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Original Research Article

Validated Assay Method for Fexofenadine Hydrochloride in Powder Preparations of Allegra® 60 mg Tablets to Develop a New Method for Grinding Tablets on Dispensing in Japan

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Abstract: The aim of the present study was to develop and validate a HPLC method for assaying fexofenadine hydrochloride(FEX) in powder preparations prepared from Allegra® 60 mg tablets. A chromatographic system comprising a YMC AM12S05-1506WT column, mobile phase of CH_3CN:H_2O:$HClO_4$:$NaClO_4$=500:500:1:5 (V/V/V/W), flow rate of 1 mL/min, and UV detector set at 220 nm was used. The retention time of FEX was approximately 6.6 min. A regression analysis revealed that the method was linear over the standard curve range from 0.2 to 80 µg/mL. Intra-day precision and accuracy ranged between 0.1 and 19.6% and between -34.0 and 1.0%, respectively. The accuracy value at 0.50 µg/mL was -13.6%, which was out of the range of -10% to 10%. Therefore, the lower limit of quantification was inferred to be 0.50 µg/mL. Inter-day precision and accuracy values between 0.5 and 80 µg/mL ranged within 10% and from -10% to 10%, respectively, which were acceptable. The lower limit of quantification was established to be 0.50 µg/mL from validation data. The content of Allegra® 60 mg tablets was 100.60 ± 0.40% (mean ± SD, n=3). The method developed herein is useful for evaluating grinding tablets on dispensing when Allegra® 60 mg tablets are used as a model preparation.
Keywords: Fexofenadine hydrochloride, Powder preparation, HPLC, Allegra® 60 mg tablets, Determination, Grinding tablets on dispensing.

INTRODUCTION

When pharmaceutical preparations are available for adults, but not for children, "grinding tablets on dispensing" is performed in Japan. A pharmaceutical preparation containing sildenafil citrate (SIL) for pulmonary arterial hypertension, Revatio® Tablets 20 mg from Pfizer Japan Inc., is a typical example. When SIL is administered to infants with persistent pulmonary hypertension of the newborn (PPHN) [1], Revatio® Tablets 20 mg are ground in a mortar to make a powder. Lactose is added to the powder as a diluent, and is mixed well in the mortar. The mixed powder is packaged for each dose using an automatic packaging machine. These processes are typically performed as dispensing work in a Prescription Department, and are referred to as "grinding tablets on dispensing" in Japan. The grinding of tablets is associated with weight and drug losses [2-5], while the automatic packaging process results in drug loss [6, 7].

We previously reported that a method for assaying SIL in the powder prepared from Revatio® Tablets 20 mg was developed to clarify the exact dose of SIL administered to infants with PPHN, and this method was accurate and had a sufficiently low limit of quantification for powder preparations of SIL [8]. In addition, the application data in the study indicated the possibility of weight and drug losses in the tablet grinding process [8]. This result agreed with the previously reported findings [2-5].

Necrotizing enteritis is a severe complication in premature infants that may be caused by high osmotic pressure in the intestines [9]. The osmotic pressure of an oral dosing solution used in NICU should decrease. Therefore, the addition of lactose to powder as a diluent in grinding tablets on dispensing is considered to be inappropriate. Other diluents that result in high osmotic pressure need to be identified.

Previous studies on the "grinding tablets on dispensing" process for providing to NICU were found to have 2 kinds of important points described above. Therefore, we started the studies. Tablets with fexofenadine hydrochloride (FEX), Allegra® 60 mg tablets, were selected as a model preparation for the

development of methods to decrease weight and drug losses. A method to assay FEX in a powder preparation was initially developed.

The quantitation of FEX in pharmaceutical dosage forms was previously achieved using spectrophotometric methods based on ion complex reactions [10] and HPLC methods with ultraviolet detection [11-13]. However, the concentration ranges of these methods were narrow. Therefore, a method was developed to assay FEX in a powder preparation from Allegra® 60 mg tablets.

MATERIALS AND METHODS

Materials

Reagent grade FEX, lot number 6KE8G-QS, was purchased from Tokyo Chemical Industry Co.,Ltd.. Allegra® 60 mg tablets made by Sanofi Co., Ltd. (Tokyo, Japan) were used. 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 LC-solution on PC, a Model SPD-20A UV spectrophotometric detector, Model CTO-20A column oven, and Model SIL-20A autoinjector, all from Shimadzu Corporation (Kyoto, Japan). The mobile phase was acetonitrile-water-perchloric acid (60%)-sodium perchlorate monohydrate=500:500:1:5, (V/V/V/W) for FEX. 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. The wavelength used to measure FEX was 220 nm. The injection volume for HPLC was 20 µL.

Standard solution

FEX (100.45 mg) was dissolved in 100 mL of methanol:water=1:1 solution (diluted methanol). This solution at 1 mg/mL was used for each experiment and stored at 4°C for 2 months.

Calibration curve samples

FEX solution at 1 mg/mL was diluted using diluted methanol to make FEX solutions at 0.20, 0.50, 1.0, 2.0, 5.0, 10, 20, 40, 60, and 80 µg/mL. Each solution (20 µL) was injected onto the HPLC column. One set of these solutions was prepared on each experimental day, except for experiments for intra-day precision and accuracy.

Content of FEX in one Allegra® 60 mg tablet

One Allegra® 60 mg tablet was added to 40 mL of water and disintegrated in the solution. After an ultrasonic treatment for 5 min, 40 mL of methanol was added to the suspension. The ultrasonic treatment of the suspension was performed again for 10 min. Diluted methanol was added, and the volume was adjusted to 100 mL. One milliliter of the suspension was added to 9 mL of diluted methanol. The solution was stirred well on a vortex mixer, and then filtered using the syringe filter E131 from Pall Corporation (Tokyo, Japan). The filtrate was assayed by HPLC. Six milliliters of the standard solution was added to 94 mL of diluted methanol. This solution was also assayed by HPLC. The content of FEX in the tablet was calculated from a comparison of peak areas of the solutions.

Determination method in the grinding tablet process

A mortar and pestle was set on A3 paper. One Allegra® 60 mg tablet was added to the mortar and ground to a powder. The powder was removed from the mortar, and added to a 100-mL flask. Approximately 70 mL of diluted methanol was added to the flask and an ultrasonic treatment was performed for 10 min. Diluted methanol was added, and the volume was adjusted to 100 mL. One milliliter of the suspension in the flask was added to 9 mL of diluted methanol. The solution was stirred well on a vortex mixer and then filtered using the syringe filter E131. The filtrate was assayed by HPLC. Powder remaining on the mortar and pestle surfaces was washed with diluted methanol. The diluted methanol used was collected and added to a flask. Using the suspension in the flask, a sample solution for HPLC was prepared by the same method. Scattered powder on the paper was placed into a flask. Approximately 70 mL of diluted methanol was added to the flask, and an ultrasonic treatment was performed for 10 min. Diluted methanol was added, and the volume was adjusted to 100 mL. The solution in the flask was stirred well, and then filtered using the syringe filter E131. The filtrate was assayed by HPLC.

RESULTS AND DISCUSSION

The retention time of FEX was approximately 6.6 min. A linear regression analysis gave a slope, intercept, and correlation coefficient of Y=41450.87X +1785.55, and r=0.99998, respectively. Intra-day precision and accuracy were assessed by analyzing tree replicates at each drug concentration, which are shown in Table 1. Precision ranged between 0.1% and 19.6%. The accuracy value ranged between -34.0% and 1.0%. The accuracy value at 0.50 µg/mL was -13.6%, which was out of the range from -10% to 10%. Therefore, the lower limit of quantification was inferred to be 0.50 µg/mL. Inter-day precision and accuracy were assessed by analyzing each standard concentration, except at a concentration of 0.20 µg/mL, over 6 different days. The result for the calibration curve is shown in Table 2. Precision from 0.50 µg/mL to 80 µg/mL was between 8.9% and 0.2%. Accuracy ranged between -7.2% and 0.5%. Inter-day precision and accuracy values ranged within 10% and between -10% and 10%, respectively, which were acceptable. The lower limit of quantification was established to be 0.50 µg/mL based on validation data, as shown in Tables 1 and 2.

Table-1: Intra-day precision and accuracy of FEX measurements

Actual concentration (μg/mL)	Concentration found (μg/mL) (mean ± SD, n=3)	Precision (%)	Accuracy (%)
0.20	0.1326± 0.0260	19.6	-34.0
0.50	0.4339± 0.0243	5.6	-13.6
1.0	0.9448± 0.0218	2.3	-5.9
2.0	1.966± 0.0067	0.3	-2.1
5.0	4.954± 0.1090	2.2	-1.4
10	10.104± 0.0633	0.6	0.6
20	20.288± 0.0182	0.1	1.0
40	40.259± 0.0701	0.2	0.2
60	60.242 ± 0.2786	0.5	0.0
80	80.291 ± 0.1714	0.2	-0.1

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 FEX measurements

Actual concentration (μg/mL)	Concentration found (μg/mL) (mean ± SD, n=3)	Precision (%)	Accuracy (%)
0.50	0.4661± 0.0407	8.7	-7.2
1.0	0.9737± 0.0378	3.9	-3.1
2.0	1.991± 0.0348	1.7	-0.9
5.0	4.985± 0.0862	1.7	-0.7
10	10.080± 0.0633	0.6	0.4
20	20.191± 0.0960	0.5	0.5
40	40.175± 0.2220	0.6	0.0
60	60.330± 0.1526	0.3	0.1
80	80.293± 0.1868	0.2	-0.1

Precision and accuracy values were calculated using the following equations:
Precision (%) = (SD/mean) x 100.
Accuracy (%) = ((concentration found – actual concentration)/ actual concentration) x 100.

The content of Allegra® 60 mg tablets was 100.60± 0.40% (mean ± SD, n=3). This is acceptable, indicating the suitability of the extraction system for FEX.

The concentrations of the sample solutions from powder removed from the mortar, powder remaining on the mortar and pestle surfaces, and powder scattered on the paper were 45.86, 11.39, and 2.0μg/mL, respectively. The amount of FEX in these powders calculated from the concentration data were 45.9, 11.4, and 0.2 mg, respectively. This application data revealed that the method developed herein is useful for evaluating the grinding tablets on dispensing process when Allegra® 60 mg tablets are used as a model preparation.

CONCLUSION

A method to measure FEX in powder preparations prepared from Allegra® 60 mg tablets was developed herein. The results obtained indicated that this method is accurate and has a sufficiently low limit of quantification for powder preparations of FEX. This method will make an important contribution to the prevention of drug loss in the "grinding tablets on dispensing" process in Japan.

REFERENCES

1. Yaseen H, Darwich M, Hamdy H; Is sildenafil an effective therapy in the management of persistent pulmonary hypertension? Journal of Clinical Neonatology, 2012; 1 (4): 171-175.
2. Murakami M, Tanoue N, Nakamura T, Tsuruta S, Iwaoku R, Nakano M; Investigation of loss in weight by grinding of tablet. Jpn. J. Hosp. Pharm., 1991; 17(5): 381-387.
3. Kuwana Y, Hiramatsu H, Furuichi K, Sumida K; Loss in weight by grinding tablets on dispensing. Jpn. J. Hosp. Pharm., 1978; 4(1): 16-19.
4. Yano H, Ishimaru Y, Hidaka N, Tatsukawa T, Matsuoka A, Tanaka A, Tanaka M, Araki H; Comparison of the mass loss rate and the divided variability with warfarin potassium crushing tablet and powder medicine. J. Japanese Society Hospital Pharmacists, 2014; 50(4): 461-465.
5. Miyamoto S, Suzuki M, Kohda Y; Drug-loss in dispensing and ingestion process, digoxin products as model drug. Jpn. J. Hosp. Pharm., 1999; 25(3): 292-298.
6. Sasaki M, Sano M, Tanaka Y, Yamamoto I; Drug loss due to grinding, sifting and automatic packaging of carvedilol tablets. Jpn. J. Pharm. Health Care Sci., 2006; 32(5): 420-423.

7. Wakui N, Ookubo T, Iwasaki Y, Ito R, Kobayashi T, Hayakawa K, Mitsui M, Yano Y, Saito K,Nakazawa H; Estimation of infant medicine content and drug loss after grinding small amount of tablets. Jpn. J. Pharm. Health Care Sci., 2011; 37(7): 425-430.
8. Tokumura T, Kawakami M, Kitada R, Yamamoto H, Yamamoto H, Kurita T; Determination of sildenafil citrate in powder preparations prepared from revatio tablets 20 mg for infants with persistent pulmonary hypertension of the newborn. Sch. Acad. J. Pharm., 2015; 4(8): 370-375.
9. Hisata K, Shimizu T; J. Pediatric Practice, 2012; 175(9): 1578-1585.
10. Gazy AA, Mahgoub H, El-Yazbi FA, El-Sayed MA, Youssef RM; Determination of some histamine H1-recepter antagonists in dosage forms. J. Pharm. Biomed. Anal., 2002; 30: 859-867.
11. Breier AR, Menegola J, Paim CS, Steppe M, Schapoval EES; Development and validation of a liquid chromatographic method for fexofenadine hydrochloride in capsules. J. of AOAC Int., 2004; 87: 1093-1097.
12. Radhakrishna T, Reddy GO; Simultaneous determination of fexofenadine and its related compounds by HPLC. J. Pharm. Biomed. Anal., 2002; 24: 755-767.
13. Oliveira DC, Weigch A, Rolim CM; Simple and reliable HPLC analysis of fexofenadine hydrochloride in tablets and its application to dissolution studies. Pharmazie, 2007; 62(2): 96-100.