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Research Article

DEGRADATION RATE OF FLUTICASONE PROPIONATE IN AN ALKALINE SOLUTION OF 0.1N NaOH : METHANOL = 1 : 1

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Abstract: Fluticasone propionate (FLT)contains an ester group in its chemical structure. We herein investigated its stability in acidic and alkaline solutions with methanol. Each aqueous solution, which contained0.1N HCl, buffer solutions at pH 2, 4, 6 and 8, and 0.1N NaOH, with an equivalent volume of methanol, was mixed and used in stability studies at 37°C. The residual percentage of 0.1N NaOH : methanol = 1:1 at 37°Cfor 24 h was 1.73%. The degradation of FLT was observed. However, FLT was not degraded in solutions containing0.1N HCl, and buffer solutions at pH 2, 4, 6, and 8 at 37°C for 24 h. The degradation of FLT in 0.1N NaOH: methanol=1:1at 37°C was an apparent first order reaction with a rate constant of0.169± 0.003 (mean ± SD, n=3) h^{-1}. Four degradation products were detected on a HPLC chart. The chart pattern obtained indicated that two peaks with shorter retention times of 3.7 and 4.4 min were the end products, while other peaks with later retention times of 4.6 and 5.8 min when that of FLT was 6.8 min were intermediate degradation products.
Key words: Fluticasone propionate, Degradation, Apparent first order reaction, Alkaline solution, Degradation product

INTRODUCTION

Fluticasone propionate (FLT), S-Fluoromethyl 6□, 9□-difluoro-11□-hydroxy-16□-methyl-3-oxo-17□-propionyloxyandrosta-1, 4-diene-17□-carbothioate, is an inhaled corticosteroid with potent anti-inflammatory properties that is used in the topical treatment of asthma[1]. We previously described a method to determine FLT in 50% methanol using HPLC, the adsorption of FLT, a method to avoidits adsorption in experimental tools, and the solubility of FLT in aqueous solutions[2]. A more detailed understanding of the stability of FLT as well as its solubility is important for developing new dosages. Since FLT contains an ester group in its chemical structure, it may be degraded by hydrolysisin aqueous solutions. However, the stability of FLT in aqueous solutions has not yet been established; therefore, in the present study, we investigated its stability in acidic and alkaline solutions with methanol. We employeda mixed solution system with methanol becausethe solubility of FLT in aqueous solutions was previously shown to be poor and a mixed solution is considered to bemore suitable for avoiding the adsorption of FLT in experimental tools[2].

MATERIALS AND METHODS

Fluticasone propionate (FLT) was donatedby Alps Pharmaceutical Ind. Co., Ltd. (Gifu, Japan). Other chemicals were of reagent or HPLC grade.

FLT was dissolved in methanol to make a 2 mg /mL solution. A 2.5 mL aliquot of 0.1N NaOH, buffer solutions at pH 2, 4, 6, and 8, or 0.1N HCl with 2.45 mL of methanol was pre-incubated for 15 min at 37°C. The buffer solutions used were prepared by mixing 0.2M solutions of Na_3PO_4 and H_3PO_4.Experiments were initiated by adding the FLT solution to produce a final concentration of 20□ g/mL. A 100□ L aliquot of the sample solution was removed at appropriate intervals. The solution was added to 100 □ L of a solution of 0.1N HCl : methanol = 1:1, and mixed well. Twenty microliters of this solution wasthen injected into an HPLC column.

The HPLC assay was performed according a previously described method[2].The mobile phase was acetonitrile-water-perchloric acid (60%)-sodium perchlorate monohydrate (660:340:1:5, V/V/V/W). The chromatographic column was a YMC Pack AM12S05-1506WT ODS (150 mm x 6 mm I.D., particle diameter 5 μm) from YMC Co., Ltd. (Kyoto, Japan). The flow rate, wavelength for determination, and temperature of the column were 1 mL/min, 240 nm, and 40°C, respectively.

RESULTS AND DISCUSSION

Table I shows the values of the residual percentagesof FLT in the solutions examined at 37°Cfor 24 h. No degradation was observed in the 0.1N HCl, and buffer solutions at pH 2, 4, 6, and 8 at 37°C for 24 h. FLT was degraded in 0.1N NaOH : methanol = 1:1, and the residual percentage was 1.73%.

Table 1: Stability of FLT in mixed solutions of aqueous solution : methanol =1:1 at 37°C for 24 h

Aqueous solution	Residual percentage (%, mean ±SD, n=3)
0.1N HCl	101.5 ± 0.3
pH 2*	101.6 ± 0.5
pH 4*	100.6 ± 3.2
pH 6*	99.7 ± 0.5
pH 8*	100.3 ± 0.5
0.1N NaOH	1.73 ± 0.09

*: Buffer solutions at pH2, 4, 6 and 8 were prepared by mixing 0.2M solutions of Na_3PO_4 and H_3PO_4.

The above result demonstrated that FLT was degraded in the solution of 0.1N NaOH: methanol =1:1. Further experiments were performed. Figure 1 shows the relationship between the residual FLT percentage on a logarithmic scale and the time needed for the degradation of FLT. The plot in Figure 1 is linear. This result indicated that the degradation reaction of FLT was an apparent first-order reaction.The apparent first-order rate constant, k, was calculated from the slope of straight line shown in Figure 1. The apparent first-order rate constant, k, was 0.169 ± 0.003 (mean ± SD, n=3) h^{-1}.

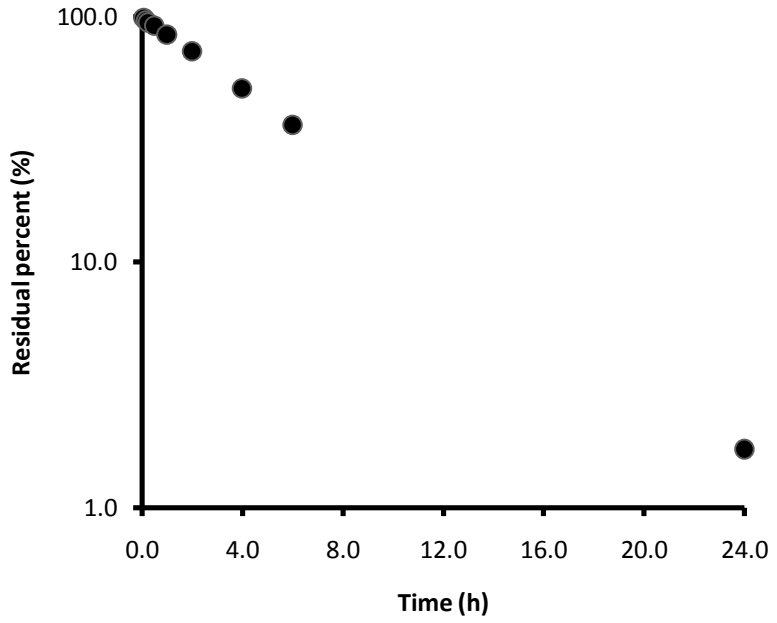

Figure 1: First-order plots for the degradation of FLT in a solution of 0.1N NaOH : methanol=1:1 at 37°C. Each point is the mean of 3 experimental runs.

Four degradation products were observed on HPLC chats, and their retention times were 3.7, 4.4, 4.6, and 5.8 min, respectively, when that of FLT was 6.8 min. These products were referred to as products 1, 2, 3, and 4. Figure 2 shows the variation of peak areas for the degradation products. Product 2 was the main degradation product of FLT as indicated by the largest peak area, and its peak area reached a plateau, demonstrating that product 2 was stable in the solution. Products 3 and 4 were the intermediate degradation products. The peak area variation in product 1 had a lag time and increased within 72h. This result demonstrated that product 1 was the final degradation product of FLT and produced from products 3 and/or 4.Further studies will be performed to confirm the chemical structures of the degradation products.

These results indicated that FLT was stable in aqueous solutions without strong alkaline solutions. However, budesonide, which is a corticosteroid that has potent anti-inflammatory propertied and is used in the topical treatment of asthma similar to FLT, was shown to be degraded in propylene glycol solution[3]. More detailed stability studies need to be conducted for FLT.

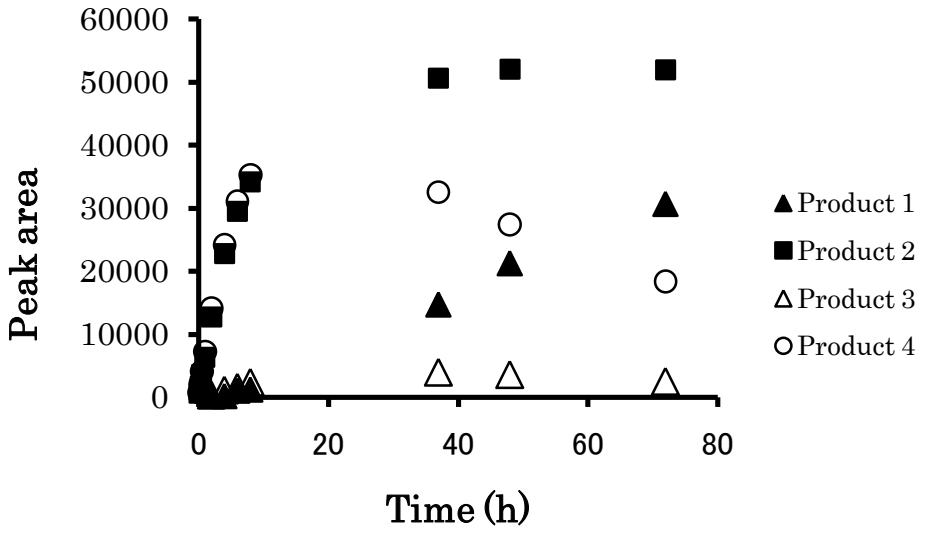

Figure 2: Variations in peak areas of the degradation products of FLT in a solution of 0.1N NaOH : methanol=1:1 at 37°C for 72 h.
(▲): Product 1, (■): product 2, (△) :product 3, (○) product 4.

The retention times of products 1, 2, 3 and 4 were 3.7, 4.4, 4.6 and 5.8 min, respectively, when that of FLT was 6.8 min.

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