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A Validated HPLC Pranlukast Assay Method for Cleaning Validation on an Automatic Packaging Machine

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Abstract | **Research Article**

Automatic packaging machines are used for preparing one-dose packages with powders, granules, tablets and capsules in pharmacies in Japan. The packaging machines are not dedicated to an individual patient, which leads to contamination of the packaging for the next patient. Cleaning validation for pharmaceutical manufacturing plants is therefore considered essential for packaging machines. The purpose of the present study was to develop and validate an HPLC method for assaying pranlukast (PLK) for use as PLK cleaning validation on an automatic packaging machine. A chromatographic system comprising a YMC AM12S05-1506WT column, mobile phase of CH_3CN:H_2O:$HClO_4$:$NaClO_4$=650:350:1:5 (V/V/V/W), flow rate of 1 mL/min, and UV detector set at 254 nm was used. Candesartan cilexetil (CDC) was used as an internal standard. The PLK and CDC retention times were approximately 7.1 and 10.2 min, respectively. Regression analysis found that the method was linear over the standard curve range from 0.001 to 2.000 mg/tube. Inter-day precision and accuracy ranged between 0.40 and 19.95%, and -5.05 and 26.31%, respectively. The precision and accuracy values were under 10% and inside a range of -10% to 10% without 0.001 mg/tube. Therefore, the lower limit of quantification was inferred to be 0.001 mg/tube. A swabbing procedure using non-woven fabric swabs containing ethanol for disinfection was validated. Mean recoveries from a stainless steel tray and a plastic tray for Onon® drysyrup which was a pharmaceutical preparation of PLK were101.6 ± 2.55% (mean ± SD, n=3) and 101.9 ± 0.85%, respectively.
Keywords: Pranlukast hydrate, Automatic packaging machine, HPLC, Cleaning validation, Determination, Swabbing method.

INTRODUCTION

An automatic packaging machine is used in pharmacy dispensaries in Japan to prepare one dose packages for each patient. The machine can prepare one dose packages containing tablets, capsules, powders or granules. However, the machine is not dedicated to an individual patient, which is the general operating method in Japan, and this may lead to contamination of the package for the next patient.

For pharmaceutical manufacturing plants, documented equipment maintenance and cleaning is required to establish the cleanliness of equipment before its subsequent release for use in the manufacture of intermediates and active pharmaceutical ingredients [1]. Non-dedicated equipment should be cleaned at product changeover to prevent cross-contamination. Cleaning procedures should contain sufficient detail to enable operators to clean each type of equipment in a reproducible and effective manner, and these procedures should include a complete description of the methods and materials, including dilution of cleaning agents used to clean equipment. In addition, the cleaning validation master plan requires that detergent used to clean the manufacturing equipment in the cleaning validation phase is shown to be removed to an acceptable level in terms of commercial manufacturing [2].

Cleaning validation must be done for the machines to avoid cross-contamination. However, there is no report on drug levels remaining on the surfaces of the machine after use for one patient. Particularly, after preparing powders and granules, the drug levels remaining on the surfaces of the machine are important because operation with powders and granules carries

the highest risk of cross-contamination. Therefore, we examined cleaning validation for an automatic packaging machine. First, the development of drug determination methods by HPLC from swab samples using a swabbing method was considered necessary.

Pranlukast is an interleukin-1cysteinyl leukotriene-receptor antagonist [3]. Pranlukast is one of the most efficacious antiallergic drugs for the treatment of bronchial asthma at present and is expected to reduce the dose of glucocorticoid necessary to control airway inflammation [4].

Pranlukast, an important drug as noted above, was selected as the fourth drug to develop the determination method for cleaning validation of the machine. In this report, we describe the linearity, precision, accuracy and the limit of quantification, and report the percentage recovery from surfaces of a stainless steel tray and a plastic tray using the swabbing method, following on the reports for theophylline [5], acetaminophen [6], ketotifen fumarate [7], and nicotinamide [8].

MATERIALS AND METHODS

Materials

Pranlukast hydrate (PLK) was purchased from Kyongbo Pharmaceutical Co. Ltd. (Chungchongnam, Krea). Onon® drysyrup as a pharmaceutical preparation of PLK was purchased from Ono Pharmaceutical Co., Ltd. (Osaka, Japan). Candesartan cilexetil (CDC) was purchased from Yungjin Pharmaceutical Co. Ltd. (Seoul, Korea). Other chemicals were of special reagent or HPLC grade.

Apparatus and chromatographic conditions

The HPLC system consisted of a Model LC-20AS pump, equipped with an LC-solution on a PC, a Model SPD-20A UV spectrophotometric detector, a Model CTO-20A column oven, and a Model SIL-20A autoinjector, all from Shimadzu Corporation (Kyoto, Japan). The mobile phase was acetonitrile-water-perchloric acid (60%)-sodium perchlorate monohydrate=650:350:1:5, (V/V/V/W) for PLK. The chromatographic column was a YMC Pack AM12S05 ODS (150 mm x 6 mm I.D., particle diameter of 5 µm) obtained from YMC Co., Ltd. (Kyoto, Japan). The flow rate and temperature of the column were 1 mL/min and 40°C, respectively. The wavelength used to measure PLK was 254 nm. The injection volume for HPLC was 0.01 mL.

Calibration curve samples

PLK (50 mg) was dissolved in 50 mL of dimethyl sulfoxide: ethanol=9:1 (diluted DMSO). This PLK solution was diluted by diluted DMSO, and PLK solutions at 1.0 and 0.02 mg/mL were prepared. Then, 0.05, 0.1, 0.2, and 0.5 mL of the PLK solution at 0.02 mg/mL were added to 50-mL centrifuge tubes. Next, 0.05, 0.1, 0.2, 0.5, 0.75, 1.0 and 2.0 mL of the PLK solution at 1.0 mg/mL were added to 50-mL centrifuge tubes. As a result, centrifuge tubes containing 0.001, 0.002, 0.004, 0.01, 0.05, 0.1, 0.2, 0.5, 0.75, 1.0 and 2.0 mg of PLK were prepared. After that, 1 mL of internal standard (IS) solution and 39 mL of diluted DMSO were added to the centrifuge tubes. An 1-mg/mL solution of CDC in diluted DMSO was used as an IS solution. Each centrifuge tube was well stirred. Each solution (0.1 mL) was injected into the HPLC column. One set of these solutions was prepared on each experiment day. Concentrations from 0.001 to 0.05 mg/tube were used for a lower range calibration curve, and from 0.05 to 2.0 mg/tube for a higher range calibration curve. Values of Peak area ratio, PLK/CDC were calculated, and the values were used for a calibration curve and to calculate the amount of PLK.

Swabbing procedure

Fifteen mg of the PLK pharmaceutical preparation was scattered on a stainless steel tray and a plastic tray. The base areas of the trays were both 236 cm^2. PLK in the preparation on the trays was recovered by wiping the surfaces of the trays using swab pad® ethanol for disinfection (SWP, Libatape Pharmaceutical Co., Ltd., Kumamoto, Japan), which is a non-woven fabric wet swab containing ethanol for disinfection. The surfaces of the trays were wiped with one side of the SWP. After this operation, the surface was wiped again using a new SWP by the same method. The two SWPs used were put into a 50-mL centrifuge tube.

Determination method for swabbing samples

Two SWPs were contained in each centrifuge tube. Approximately 39 mL of diluted DMSO, and 1 mL of IS solution were added to the centrifuge tubes. Each centrifuge tube was well stirred. After ultrasonic treatment for 5 min, each centrifuge tube was well stirred. Then, 5 mL of the solution in the centrifuge tube was withdrawn using a 5-mL syringe, and filtered using a syringe filter Minisart RC15 from Sartorius (Goettingen, Germany). Finally, 4 mL of filtrate for each syringe was discarded, and the next 1 mL of filtrate was used for the HPLC assay.

RESULTS AND DISCUSSION

The retention times of PLK and CDC were approximately 7.1 and 10.2 min, respectively. A linear regression analysis gave slope, intercept, and correlation coefficients of Y=2.82840X + 0.00409, and r=0.99999, respectively. The linearity was confirmed at concentrations from 1.0 to 2000 µg/tube. When a calibration curve to determine samples is prepared in the concentration range, no acceptable values for accuracy may be observed around the original. Therefore, two calibration curves, for lower concentrations from 1.0 to 50 µg/tube and for higher concentrations from 50 to 2000 µg/tube, were calculated.

Inter-day precision and accuracy for lower concentrations were assessed by analyzing each drug concentration 4 - 8 times on different days, as shown in Table 1. Precision ranged between 0.40% and 19.95%. The accuracy values ranged between -5.05% and 26.31%. The values without 19.95 and 26.31% at 1.0 µg/tube were acceptable. The precision and accuracy values were under 10% and inside the range of -10% to 10%, respectively, without 1.0 µg/tube. Therefore, the lower limit of quantification was inferred to be 1.0 µg/tube, which was the lowest concentration providing validation data.

Inter-day precision and accuracy for higher concentrations were assessed by analyzing each drug concentration 4 - 8 times on different days, as shown in Table 2. Precision ranged between 0.56% and 5.04%. The accuracy value ranged between -2.35% and 0.83%. All values were acceptable.

Table-1: Inter-day precision and accuracy of PLK measurements for lower concentrations

Actual concentration (µg/tube)	Concentration found (µg/tube) (mean ± SD, n=10)	Precision (%)	Accuracy (%)
1.0	1.3 ± 0.3	19.95	26.31
2.0	2.2 ± 0.1	6.63	9.03
4.0	4.0 ± 0.2	6.10	0.53
10.0	9.5 ± 0.3	3.62	-5.05
50.0	50.3 ± 0.2	0.40	0.61

Precision and accuracy values were calculated using the following equations:

Precision (%) = (SD/mean) x 100.

Accuracy (%) = ((concentration found – actual concentration)/ actual concentration) x 100.

Table-2: Inter-day precision and accuracy of PLK measurements for higher concentrations

Actual concentration (µg/tube)	Concentration found (µg/tube) (mean ± SD, n=10)	Precision (%)	Accuracy (%)
50	48.8 ± 2.5	5.04	-2.35
100	99.7 ± 2.2	2.23	-0.35
200	201.7 ± 3.9	1.92	0.83
500	503.6 ± 5.4	1.07	0.72
750	754.5 ± 4.2	0.56	0.60
1000	1003.7 ± 9.8	0.97	0.37
2000	2008.1 ± 12.5	0.62	0.40

Precision and accuracy values were calculated using the following equations:

Precision (%) = (SD/mean) x 100.

Accuracy (%) = ((concentration found – actual concentration)/ actual concentration) x 100.

Recoveries of PLK from PLK preparation on a stainless steel tray and a plastic tray were 101.6 ± 2.55% (mean ± SD, n=3) and 101.9 ± 0.85%, respectively. These values were acceptable. It was found from the recovery data that the swabbing procedures using SWP for stainless steel and plastic surfaces, as well as the extraction method, were appropriate and effective. The procedure may be useful to confirm the amount of residual drugs on the surfaces of automatic packaging machines.

CONCLUSION

A method to measure PLK in swab samples used in a cleaning validation procedure was developed. The results suggested that this method is accurate and has a sufficiently low limit of quantification for PLK swab samples. This method may make an important contribution to the cleaning validation of automatic packaging machines in Japan.

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