

Improved Stability of OPALMON[®] Tablets under Humid Conditions. III: Application of the Rotary Vacuum Drying Method to Dry Opalmon Tablets

Noboru SEKIYA,* Nobutaka ABE, Masanobu YAMAMOTO, and Kazuhisa TAKEDA

Pharmaceutical Development Laboratories, Ono Pharmaceutical Co., Ltd.; 3-1-1 Sakurai, Shimamoto-cho, Mishima-gun, Osaka 618-8585, Japan. Received October 25, 2006; accepted January 6, 2007

In stability studies on moisture-resistant Opalmon tablets in press-through-packages (PTP), which were placed in aluminum bags, we found that the degradation rate of the dextran formulation is faster than that of the lactose formulation. The fast degradation of the dextran formulation is attributed to residual moisture in the package because drying the tablets before packaging suppressed the degradation and there is a good correlation between the stability of the drug and the water-activity of the tablets. Therefore, we developed a new drying method for the tablets, *i.e.* the rotary vacuum drying method, and investigated the effects of the operating conditions such as heating temperature, rotation speed, and vacuum degree on the drying time, and the appearance of the tablets. Using the rotary vacuum drying method, the tablets were dried over a short time (30 min) on a mass production scale so that the water activity was less than 0.03. Furthermore, the tablets suffered negligible damage such as breaking and chipping during the drying process. These results indicate that the rotary vacuum drying method is useful for drying tablets on mass production scales.

Key words opalmon; stability; limaprost-alfadex; dextran; rotary vacuum drying method

Limaprost alfadex is an inclusion compound of Limaprost, a PGE₁ derivative with α -cyclodextrin, and is the active pharmaceutical ingredient of Opalmon tablets. The main degradation product of Limaprost under humidity is 17S,20-dimethyl-*trans*- Δ^2 -PGA₁ (11-deoxy- Δ_{10}), as shown in Fig. 1. In previous papers,^{1,2)} we have investigated the stability of Limaprost alfadex in tablets removed from their blister packages under high humidity, and have reported that the stability of the drug under high humidity is significantly improved by the addition of dextran compared to the addition of lactose and that the Opalmon tablet including dextran in the one-dose package is stabilized even under high humidity. However, herein we report that the stability of the drug is reversed when the tablets are packaged in PTP and placed in aluminum bags, *i.e.* the degradation rate under low humidity is the dextran formulation > the lactose formulation. To make a post-approval formulation change of a drug product, it is necessary to demonstrate the equivalence of the stressed stability in the market package before and after the formulation change. Therefore, we carried out to improve the stability of the formulation in PTP and aluminum package.

The poorer stability of the drug is attributed to the residual moisture of the dextran formulation, suggesting that the drug can be stabilized by drying the formulation before the PTP

process. We considered that drying tablets before PTP process is more efficient than drying raw materials or blended powder because the powder would absorb moisture in the following tableting process. However, manufacturing processes rarely dry tablets like they dry excipients and pellets. Although tray- and fluid-bed driers are commonly used for drying, it is difficult to dry tablets using the former apparatus due to the complicated procedures required to load and collect the tablets and the latter apparatus makes the tablets friable due to the intense motion of the tablets in the drier. Therefore, in this study, we developed the rotary vacuum drying method to dry tablets on a mass production scale, *i.e.* tablets were dried in a rotary vacuum drying drum, which was heated by hot water circulating outside of the machine. Because drying tablets would lead to the inferior products due to the degradation of the drug, retardation of disintegration or damage of the tablets, we studied the appropriate operating parameters of the tablet drying process. The drying time was optimized by monitoring the water activity of the tablets at different heat temperatures, drum rotation speeds, and degrees of the vacuum. Damage of the tablets due to the motion in the drum was evaluated by visually observing the chips and breaks of the dried tablets.

Experimental

Materials Limaprost alfadex specified in the Japanese Pharmaceutical Codex 2002 was used. All excipients used in this study were as follows: Lactose, dextran 40, cornstarch, dextrin, silicon dioxide, and stearic acid specified in Japanese Pharmacopoeia XV and sodium calboxymethylstarch specified in the Japanese Pharmaceutical Excipients. Dextrin was chemically equivalent to glucose 8. Blister films (VSL: polyvinyl chloride/polyvinylidene chloride/polyethylene laminated film and FCL: polyvinyl chloride/polychlorotrifluoroethylene laminated film) were purchased from Sumitomo Bakelite Co., Ltd. while silica gel (2 g in a bag) was purchased from Yamani Yakuhin Co., Ltd.

Preparation of Tablets The tablets were prepared at weight ratios specified in the formulation, which are listed in Table 1. The freeze-dried composites were prepared as follows: Limaprost alfadex and dextran 40 were dissolved in distilled water at a ratio of 1 : 7 (w/w%), freeze-dried using a Triomaster machine (Kyowa Vacuum Engineering Ltd.), and sieved. The

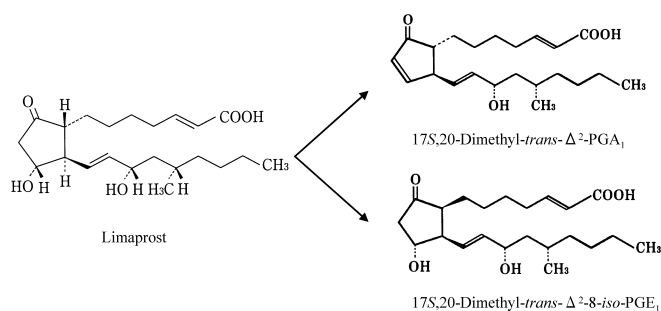


Fig. 1. Decomposition Pathway of Limaprost in the Solid State

* To whom correspondence should be addressed. e-mail: sekiya@ono.co.jp

Table 1. Formulations of Opalmon Tablets Containing Lyophilized Dextran (Left) and Lactose (Right)

Additives	Dextran formulation (mg/tablet)	Lactose formulation (mg/tablet)
Lyophilized Limaprost alfadex with dextran	1.33	
Lyophilized Limaprost alfadex with lactose		1.33
dextrin	8.67	
lactose	84.3	51.97
Microcrystalline cellulose		40
Povidone		5
Silicon dioxide	0.2	0.2
Stearic acid	0.5	1.5
Corn starch	5	
Total	100	100

Table 2. HPLC Conditions

Detector	UV wave (215 nm)
Column	ϕ 4.6 mm, 15 cm length, ODS column
Column temp.	35 °C
Mobile phase	0.02 mol/l potassium dihydrogenphosphate (pH 3.0)/ acetonitrile/isopropyl alcohol (9 : 4 : 2, volume ratio)
Flow rate	0.8 ml/min

freeze-dried composites were blended with dextrin, lactose, silicon dioxide, cornstarch, and stearic acid. The mixture was compressed with a rotary tablet-press machine (Virgo, Kikusui Seisakusyo Ltd.) at a 800 kg compressing force to make tablets, which measured 100 mg/6.5 mm in diameter. The same procedure was used to prepare the placebo tablets, but without Limaprost alfadex in the freeze-dried composite.

Assay of Limaprost and Related Substances Ten tablets were dissolved in 3.0 ml of purified water, to which an internal standard (2 ml of *p*-hydroxybenzoic acid *n*-propyl ester/ethanol) was added, and the solution was mixed by a vortex mixer. Two hundred microliters of the solution was analyzed by a HPLC system (LC2010CHT, Shimadzu Co., Japan) for Limaprost and its degradation products, 17S,20-dimethyl-*trans*- Δ_2 -PGA₁ (11-deoxy- Δ_{10}) and 17S,20-dimethyl-*trans*- Δ_2 -8-iso-PGE₁. The ratios of the main product of Limaprost, 17S,20-dimethyl-*trans*- Δ_2 -PGA₁, to the total amount of Limaprost, 11-deoxy- Δ_{10} , and 17S,20-dimethyl-*trans*- Δ_2 -iso-PGE₁ were calculated and used as the stability index. Table 2 describes the HPLC conditions employed.

Stability Test of Opalmon Tablets in a Package A blister package (VSL/Aluminum), which contained ten tablets, was placed in an aluminum bag with silica gel, and the stability test was performed at 60 °C. Two blister packages (FCL/Aluminum), which contained 21 tablets, were placed in an aluminum bag with silica gel, and the stability test was performed at 40 °C. Water activity of the tablets was measured using an Aqualab CX3TE apparatus (Decagon Co. Ltd.). Each experiment was repeated at least three times and the results were expressed as mean values or mean values \pm standard deviation of the mean.

Moisture Absorption of Freeze-dried Composites The equilibrium moisture content in the freeze-dried composites was evaluated by measuring the weight change of the samples after storage at different relative humidities at 25 °C for 60 min using a Symmetrical Vapor Sorption Analyzer (SGA 100, VTI Co.). The samples were preliminarily dried for 2 h at 60 °C in a nitrogen gas atmosphere, and the atmospheric condition surrounding the samples was stepwise changed from low to high humidity in 5% increases in relative humidity (RH).

Correlation between Water Activity and Stability in Package Opalmon tablets (dextran formulation) were prepared according to the procedure shown in Fig. 2. The tablets were humidified at 25 °C and 60% RH, and then vacuum-dried for various drying times to obtain tablets with different moisture levels. A blister package (FCL/Aluminum) that contained ten tablets was placed in an aluminum bag with silica gel, and the stability test was performed at 40 °C. The amount of the degradation product, 11-deoxy- Δ_{10} , formed after storing was measured by HPLC under the conditions listed of

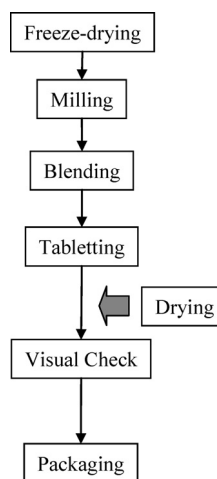


Fig. 2. Flowchart of the Manufacturing Process of Opalmon Tablets

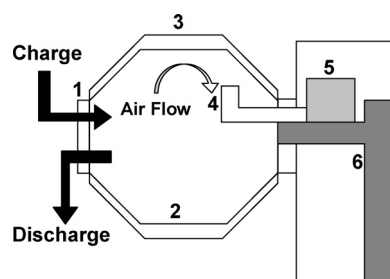


Fig. 3. Schematic Diagram of Rotary Vacuum Drier

The tablets are charged through the window (1) into the drum (2). The drum is heated by the hot water circulating jacket (3). The air in the drum is sucked through the suction tube with filter (4) by vacuum pump (5). The drum is rotated by the drive (6). After drying is completed, tablets are discharged through the window (1).

Table 2. Replicate determinations of new samples did not significantly differ from the original data sets.

Effect of Heating Temperature Tablets, which were placed in open glass bottles, were heated in a tray drier at heating temperatures of 60, 70, or 80 °C for 1, 2, 3, or 4 h, and changes in the appearance, purity, and disintegration time of the tablets were evaluated. The reported results of purity test are obtained from the assay of ten tablets.

Disintegration Test The disintegration test was performed in accordance with JP15 disintegration test (NT-20, Toyama Sangyo Co., Ltd.). The results reported are mean values of six experiments.

Drying of Tablets Using Rotary Vacuum Drier The vacuum drying was performed using a rotary vacuum drier (VG-50, Kikusui Seisakusyo Ltd.). The schematic diagram of the drier was shown in Fig. 3. The drying commenced after 300000 tablets were charged into a preheated drum. The dried tablets were removed from the drum every 30 min for up to 2 h, and the water activity of the tablets was measured. The appearances of the tablets after the drying were visually inspected, *i.e.* the number of tablets with chips bigger than 1 mm diameter was measured, and its ratio to the total number of tablets was exhibited as defected ratio(%) in Table 4. In experiments 1 and 2 (Table 4), the heating temperatures were set at 65 °C and 75 °C, respectively, the drum rotation speed was at 2 rpm, and the vacuum degree was 0.1 kPa or less. In experiments 3 and 4, the drum rotation speeds were set at 2 rpm and 4 rpm, respectively, the heating temperature was at 70 °C, and the vacuum degree was 0.1 kPa or less. In experiment 5, the vacuum degree was set at 0.27 kPa. Experiments 1, 2, 3, 4, and 5 were performed using placebo tablets without Limaprost alfadex, whereas experiment 6 was conducted using active tablets that contained Limaprost alfadex.

Results and Discussion

Stability of Dextran Formulation in Package Opalmon tablets (dextran and lactose formulations) packed in PTP were placed in an aluminum bag and subjected to stability

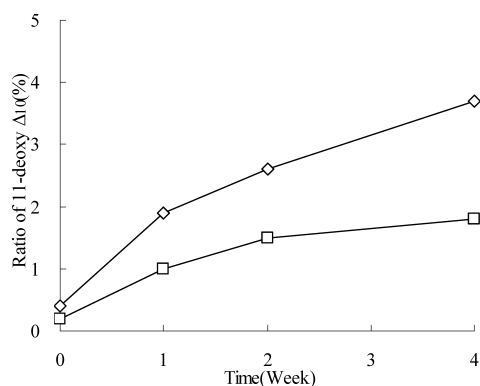


Fig. 4. Stability of Opalmon Tablets (Lactose Formulation (□) and Dextran Formulation (◇) in PTP/Aluminum Package at 60 °C

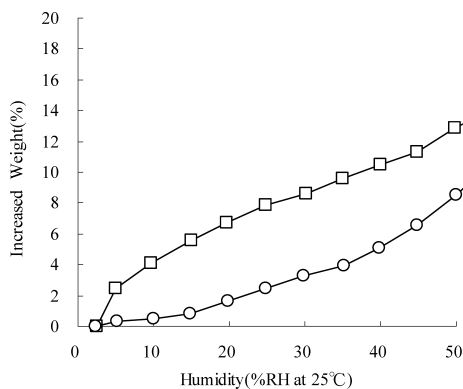


Fig. 5. Moisture Adsorption Profiles of Lyophilized Lactose Composite (○) and Dextran Composite (□) at Different Relative Humidities

tests. As shown in Fig. 4, the drug in the dextran formulation degraded faster than that of the lactose formulation when it was in the package, *i.e.* the lactose formulation gave 1.8% of the degradation product, 11-dexoy- Δ_{10} , at 60 °C in four weeks, while the dextran formulation gave 3.7% of the product. And the water activities of the tablets (Lactose formulation) and Dextran formulation were initially 0.076 ± 0.002 and 0.155 ± 0.04 , respectively. We studied the moisture uptake behavior of the freeze-dried lactose and dextran composites. Figure 5 shows the moisture uptake ratios of the composites at different relative humidities (3–50% RH) at 25 °C. The moisture uptake of the dextran composite is 6.7 and 10.4% at 20 and 40% RH, respectively, and those of the lactose composite are 1.6 and 5.1% at 20 and 40% RH, respectively. These results suggest that tablets including dextran, which absorbed humidity, are enclosed in PTP package. And the humidity surrounding the tablets in the PTP is supposed to be low because the water activities of the tablets were 0.076 or 0.155.

We have already reported that in high humidity such as 60% RH, 75% RH at 25 °C, the degradation rate of Dextran formulation is smaller than Lactose formulation.¹⁾ But in the PTP/Aluminum package, which is closed circumstance in very low humidity, the Opalmon tablet (Lactose formulation) degrades slower than the Opalmon tablet (Dextran formulation). We consider this is owing to the difference of the moisture absorption manner of lactose between under high humidity and low humidity.

The Lactose composite is the freeze-dried formulation of

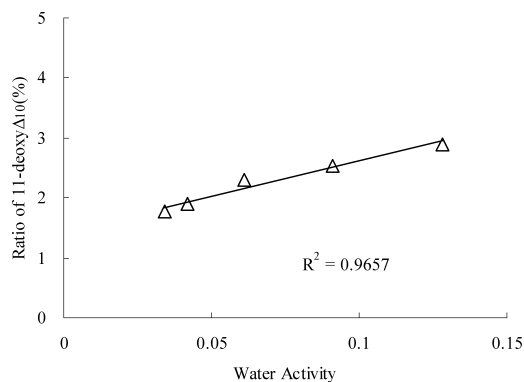


Fig. 6. Relationship between the Stability of Opalmon Tablets Containing Lyophilized Dextran Composite and the Water Activity

Horizontal axis shows the water activity before the PTP packaging. Vertical axis shows the amount (% of total amount) of 11-deoxy- Δ_{10} after storing for six months at 40 °C.

Table 3. Effect of Drying Temperature on the Appearance and Degradation of Limaprost in Opalmon Tablets: (a) Appearance, (b) Amount (%) of 11-Deoxy- Δ_{10} and Disintegration Time

(a)

Temperature (°C)	1 h	2 h	3 h	4 h
60	No change	No change	No change	No change
70	No change	No change	No change	No change
80	Gloss lost	Gloss lost	Gloss lost	Gloss lost

(b)

Temperature (°C)	11-Deoxy- Δ_{10} (%)	Disintegration time
Initial	0.44	3 min 20 s
60	0.44	3 min 38 s
70	0.42	3 min 50 s
80	0.59	4 min 15 s

Limaprost alfadex with lactose. Freeze-dried lactose is amorphous and dehydrated, which absorbs moisture in the form of crystalline water, changing to α -lactose monohydrate under low humidity. The crystalline water doesn't cause the degradation of the Limaprost and the degradation rate of Limaprost in lactose composite is slower than one in dextran composite. Under high humidity, lactose cannot absorb all moisture in the form of crystalline water. Therefore Limaprost degrades faster in lactose composite than in dextran composite under high humidity.

These results indicate that the stability of the drug in the package can be improved by drying of the tablets before the packaging process.

Correlation of Stability to Water Activity in Dextran Formulation We investigated how the water activity affects the stability of the drug in the package. The water activity is employed as an index of the dried state of a sample, especially for chemically labile drugs because free water molecules in solid preparations move easily, depending on environmental temperature and humidity,^{3–5)} and significantly affect the stability of solid drugs.⁶⁾ These differently humidified tablets were packed in PTP and placed in an aluminum bag, and their stability was investigated. Figure 6 shows the

Table 4. Effect of Operating Parameters of the Rotary Vacuum Drier on Drying of Opalmon Tablets

		Heating temp. (°C)	Drum rotation speed (rpm)	Vacuum (kPa)	Drying time (min)	Defected ratio (%)	Disintegration time
Initial	Placebo	—	—	—	—	0.02	3 min 41 s
Experiment 1	Placebo	65	2	<0.1	30	0.36	4 min 09 s
Experiment 2	Placebo	75	2	<0.1	30	0.32	3 min 20 s
Experiment 3	Placebo	70	4	<0.1	30	0.32	3 min 26 s
Experiment 4	Placebo	70	2	<0.1	30	0.35	3 min 13 s
Experiment 5	Placebo	70	2	0.27	60	0.96	3 min 37 s
Experiment 6	Active	70	2	<0.1	30	0.17	3 min 20 s

Drying time: the time which is necessary for the water-activity of tablets to decrease to 0.03 or less.

amount of the degradation product, 11-deoxy- Δ_{10} , after storing at 40 °C for six months *versus* the water activity of the dextran formulation. The water activity of the tablets and the amount of the degraded product are positively correlated, clearly suggesting that drying Opalmon tablets (dextran formulation) before packaging effectively results in more stable tablets.

Effect of Heating Temperature Heating and vacuum drying is considered to be useful for preparing Opalmon tablets (dextran formulation) with a higher stability in the PTP/Aluminum package form. However, it is expected that heat from the drum during the drying process deteriorates the product's quality such as purity, appearance and disintegration of tablets. Therefore, the effects of the heating temperature on the appearance of the tablets, purity and the disintegration time of tablets were investigated using a tray drier. As shown in Table 3a, the appearance of the tablets didn't change from 1 to 4 h at 60 and 70 °C, but at 80 °C, the gloss was lost from 1 h. Table 3b shows the purity and disintegration time of the tablets, which was dried at 60, 70, 80 °C. Degraded substance doesn't increase at 60 and 70 °C from initial value, but, it is greater at 80 °C than at 60 and 70 °C. And disintegration time slightly increase according as the heating temperature increase. It is known that over-blending could cause lubricants such as magnesium stearate to coat the surface of granules and to result in the retardation of tablet disintegration time. In our case, the retardation of the tablets is attributed to the melting of stearic acid. Its melting point is between 56—72 °C and it is supposed that stearic acid in the tablets melts due to the heat in the tray-drier and that melted stearic acid coats the surface of the tablets. The loss of the gloss is also attributed to that the melting of stearic acid causes the change of its crystal shape. These results suggest that heating in the drier must be conducted below 80 °C.

Drying of Tablets Using Rotary Vacuum Drier The rotary vacuum drying method may be suitable for drying tablets because it is easier to charge and recover dried products in a rotary drier than a tray drier. In addition, the motion of the product in the drum is not as intense as that in a fluid-bed drier. Therefore, we investigated how to most efficiently perform the drying process and how to minimize the chipping of the tablets in the drying drum, *i.e.* the fast drum rotation speed produces a shorter drying time, but may cause more damage to the tablets in the drum. Furthermore, the heating temperature and vacuum degree may affect the drying efficiency. Therefore, we studied the effect of heating temperature, drum rotation speed, and vacuum degree on the drying. Table 4 shows the results. In experiments 1, 2, 3, and

Table 5. Stability of Opalmon Tablets (Lactose and Dextran Formulations) in an Aluminum Package

	Initial	40 °C 6 months
Lactose formulation	0.79±0.08	1.13±0.06
Dextran formulation	0.68±0.19	1.20±0.10

Values are 11-deoxy- Δ_{10} (%).

4, the water activity decreased to less than 0.03 under the present conditions (heating temperature of 65—70 °C, drum rotation of 2—4 rpm, and vacuum of <0.1 kPa) within 30 min. In experiment 5, a longer drying time (60 min) was necessary to reduce the water activity to less than 0.03 due to the low vacuum degree of 0.27 kPa, suggesting that the vacuum degree is important for drying in a rotary vacuum drier. It was confirmed that tablets can be dried in less time on a mass production scale (300000 tablets per lot) by optimizing the heating temperature, drum rotation speed, and vacuum degree of the rotary vacuum drier. Furthermore, experiments 1—4 clearly show that the percentage of broken or chipped tablets after the drying was less than 0.4%. We had considered that less than 0.5% of defected ration was desirable. The results satisfied the criteria but only experiment 5 produced 0.96% of defected tablets. This suggests that the process time should be shorter than 60 min and the low vacuum degree is necessary to obtain the less damaged tablets in this process. In experiment 6, which used tablets containing Limaprost alfadex, the water activity decreased to less than 0.03 within 30 min and the percentage of broken or chipped tablets was only 0.17%. These results indicate that Opalmon tablets (dextran formulation) can be efficiently dried with a short processing time and even on a mass production scale using the rotary vacuum drying method.

Comparison of Stability of Opalmon Tablets (Dextran and Lactose Formulations) in Package As described above, we developed the dextran formulation to improve the stability of Opalmon tablets under high humidity. The dextran formulation is superior to the lactose formulation in regard to the stability under humidity, although the stability of dextran formulation is inferior to the lactose formulation in the blister/aluminum package. Because it is necessary to obtain at least the same level of stability between the dextran and lactose formulations in the blister/aluminum package and the manufacturing process of Opalmon tablets (lactose formulation), which was on the market before the formulation change, does not include the tablet drying process, we compared the stability of the dextran formulation dried in a

rotary vacuum drier to that of the lactose formulation without drying. Table 5 shows the results of this study. Differences in the stability between the lactose and dextran formulations were not observed in the stability test at 40 °C and when stored for six months, indicating that both formulations in the package have equivalent stabilities.

Conclusion

The stability of Opalmon tablets (dextran formulation) in PTP/aluminum packages without drying was inferior to that of Opalmon tablets (lactose formulation) due to the residual moisture in the product. The stability of Limaprost alfadex in the tablets exhibited a good correlation with the water activity of the tablets after vacuum-drying, suggesting that vacuum drying of tablets before packaging effectively results in

more stable Opalmon tablets. As shown in this study, the rotary vacuum method can efficiently dry the tablets, even on a mass production scale. In addition, this study demonstrated that Oplamon tablets (dextran formulation) and Opalmon tablets (lactose formulation) are equally stable in PTP/aluminum packages.

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