Degradation rates and products of fluticasone propionate in alkaline solutions

Tadakazu Tokumura\textsuperscript{a,b,*}, Naoko Yoshida\textsuperscript{b}, Kanami Mori-Yasumoto\textsuperscript{c}, Osamu Shirot\textsuperscript{c}, Takuro Kurita\textsuperscript{a}

\textsuperscript{a} Laboratory of Pharmacognosy and Natural Products Chemistry, Kagawa School of Pharmaceutical Sciences, Tokushima Bunri University, Shido 1314-1, Sanuki, Kagawa 769-2193, Japan
\textsuperscript{b} Department of Pharmaceutical Sciences, School of Pharmacy, International University of Health and Welfare, 2600-1 Kitakanemaru, Ohtawara, Tochigi 324-8501, Japan
\textsuperscript{c} Laboratory of Pharmaceutics, Kagawa School of Pharmaceutical Sciences, Tokushima Bunri University, Shido 1314-1, Sanuki, Kagawa 769-2193, Japan

\section*{ABSTRACT}

The apparent degradation rate constant of fluticasone propionate (FLT) in 0.1 M NaOH:methanol=1:1 at 37 °C was previously reported to be 0.169 ± 0.003 h\textsuperscript{-1}, and four degradation products (products 1–4) were observed in the solution. The aims of the present study were to assess the degradation rates of FLT in other alkaline solutions and clarify the chemical structures of the four degradation products in order to obtain basic data for designing an enema for inflammatory bowel disease. The apparent degradation rate constants in 0.05 M NaOH and 0.1 M NaOH:CH\textsubscript{3}CN=1:1 were 0.472 ± 0.013 h\textsuperscript{-1} and 0.154 ± 0.000 h\textsuperscript{-1} (n=3), respectively. The chemical structures of products 1–4 in 0.1 M NaOH:methanol=1:1 were revealed by nuclear magnetic resonance (NMR) and mass spectrometry data. The chemical structure of products 2 was that the 17\textsuperscript{th}-position of the thioester moiety of FLT was substituted by a carboxylic acid. The degradation product in 0.1 M NaOH:CH\textsubscript{3}CN=1:1 was found to be product 2 based on \textsuperscript{1}H NMR data. The degradation product in 0.05 M NaOH was considered to be product 2 based on the retention time of HPLC. These results are useful for detecting the degradation products of FLT by enzymes of the intestinal bacterial flora in the large intestine after dosing FLT as an enema.

\section*{1. Introduction}

Fluticasone propionate (FLT) is an inhaled corticosteroid with high anti-inflammatory potency that is used for the topical treatment of asthma [1]. Its high lipophilicity and associated low aqueous solubility [2] result in high concentrations in pulmonary tissue as well as delayed absorption from the lung into the systemic circulation after inhaled administration [3,4]. FLT is a new-generation glucocorticoid that exerts potent anti-inflammatory effects when administered topically [5]. When administered orally, almost 100\% of the drug is subjected to first-pass metabolism and metabolized by the cytochrome P-450 system in the liver [6,7]. The combination of FLT and salmeterol xinafoate has recently been used for the topical treatment of asthma and chronic obstructive pulmonary disease [8,9].

Inflammatory bowel disease (IBD) is a group of disorders that cause sections of the gastrointestinal tract to become inflamed and ulcerated [10]. There are two main forms of IBD: Crohn’s disease and ulcerative colitis [11], which are typically lifelong diseases that require ongoing medication. Mesalazine, glucocorticoids, cyclosporin, azathioprine, and anti-TNF-\textalpha{} are generally used to treat IBD [12]. These drugs are administered orally, except for anti-TNF-\textalpha{}. Mesalazine and glucocorticoids also have preparations for rectal application: suppositories and enemas. Glucocorticoids constitute a major part of the medical treatment for IBD [6,13]; however, conventional glucocorticoids cause systemic side effects, such as acne, moon-face, hypertension, dyspepsia, mood disturbances, insomnia, and impaired glucose tolerance [14]. Enemas containing glucocorticoids have been developed for distal ulcerative colitis and proctitis in order to avoid these side effects. However, enemas containing hydrocortisone and prednisolone were found to be of little or no use due to their effects on adrenal gland functions and other systemic side effects [5]. Therefore, a new preparation for topical use is required.

FLT exhibits strong activity and high first-pass metabolism, which make it a candidate for topical preparations for the treatment of IBD. Thakral et al. [5] reported an oral colon-targeting preparation of FLT with improved aqueous solubility by hydroxypropyl \beta-cyclodextrin.
(HP)-CD) and coated with Eudragit S100 to achieve colon targeting. However, the physicochemical properties of FLT which need to be considered when developing an enema containing this glucocorticoid were not reported enough. We previously reported adsorption to experimental tools, a method to avoid this adsorption, solubility in aqueous solutions [15], and improvements in the solubility of FLT by cyclodextrins [16]. FLT contains an ester group in its chemical structure; therefore, it may be degraded by hydrolysis in aqueous solutions. We investigated its stability in acidic and alkaline solutions with methanol. Our findings showed that the degradation of FLT in 0.1 M NaOH:CH$_3$OH=1:1 at 37 °C was an apparent first order reaction with a rate constant of 0.169 ± 0.003 (n=3), and four degradation products were detected on a HPLC chart [17]. Their retention time was 3.7, 4.4, 4.6, and 5.8 min when that of FLT was 6.8 min, and these products were referred to as products 1, 2, 3, and 4 [17]. Based on variations in peak areas for the degradation products, product 2 was assumed to be the main degradation product, with products 3 and 4 being intermediate degradation products [17]. Product 1 was considered to be the final degradation product from these variations [17]. These stability data were sufficient for an oral dosage form design. However, further data are required in order to develop an enema with FLT because this glucocorticoid co-exists with the intestinal bacterial flora in the large intestine after its administration. Therefore, we attempted to confirm the chemical structures of the four degradation products of FLT in 0.1 M NaOH:me thanol=1:1. In addition, since methanol may affect the degradation pathway, the degradation rate of FLT in 0.05 M NaOH as well as the degradation rate and products in 0.1 M NaOH:CH$_3$CN=1:1 was examined. We herein present the results obtained.

2. Materials and methods

2.1. Materials

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

2.2. Stabilities of FLT and its degradation products 3 and 4 in alkaline solutions

The degradation rates of FLT and its degradation products 3 and 4 in alkaline solutions at 37 °C were assessed using a similar method reported previously [17]. The degradation rates of FLT were measured in alkaline solutions of 0.1 M NaOH:CH$_3$CN=1:1 and 0.05 M NaOH. The initial concentrations of FLT were 20 μg/mL and 0.1 μg/mL for 0.1 M NaOH:CH$_3$CN=1:1 and 0.05 M NaOH, respectively. In the case of 0.05 M NaOH, 100 μL of the sample solution was injected into an HPLC column. The injection volume for the HPLC column in other experiments was 10 μL.

The solution of product 4 eluted from Bond Elut LRC-C18 500MG (Bond Elut, Agilent Technologies, Lake Forest, CA) columns described in the next preliminary study was used. The solution of product 3 eluted from HPLC in the next preliminary study was diluted with water, and again placed on prepared Bond Elut columns. The solution of product 3 eluted from Bond Elut columns was used.

2.3. Preliminary study to isolate degradation products 1, 2, 3, and 4 of FLT

In order to start the degradation reaction, 2.1 mL of 5 M NaOH and 2.1 mL of methanol were added to 100 mL of the FLT solution at 10 μg/mL in CH$_3$OH:H$_2$O =1:1, and the mixed solution was kept at 37 °C. After 20 h, 2 mL of 6 M HCl was added to the solution to stop the degradation reaction. The pH of the solution was 2.1. Two hundred milliliters of water was added to the solution. Bond Elut columns (Agilent Technologies, Lake Forest, CA) were prepared by flushing columns with 5 mL of methanol followed by 5 mL of water. The diluted solution was placed on Bond Elut columns that were then washed with 5 mL of water. The degradation products on the columns were eluted with the acetonitrile solution with different water contents. Product 1 was eluted with 18% acetonitrile solution, products 2 and 3 were eluted with 30%, and product 4 with 40%. Products 2 and 3 were separated with HPLC. The HPLC conditions used are as follows: the column was a YMC-Pack ODS-AM125S05-1506WT (YMC, Kyoto, Japan). The mobile phase was CH$_3$OH:H$_2$O=520:480 (v/v). Products 3 and 4 obtained in the preliminary study were used in the stability study to examine the degradation process of FLT in the solution of 0.1 M NaOH:CH$_3$OH=1:1.

2.4. Isolation of FLT degradation products 1, 2 and 3

Ten milligrams of FLT was dissolved in 100 mL of methanol. Ninety milliliters of water was added to the methanol solution and stirred well. In the case of isolation for degradation product 3, recovered product 4 was used as a starting material. In order to start the degradation reaction, 10 mL of 1 M NaOH was added to the solution, which was kept at 37 °C. For isolation of products 1 and 2, after 10 days, 20 mL of 1 M HCl was added to the solution in order to stop the degradation reaction. For product 3, after 24 h, 11 mL of 1 M HCl was added to the solution. The degradation products 1 and 2, and 3 in the solutions were isolated using Bond Elut columns. Degradation products 1 and 2 on the columns were eluted with 18% acetonitrile solution, followed by product 2 eluted with 30% acetonitrile solution. Each eluted solution with products 1 and 2 was evaporated to dryness. Isolated products 1 and 2 were further dried under a vacuum for 18 h. The purity of HPLC were >98%. In the case of product 3, thirty milliliters of 30% acetonitrile solution with 0.02 M phosphate buffer solution at pH 8.0 was flowed through the columns in order to obtain product 3. After obtaining product 3, the columns were washed with 10 mL of the acetonitrile solution of CH$_3$CN:H$_2$O=1:1. Product 4 and FLT were eluted. FLT and product 4 were repeatedly used as the starting materials to obtain product 3. The repetition of the experiment was performed to obtain >3 mg of product 3.

2.5. Isolation of degradation product 4

The experiment described in Section 2.3 was repeated. Product 4 eluted from Bond Elut columns was collected and evaporated to dryness. Isolated product 4 was dried further under a vacuum for 18 h. The purity of HPLC was >98%.

2.6. Isolation of degradation products of FLT in 0.1 M NaOH:CH$_3$CN=1:1

The degradation product was made by the method described in Section 2.4 using acetonitrile instead of methanol. The degradation conditions were at 37 °C for 48 h. The degradation product in the solution was isolated using Bond Elut columns. The purity of HPLC was >98%. The weight of the degradation product was approximately 8.77 mg.

2.7. Nuclear magnetic resonance spectroscopy (NMR)

$^1$H and $^{13}$C NMR data for the degradation products of FLT dissolved in DMSO-$d_6$ were recorded at 700 MHz and 175 MHz, respectively, on a Bruker AVANCE 700 MHz spectrometer. Chemical shift values were reported on the δ scale in ppm with respect to dimethyl sulfoxide (DMSO)-$d_6$ (δ$_H$=2.50 ppm, δ$_C$=39.6 ppm) as internal standards.
2.8. Mass spectrometry

The high resolution electrospray ionization time-of-flight mass spectrometry (HR-ESI-TOF-MS) spectra of the degradation products of FLT were recorded on a Waters/Micromass Q-Tof micro mass spectrometer.

3. Results and discussion

3.1. Degradation rates of FLT in alkaline solutions not containing methanol

The degradation rates of FLT in solutions of 0.05 M NaOH and 0.1 M NaOH:CH₃CN=1:1 compared to that in the solution of 0.1 M NaOH:CH₃OH=1:1 are shown in Fig. 1. Rate constants and half-lives are summarized in Table 1. The degradation rate in 0.1 M NaOH:CH₃CN=1:1 was similar to that in 0.1 M NaOH:CH₃OH=1:1, as shown in Fig. 1. The rate constant in 0.05 M NaOH was the largest among the 3 kinds of alkaline solutions tested. The reductions observed in the rate constants in 0.1 M NaOH:CH₃CN=1:1 and 0.1 M NaOH:CH₃OH=1:1 were attributed to decreased water concentrations.

A degradation product of FLT in 0.05 M NaOH and 0.1 M NaOH:CH₃CN=1:1 was observed on the HPLC chart, with a retention time that fit that of degradation product 2 in 0.1 M NaOH:CH₃OH=1:1 (Fig. 2). The degradation product in 0.1 M NaOH:CH₃CN=1:1 was isolated and its chemical structure was confirmed. Variations in the peak areas for the degradation product and FLT in 0.1 M NaOH:CH₃CN=1:1 are shown in Fig. 3.

![Fig. 1. First-order plots for the degradation of FLT in alkaline solutions at 37 °C. ◇: 0.05 M NaOH, ●: 0.1 M NaOH:CH₃CN=1:1, ◊: 0.1 M NaOH:CH₃OH=1:1. Each point is the mean of 3 experimental runs. The error bar of each point cannot be shown due to the small SD value. a Previously reported data [17].](image1)

![Fig. 2. HPLC chromatograms of FLT and its degradation products. (a) FLT standard solution at 10 μg/mL, (b) FLT stored in 0.05 M NaOH at 37 °C for 2 h, (c) FLT stored in 0.1 M NaOH:CH₃CN=1:1 at 37 °C for 2 h, and (d) FLT stored in 0.1 M NaOH:CH₃OH=1:1 at 37 °C for 2 h. The initial concentrations of FLT for b and for c and d were 0.1 and 20 μg/mL, respectively. The Shimadzu LC-20 system was used as the HPLC apparatus. The chromatographic column was a YMC-Pack ODS-AM12S05-1506WT (YMC, Kyoto, Japan). The mobile phase was acetonitrile-water-perchloric acid (60%)-sodium perchlorate monohydrate=520:480:1:5 (V/V/V/m). The flow rate, temperature of the column, and wavelength for detection were 1 mL/min, 40 °C, and 240 nm, respectively.](image2)

![Fig. 3. Variations in peak areas of the degradation product of FLT in a solution of 0.1 M NaOH:CH₃CN=1:1 at 37 °C. ●: FLT, Δ: degradation product. Each point is the mean of 3 experimental runs. The error bar of each point cannot be shown due to the small SD value.](image3)

### Table 1

| Alkaline solution      | Rate constant (h⁻¹) | Half-life (t₁/₂, h) |
|------------------------|---------------------|-------------------|
| 0.05 M NaOH            | 0.472 ± 0.013       | 1.47 ± 0.04       |
| 0.1 M NaOH:CH₃CN=1:1   | 0.154 ± 0.000       | 4.50 ± 0.00       |
| 0.1 M NaOH:CH₃OH=1:1   | 0.169 ± 0.003       | 4.10 ± 0.06       |

Each value represents the mean ± SD of 3 measurements.

* Previously reported data [17].

3.2. Degradation products from products 3 and 4 in the solution of 0.1 M NaOH:CH₃OH=1:1

Variations in the peak areas for degradation products from product 4 detected on the HPLC chart are shown in Fig. 4. When product 4 was degraded in the alkaline solution, products 1, 2, and 3 were produced in the solution. Product 3 was considered to be an intermediate degradation product due to it exhibiting the maximum variation in the peak area. The peak area variation in product 1 had a lag time and increased within 168 h, which demonstrated that product 1 was the...
These results showed that the degradation product of product 3 was
1H NMR (700 MHz) data for FLT and products 1
Table 2
3 in the solution of 0.1 M NaOH:CH3OH=1:1 are shown in Fig. 5.
final degradation product in the degradation of product 4.
Product 2 was a minor degradation product in the degradation of product 4.
Variations in the peak area for a degradation product from product 3 in the solution of 0.1 M NaOH:CH3OH=1:1 are shown in Fig. 5. These results showed that the degradation product of product 3 was product 1. These results and previously reported findings [17] indicated that products 4 and 2 were produced from FLT in 0.1 M NaOH:CH3OH=1:1, that product 4 became product 3, and that product 3 became product 1. The reaction from product 4 to product 2 was observed, and the reaction rate was very slow. These results for the degradation pathway were important for confirming the chemical structures of products 1–4.

3.3. Chemical structures of products 1, 2, 3, and 4

The structural elucidation of products 1–4 was based on comparisons of their spectroscopic data with the FLT standard shown in Tables 2 and 3. Products were also confirmed by two-dimensional (2D) NMR data obtained from 1H-1H correlated spectroscopy (1H-1H-COSY), heteronuclear single quantum coherence (HSQC), and heteronuclear multiple bond correlation (HMBC).
The main differences between the NMR data of FLT and products 1–4 were observed for the carbon and proton signals of ring D and the side chain in the steroid moiety.
The molecular formula of product 1 was established as C21H25F2O5 by HR-ESI-TOF-MS in which the observed m/z 395.1569 was calculated for [M - H] 395.1670. A comparison of the molecular formula of product 1 with the FLT standard revealed four less carbons, one less fluorine, one less sulfur, and five less hydrogens incorporated into FLT, implying that product 1 is a reduction product of FLT. An inspection of NMR (DMSO-d6) spectra indicated that product 1 contained the same steroid moiety as FLT. Based on the upfield chemical shift of C-17 (δC 85.6), the lack of one ethyl proton doublet (−CH2F), one methyl proton doublet (H-1'), one ethyl proton quintet (H-2'), one thioester carbon (C-20), and one ester carbon, and the appearance of one carboxylic signal (C-20, δC 174.8), product 1 had a hydroxy group and carboxylic acid at C-17 instead of a propionic ester and thioester. The chemical structure of product 1 is shown in Fig. 6.
The molecular formula of product 2 was established as C22H28F2O5 by HR-ESI-TOF-MS, in which the observed m/z 451.1932 was calculated for [M - H] 451.1932. A comparison of the 1H NMR data of product 2 with FLT showed the significant upfield shift of C-17 (δC 91.7) and the lack of one ethyl proton doublet (−CH2F), indicating that the 17-positio of the thioester moiety of FLT was substituted by a carboxylic acid (C-20, δC 174.8), as shown in Fig. 6. Product 3 exhibited the molecular formula of C22H28F2O5Na by

![Fig. 4. Variations in peak areas of the degradation products from degradation product 4 in a solution of 0.1 M NaOH: CH3OH =1:1 at 37 °C. ▲: Product 1, ■: product 2, Δ: product 3, ○: product 4.](image)

![Fig. 5. Variations in peak areas of the degradation product from degradation product 3 in a solution of 0.1 M NaOH: CH3OH =1:1 at 37 °C. ▲: Product 1, Δ: product 3.](image)

| Position | FLT | Product 1 | Product 2 | Product 3 | Product 4 |
|----------|-----|-----------|-----------|-----------|-----------|
| 1        | 7.25 d (10.2) | 7.27 d (10.2) | 7.26 d (10.2) | 7.28 d (9.8) | 7.26 d (10.2) |
| 2        | 6.30 d (10.2) | 6.28 d (10.2) | 6.28 d (10.2) | 6.29 d (9.8) | 6.29 d (10.2) |
| 4        | 6.11 s | 6.09 s | 6.10 s | 6.10 s | 6.10 s |
| 6        | 5.63 ddd (49.0, 11.2, 7.0) | 5.62 ddd (49.0, 11.6, 6.9) | 5.63 ddd (49.0, 11.2, 7.0) | 5.63 ddd (49.0, 11.2, 7.0) | 5.63 ddd (49.0, 11.2, 7.0) |
| 7a       | 1.51 m | 1.45 m | 1.49 m | 1.45 m | 1.50 m |
| 7b       | 2.25 m | 2.20 m | 2.23 m | 2.21 m | 2.24 m |
| 8        | 2.56 m | 2.43 m | 2.53 m | 2.44 m | 2.52 m |
| 11       | 4.21 m | 4.13 d (10.5) | 4.16 m | 4.14 d (8.4) | 4.17 d (11.2) |
| 12a      | 1.87 d (12.6) | 1.53 d (11.9) | 1.69 d (14.0) | 1.54 d (14.0) | 1.65 d (14.7) |
| 12b      | 2.12 m | 2.00 d (14.7) | 2.03 d (14.7) | 2.03 d (14.0) | 2.04 m |
| 14       | 2.10 m | 2.06 m | 2.06 m | 2.08 m | 2.07 m |
| 15a      | 1.26 ddd (11.9, 8.4, 3.5) | 1.08 m | 1.17 m | 1.11 m | 1.20 m |
| 15b      | 1.84 m | 1.65 q (11.9) | 1.78 q (11.9) | 1.67 q (11.9) | 1.80 q (11.9) |
| 16       | 3.29 m | 2.83 m | 3.15 m | 2.87 m | 3.18 m |
| 18       | 1.00 s | 0.98 s | 1.00 s | 0.93 s | 0.94 s |
| 19       | 1.48 s | 1.48 s | 1.49 s | 1.49 s | 1.48 s |
| 21       | 0.89 d (7.0) | 0.86 d (7.0) | 0.84 d (7.0) | 0.88 d (6.3) | 0.84 d (7.7) |
| 1'       | 2.37 q (7.4) | 2.30 q (7.7) | 2.30 q (7.7) | 2.32 q (7.7) |
| 2'       | 1.02 t (7.4) | 1.00 t (7.7) | 1.00 t (7.7) |
| CHF      | 5.93 d (56) | 3.64 s | 3.60 s |
| OMe      | 5.59 brd (4.9) | 5.38 brs | 5.48 brd (4.2) | 5.42 brs | 5.51 brd (3.5) |

Data are shown in ppm and J-values are shown in Hz. Positions show the number on the chemical structure of FLT in Fig. 6.
HR-ESI-TOF-MS, in which the observed m/z 433.1848 was calculated for [M + Na]+433.1803. The 1H and 13C NMR spectra of product 3 were similar to those of product 1, except for the absence of a methoxy signal (δH 3.60, δC 51.9), which was consistent with its molecular formula. HMBC correlations were observed from the proton signals at the methoxy signal (δH 3.64) to C-20. The chemical structure is shown in Fig. 6.

The molecular formula of product 4 was established as C26H31F2O6 by HR-ESI-TOF-MS, in which the observed m/z 395.1569 was calculated for [M - H]- 395.1670. The 1H and 13C NMR spectra of product 4 were very similar to those of product 2, except for the presence of a methoxy signal (δH 3.60, δC 51.8). The position of the new methoxy group was found to be C-20 by the HMBC cross peak from the methoxy signal (δH 3.60) to C-20 (δC 169.5). The chemical structure and degradation pathway from HPLC data are shown in Fig. 6.

1H NMR data for the degradation product isolated from the 0.1 M NaOH:CH3CN=1:1 solution after the degradation reaction of FLT were consistent with those for product 2. The degradation product of FLT in 0.05 M NaOH and 0.1 M NaOH:CH3CN=1:1 was product 2 based on the retention time of HPLC, which was supported by 1H NMR data.

As described above, the degradation of FLT in an alkaline solution was attributed to the degradation of a thioester at the C-17 position to a carboxylic acid (product 2). When methanol existed in the reaction system, the carboxylic acid was converted into a methyl ester (product 4). The carboxylic acid and methyl ester were generally considered to be in equilibrium. However, a new degradation reaction was observed for the methyl ester, but not for the carboxylic acid, and involved the degradation of the propionic ester at the C-17 position to a hydroxy group (product 3). Furthermore, the methyl ester of this compound was hydrolyzed to a carboxylic acid (product 1). This was the reason for the four degradation products detected in 0.1 M NaOH:CH3OH=1:1, but not for the two degradation products. This speculation was supported by variations in the peak areas on HPLC chromatograms.

4. Conclusion

The apparent degradation rate constants of FLT in 0.05 M NaOH and 0.1 M NaOH:CH3CN=1:1 were 0.472 ± 0.013 h−1 and 0.154 ± 0.000 h−1, respectively. In both solutions after reactions, the same degradation product was observed on HPLC charts.

The chemical structures of the four degradation products observed in 0.1 M NaOH:CH3OH were elucidated. The degradation product observed in 0.05 M NaOH and 0.1 M NaOH:CH3CN=1:1 was found to have the same chemical structure as product 2 in 0.1 M NaOH:CH3OH=1:1. These results are considered to be useful for detecting the degradation products of FLT by enzymes of the intestinal bacterial flora in the large intestine after dosing FLT as an enema.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Acknowledgments

The authors thank Alps Pharmaceutical Ind. Co., Ltd. for providing FLT. The authors are very grateful to Mr. Kazunari Watanabe, Miss Rika Watanabe, and Miss Shiho Harada for their assistance with the experimental work.
References

[1] British Thoracic Society, Guidelines on the management of asthma, Thorax. 48 (1993) S1–S24.
[2] S.M. Harding, The human pharmacology of fluticasone propionate, Resp. Med. 84 (Supplement 1) (1990) 25–29.
[3] R.J. Shaw, Pharmacology of fluticasone propionate, Resp. Med. 88 (Supplement 1) (1994) 5–8.
[4] B. Meibohm, H. Moellmann, M. Wagner, et al., The clinical pharmacology of fluticasone propionate, Rev. Contemp. Pharmacother. 9 (1998) 535–549.
[5] N.K. Thakral, A.R. Ray, J. Jacobsen, et al., Colon targeting of fluticasone propionate inclusion complex: a novel approach in inflammatory bowel disease, J. Incl. Phenom. Macrocycl. Chem. 75 (2013) 175–184.
[6] R. Loefberg, New steroids for inflammatory bowel disease, Inflamm. Bowel Dis. 1 (1995) 135–141.
[7] O.J. Dempsey, W.J.R. Coutie, A.M. Wilson, et al., Evaluation of buccal component of systemic absorption with inhaled fluticasone propionate, Thorax 54 (1999) 614–617.
[8] T. Miyagawa, The influence of changing inhalation device from separate diskus of salmeterol and fluticasone propionate to combination diskus in asthma patients, Jpn. J. Allergol. 57 (2008) 1134–1144.
[9] B. Weber, G. Hochhaus, A systematic analysis of the sensitivity of plasma pharmacokinetics to detect difference in the pulmonary performance of inhaled fluticasone propionate products using a model-based simulation approach, AAPS J. 17 (2015) 999–1010.
[10] K.A. Papadakis, S.R. Targan, Role of cytokines in the pathogenesis of inflammatory bowel disease, Ann. Rev. Med. 51 (2000) 289–298.
[11] S.B. Hanauer, Inflammatory bowel disease: epidemiology, pathogenesis, and therapeutic opportunities, Inflamm. Bowel Dis. 12 (2006) S3–S9.
[12] M. Watanabe, Recent advances in the treatment of inflammatory bowel disease, Nihon Naika Gakkai Zasshi 101 (2012) 643–646.
[13] C. Prantera, S. Marconi, Glucocorticosteroids in the treatment of inflammatory bowel disease and approaches to minimizing systemic activity, Ther. Adv. Gastroenterol. 6 (2013) 137–156.
[14] S.B. Hanauer, G. Stathopoulos, Risk-benefit assessment of drugs used in the treatment of inflammatory bowel diseases, Drug Saf. 6 (1991) 192–219.
[15] T. Tokumura, E. Miyazaki, H. Isaka, et al., Solubility of fluticasone propionate in aqueous solutions measured by a method avoiding its adsorption to experimental tools, Int. Res. J. Pharm. Appl. Sci. 4 (2014) 19–24.
[16] T. Tokumura, H. Isaka, M. Kanou, et al., An inclusion complex of fluticasone propionate with γ-cyclodextrin in aqueous solution and in a solid state, J. Drug Deliv. Sci. Technol. 26 (2015) 24–27.
[17] T. Tokumura, M. Kanou, E. Miyazaki, et al., Degradation rate of fluticasone propionate in an alkaline solution of 0.1 N NaOH:methanol=1:1, Int. Res. J. Pharm. Appl. Sci. 4 (2014) 1–3.