, 1 mL, 30 mg, Nihon Waters K.K., Tokyo) that was pretreated with 1 mL acetonitrile followed by 1 mL distilled water. After washing with 1 mL distilled water, prochlorperazine and chlorpromazine were eluted with 1 mL acetonitrile. The concentration of prochlorperazine was determined by LC–MS/MS (tandem MS, Alliance® 2695, Nihon Waters). The separation column was ODS column (Cadenza CD-C18, 3 μm, 150 mm × 2 mm, inside diameter, Imtakt Co., Kyoto, Japan). Mobile phase was a mixture of methanol and 10 mM ammonium acetate (85:15, v/v%), and delivered at a flow rate of 0.3 mL/min. The column temperature was set at 40 °C. A 20-μL aliquot of sample specimens was injected. The analysis time was 7 min. Prochlorperazine and chlorpromazine were detected by MS/MS detector (Quattro micro™ API, Nihon Waters) and quantified using data processor (MassLynx™, Nihon Waters). The MS conditions were optimized by using QuanLynx™ (Nihon Waters) and ionization was made by electrospray ionization method (ESI). The detection was set by positive ion mode. MRM transition was from 374.1 m/z to 141.3 m/z for prochlorperazine and from 319.1 m/z to 86.0 m/z for chlorpromazine. Cone voltage was 38 V for prochlorperazine and 28 V for chlorpromazine. Collision energy was 22 eV for prochlorperazine and 18 eV for chlorpromazine. The electrospray source temperature was set at 120 °C and the desolvation temperature was 400 °C. Gas flow rate for desolvation was 600 L/h, while cone flow rate was 50 L/h.

2.8. Validation of analysis

The calibration curve for prochlorperazine 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 ng/mL of prochlorperazine. The recovery rate from extraction with Oasis® HLB column and intra and inter days variations were calculated in triplicate using serum standard containing 0.5 ng/mL, 5 ng/mL and 25 ng/mL of prochlorperazine. The concentrations of prochlorperazine spiked in plasma were linearly related to the ratio of peak areas (prochlorperazine/chlorpromazine) with the equation of $y = 0.0204x + 0.0005$ ($r^2 = 1.00$). The detection limit was 0.1 ng/mL (signal to noise ratio is 10). The recovery rate was 90.7–104.2%.

2.9. Statistical analysis

Data were expressed as the mean ± S.D. Data on the stability test and dissolution pattern of the film preparations stored at accelerated condition were statistically analyzed by one-way ANOVA followed by Dunnett's test. Data on plasma concentration and pharmacokinetic parameters obtained from rats treated with oral solution or oral disintegrating film containing prochlorperazine were compared and the statistical difference was analyzed by t-test.

3. Results and discussion

3.1. Uniformity of dosage units of oral film preparation

The average of ingredients (%) in 10 preparations was 96.5 ± 4.2%, and the values were between 87.9% and 101.6%. Thus, the preparation met the criteria of USP27 content uniformity. Moreover, AV was 12.7%, 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 either in the aluminum package or under unwrapped condition at 40 °C and 75% in humidity for 4–8 weeks, no apparent changes in the shape, color or flexibility were observed. The content of prochlorperazine was

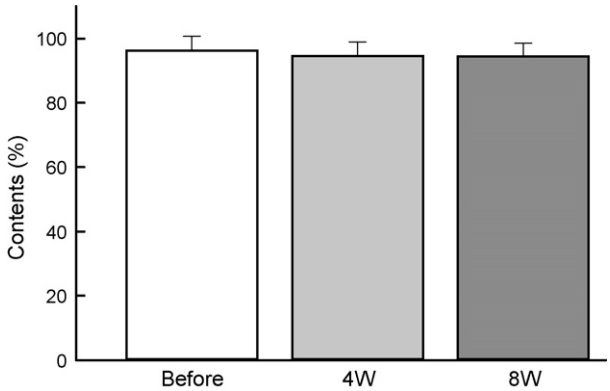

Fig. 2. Stability of oral disintegrating film containing prochlorperazine maleate. Stability was assessed before and 4 or 8 weeks after storage of the preparations stored in aluminium packages at 40 °C under 75% room humidity and 1000 lx conditions. Each column represents the mean ± S.D. of 10 experiments. Statistical analysis was performed by one-way ANOVA followed by Dunnett's test.

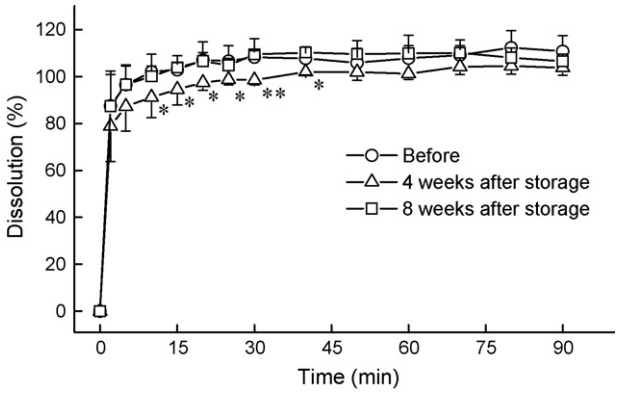

Fig. 3. Dissolution profiles of prochlorperazine maleate in the medium (pH 1.2) from oral film preparations that were stored at 40 °C and 75% room humidity in aluminum packages. Each point represents the mean ± S.D. of six experiments.

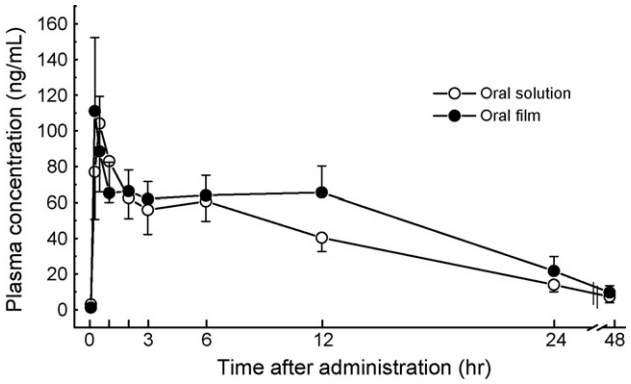

Fig. 4. Comparison of time course changes in plasma concentration of prochlorperazine administered by different oral routes in rats. Rats were administered orally with prochlorperazine solution or ingested with prochlorperazine-containing oral film preparation at a dose of 5 mg under light ether anesthesia. Each point represents the mean ± S.E. of 7 (solution) or 10 (oral film) animals.

almost constant for up to 8 weeks regardless of the stored condition (Fig. 2).

3.3. Disintegration and dissolution of film preparation

The time to disintegration tested by adding 100-μL aliquot of distilled water to the film (1 cm × 1 cm) was 21.9 ± 2.9 s (mean ± S.D., $N = 10$). As shown in Fig. 3, a rapid dissolution of the film preparation was observed and the rate over 80% attained within 2 min. Although the dissolution rates at 10–40 min in preparations stored for 4 weeks were significantly lower than those in preparations before storage, the rates of decrease were small, ranging from 5.3% to 10.7%. Chambin et al. (2004) have shown that addition of microcrystalline cellulose to the tablet increases dissolution rate, although the compound itself is not soluble in water. On the other hand, hydroxypropylmethyl cellulose tablet reveals the steady dissolution. Therefore, the rapid dissolution of the present film preparation may be due to the presence of highly amount (more than 50%) of microcrystalline cellulose in the preparation.

In the present study, the dosage uniformity test and dissolution test were carried out in acidic solution (pH 1.2) since the reproducible peak of this compound was not detected in neutral solution, possibly due to the adsorption in alkaline solution.

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

As reported earlier on the LC–MS/MS determination of prochlorperazine (Argoti et al., 2005), we successively measured the concentration of prochlorperazine in rat plasma by using LC–MS/MS. Fig. 4 shows the time course of changes in prochlorperazine concentrations in rat plasma after oral administration of prochlorperazine solution or the topical application of oral disintegrating film to the oral cavity. The pattern of changes in plasma concentrations was similar between the two groups but the concentrations were slightly and not significantly higher in oral film-treated group. There were no significant differences in pharmacokinetic parameters such as T_{max}, C_{max}, $AUC_{(\infty)}$, Ke, $t_{1/2}$, Cl_{tot} and steady-state Vd (Vd_{ss}) between the two groups (Table 1). According to the US Food and Drug Administration's approval for drug bioequivalence, the 90% CI of the ratio of the means of C_{max} and AUC between the test drug and the reference drug should be within 0.80–1.25. In the present study, the 90% CI values for ratio of C_{max} (−2.568 to 2.974) and AUC (−2.442 to 4.616) were beyond the range of the approval criteria. Therefore, we could not show the bioequivalence between the oral solution and oral disintegrating film from the present *in vivo* study.

In the present study, the elimination pattern of prochlorperazine appeared to be somewhat biphasic. This may be due to the fact that phenothiazines such as prochlorperazine is eliminated to some extent into bile acid and exhibit enterohepatic recycling (Hale et al., 1985).

In conclusion, we reported here the formulation of prochlorperazine-containing oral disintegrating film. The film preparation met the criteria of AV in the dosage uniformity test for JP15 and USP27, moreover, it revealed an excellent stability and dissolution profile. In rats, plasma concentration of prochlorperazine increased after the topical application of the film preparation to the oral cavity (5 mg) to the similar extent as that observed after oral ingestion of prochlorperazine solution (5 mg). Pharmacokinetic parameters were not significantly different between the two groups, although the bioequivalence was not shown. One of the advantages of oral film preparation is the ease in intake. The base of the present film preparation has been applied to oral care product for removing bad breath, and easily dissolve in saliva without producing insoluble materials. Moreover, the constituents of the base of the present film preparation have already been used as food

Table 1
Comparison of pharmacokinetic parameters.

	Solution ($N = 7$)	Oral film ($N = 10$)	P-Value	Ratio (90% confidence intervals)
T_{max} (h)	1.86 ± 2.09	2.95 ± 3.91	0.512	1.588 (−4.528 to 5.704)
C_{max} (ng/mL)	116.8 ± 104.6	140.5 ± 117.5	0.675	1.203 (−2.568 to 2.974)
$AUC_{(\infty)}$ (ng/mL h)	1118 ± 660	2333 ± 1687	0.061	2.087 (−2.442 to 4.616)
Ke (h^{-1})	0.058 ± 0.029	0.070 ± 0.045	0.574	1.190 (−1.740 to 2.120)
$t_{1/2}$ (h)	16.6 ± 11.8	30.1 ± 47.1	0.473	1.815 (−5.645 to 7.275)
Cl_{tot} (L/h)	4.23 ± 3.18	2.51 ± 2.22	0.206	0.593 (−2.207 to 1.393)
Vd_{ss} (L)	78.2 ± 59.9	51.6 ± 41.9	0.295	0.659 (−2.174 to 1.493)

T_{max} and C_{max} were determined from individual real value. Data were statistically evaluated by t-test.

additive and thus safe. These findings, taken together, suggest that the present oral disintegrating film containing prochlorperazine is potentially useful to patients with dysphagia or aphagia who require anti-emetic control during use of strong opioid analgesics or anti-cancer agents.

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