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Degradation kinetics of mometasone furoate in aqueous systems

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Abstract

Mometasone furoate (MF) is a synthetic glucocorticoid. There is little information available on the stability of MF and no degradation products have been unequivocally identified. Thus, the primary objective of this study was to characterize the degradation of MF, qualitatively and quantitatively. Stability of MF decreased with increasing pH (>4) and decreasing ionic strength in aqueous media. The chemical stability of MF in aqueous systems was significantly dependent on pH. MF appeared to be stable at pH < 4 but degraded to four products at higher pH. The degradation of MF in aqueous solutions follows pseudo-first-order kinetics and involved a series of parallel and consecutive reactions. The turnover of MF and its products appears to be catalyzed by the hydroxide ion. The pH dependence of these reactions should be considered, when formulating or extemporaneously compounding MF formulations. An optimal pH of stability was below pH 4. The changes in pH, however, do not appear to be the only factor of importance, since an increase in ionic strength and buffer concentration displayed a stabilizing effect on this glucocorticoid in the buffers tested. Trace metal ions are unlikely to be involved in degradation of MF in aqueous solution.

Keywords: Glucocorticoid; Stability; Degradation

1. Introduction

Mometasone furoate (MF; CAS 83919-23-7, Sch 32088) is 9α,21-dichloro-11β,17α-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione-17-(2-furoate), with the empirical formula $C_{27}H_{30}Cl_2O_6$, and a molecular weight of 521.44 g/mol (Puar et al., 1995; Budavari, 1996; Fig. 1).

MF has been formulated as several liquid-based dosage forms, including a cream, lotion (Prakash and Benfield, 1998), and an aqueous intranasal spray (Onrust and Lamb, 1998). It has also been used as a solution (Hersle et al., 1996) and a diluted 0.1% MF wet-wrap (Tang et al., 1998) in clinical therapy. This glucocorticoid is a C-17 furoate ester like other glucocorticoid esters, may be susceptible to hydrolysis and other degradation reactions in an aqueous environment.

MF has also been formulated as a solid dosage form in a dry powder inhaler (Sharpe and Jarvis, 2001). After administration of this drug as an inhaled dry powder or intranasal suspension, the drug will be in contact with the fluid in the respiratory tract. In addition, most of the dose deposited at the oropharynx will be swallowed and subsequently comes into contact with the gastric and intestinal fluid. Thus, the stability of the drug in these biological matrices will have an impact on its local potency and the systemic availability,

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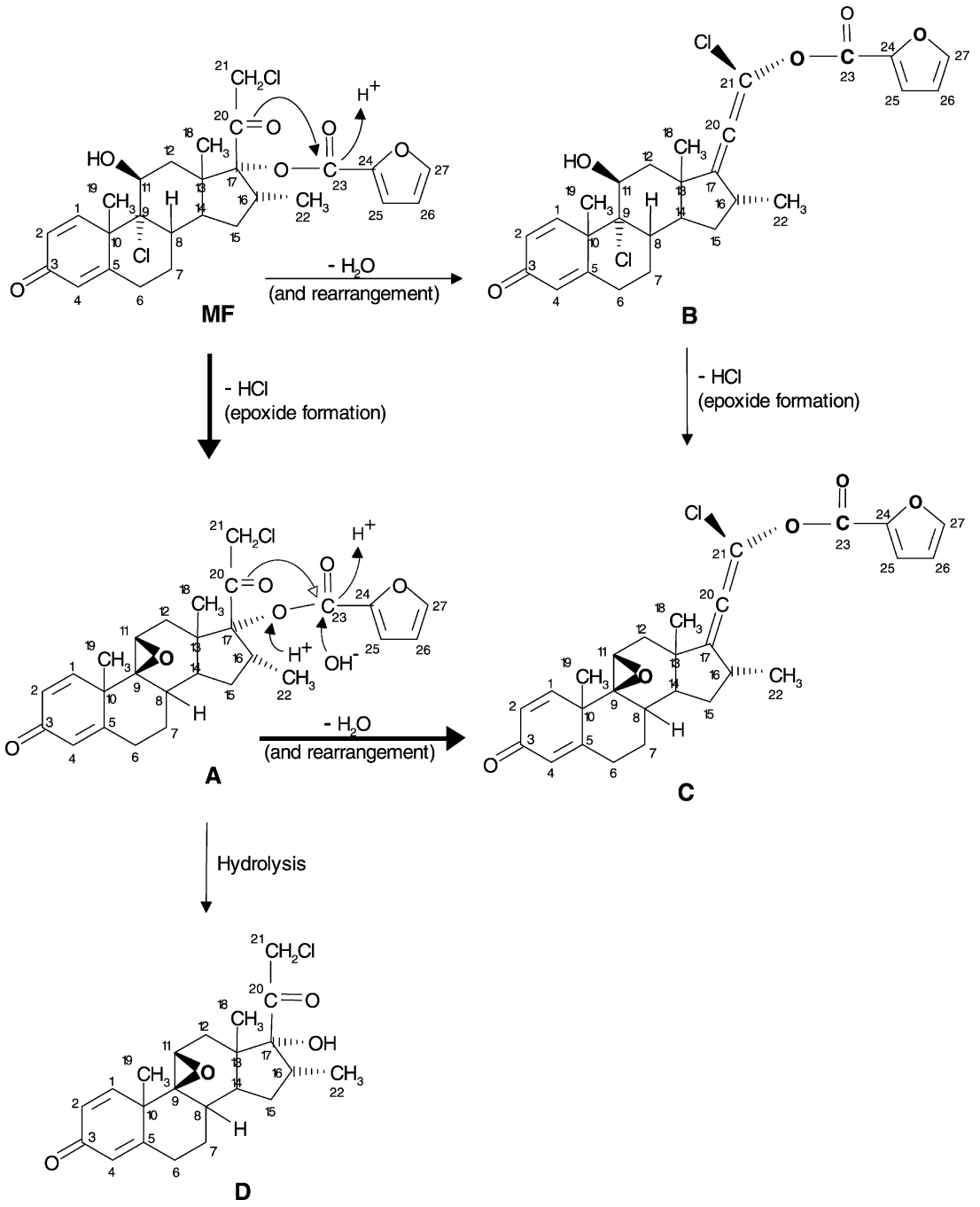

Fig. 1. Chemical structures of mometasone furoate (MF) and its degradation products, A–D, with proposed degradation pathways and 21-configuration of products B and C. Thick arrows indicate major pathways.

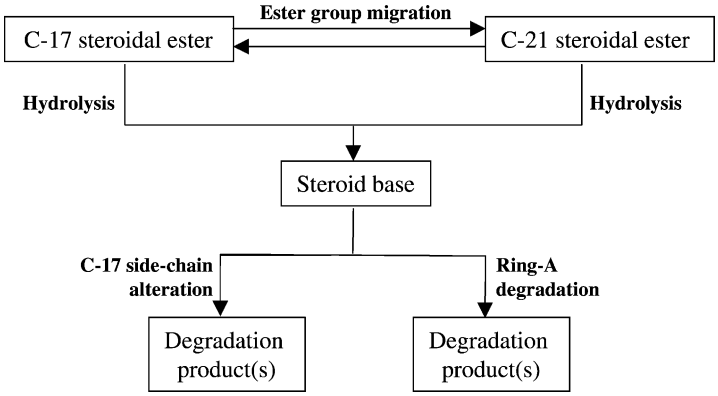

Fig. 2. Schematic graph showing general degradation pathways of synthetic steroidal esters.

and the intrinsic glucocorticoid activity of its degradation product(s) could also modulate the therapeutic efficacy and toxicity of MF.

Chemical stability of a number of corticosteroids in aqueous solutions and in various pharmaceutical preparations has previously been investigated. Studies have shown that C-17 or/and C-21 esterified corticosteroids undergo hydrolysis in aqueous and biological media, which is one of the common degradation pathways of steroids (Fig. 2). For example, beclomethasone dipropionate is rapidly hydrolyzed to beclomethasone 17-monopropionate, and then further hydrolyzed to beclomethasone slowly in simulated intestinal fluid (Würthwein and Rohdewald, 1990). In addition, steroidal esters, betamethasone 17-valerate (Bundgaard and Hansen, 1981), hydrocortisone butyrate (Yip et al., 1983), hydrocortisone hemisuccinate (Mauger et al., 1969), and hydrocortisone 21-lysinate (Johnson et al., 1985) show pH dependent hydrolysis and/or a reversible acyl migration between C-21- and C-17-hydroxy groups in aqueous media.

In previous studies, degradation of non-esterified corticosteroids has been observed under both aerobic and anaerobic conditions. The reactions primarily occur at the C-17 side-chain and some at ring-A (Fig. 2).

In general, the degradation reactions at C-17 side-chain are catalyzed by proton, hydroxide, and trace metal ions. In aqueous systems, pH has been shown to have a significant impact on the chemical stability of various steroids, such as androgenic steroid (Amin et al., 1976) and glucocorticoids (Guttman and Meister, 1958; Monder, 1968; Mauger et al., 1969; Amin and Bryan, 1973; Gupta, 1978, 1979, 1983; Hansen and Bundgaard, 1980; Bundgaard and Hansen, 1981; Dekker and Beijnen, 1982; Johnson, 1982; Timmins and Gray, 1983; Yip et al., 1983; Kenley et al., 1987). In aqueous media, most of the steroids have their maximum stability in weak acidic conditions.

Degradation in ring-A has been observed with some steroids of 1-ene-3-keto or 1,4-diene-3-keto structure, such as prednisone acetate (Barton and Taylor, 1958a,b) and hydrocortisone (Allen and Gupta, 1974). This degradation pathway has been found to be subject to photocatalysis (Barton and Taylor, 1958a,b; Hamlin et al., 1960). For example, hydrocortisone, prednisolone, and methylprednisolone underwent degradation in aqueous solution when they were exposed to UV light (Hamlin et al., 1960). The authors have also found that steroids with two double bonds in the ring-A (e.g. prednisolone and methylprednisolone) are more susceptible to UV light than those with one double bond in the ring-A (e.g. hydrocortisone; Hamlin et al., 1960).

To our knowledge, however, there are no published reports on the stability of MF in aqueous systems. The objective of this study was to evaluate the degradation kinetics of MF in aqueous solutions and simulated biological fluids and in particular to investigate the effect of pH and ionic strength and chelating agent of alkaline-earth metal ions (EDTA) on the stability of MF in aqueous matrices. Finally, a kinetic model describing the degradation process of MF was developed based on the experimental data.

2. Materials and methods

2.1. Chemical materials

Authentic MF was kindly donated by Schering-Plough Pty. Ltd. (Baulkham Hills, NSW, Australia). Chemicals purchased from Sigma Chemical Co. (St. Louis, MO) included dexamethasone 21-acetate. AR grade sodium chloride, potassium chloride (KCl), sodium dihydrogen orthophosphate, di-sodium hydrogen orthophosphate, sodium sulphate, sodium acetate, sodium carbonate, formic acid, and sodium hydroxide (NaOH) were obtained from AJAX Chemicals (Sydney, NSW, Australia). Sodium bicarbonate, ethylenediaminetetraacetic acid disodium salt (EDTA-2Na), hydrochloric acid (HCl) of AR grade, and pancreatin (from pig pancreas) were purchased from BDH Chemicals (Kilsyth, Vic., Australia). Acetic acid of AR grade was obtained from and Rhône-Poulenc Chemicals (Clayton, Vic., Australia). High purity nitrogen gas was purchased from BOC Gases (Chatswood, NSW, Australia).

2.2. pH measurement

All pH measurements were performed on a Model 209 pH/mV meter (Activon Scientific Products Co. Pty. Ltd., NSW, Australia) equipped with a glass electrode. The pH of reaction mixtures was measured at 37 °C at the beginning, in the middle (30 min), and at the end of each incubation.

2.3. HPLC apparatus and conditions

HPLC analysis was performed on a Shimadzu Class-LC10 HPLC (Kyoto, Japan) system that consisted of an LC-10AT pump, an SIL-10AXL auto injector, an FRC-10A fraction collector, an SPD-M10A photodiode-array UV-Vis spectrophotometric detector and a CBM-10A communication bus module. Data collection and integration were accomplished using Shimadzu Class-LC10 computer software version 1.64 (Kyoto, Japan).

Separation was carried isocratically on a Beckman ultrasphere octyl columns (150 mm, 2.0 mm i.d., 5 μm particle size; Beckman Instruments, Fullerton, CA) equipped with a pre-column (7.5 mm, 2.0 mm i.d.) of the same packing material, with a mobile phase consisted of methanol and water (59:41, v/v) at a flow rate of 0.28 ml/min at room temperature (22 ± 1 °C). The UV detection was at 248 nm with spectral scanning from 200 to 400 nm.

2.4. Stability kinetics of MF

Kinetic studies of degradation of MF were conducted at 37.0 ± 0.1 °C in a Thermoline Unistat II thermostatically controlled shaking (set at 75 rpm) water bath protected from light (Thermoline Scientific Equipment, Wetherill Park, NSW, Australia). The reaction was initiated by the adding a stock solution of MF to the incubation medium equilibrated to the temperature of the study, yielding the targeted initial drug concentration. Zero time samples were taken immediately after mixing the drug with the reaction medium. The remainder of the reaction mixture was then divided into aliquots of 0.5 ml each in test tubes pre-warmed in the shaking water bath (37 °C). At pre-determined time intervals, samples (0.5 ml each) were removed and the reaction was immediately terminated by adding 1 M HCl or 1 M NaOH solution to adjust pH of samples to approximately 5. Samples were treated and analyzed by a validated high-performance liquid chromatography (HPLC) assay with little modification (Teng et al., 2001). Briefly, samples were extracted immediately with 4 ml of dichloromethane after adding 0.5 ml of internal standard (10 μg/ml of ethanolic testosterone 17-acetate), followed by centrifugation at 1500 rpm for 2 min (for aqueous media) or 2500 rpm for 15 min (for simulated biological fluids) at 20 °C. The dichloromethane layer was then collected and evaporated to dryness under nitrogen at 35 °C. The dried extract was stored at −20 °C and reconstituted in 100 μl of the mobile phase prior to HPLC assay.

2.4.1. Stability kinetics in aqueous solutions of different pH

Aqueous solutions employed in the kinetic study were of various pH ranging from 1.7 to 11.8. These included HCl, sodium formate, sodium acetate, sodium phosphate, sodium carbonate, and NaOH solutions or buffers (Perrin and Dempsey, 1974). The hydrogen ion concentration of HCl solution was calculated using Eq. (1):

$$\mathrm{Log}[H^+] = 0.16 - \mathrm{pH} \quad (1)$$

while the hydroxide ion concentration of NaOH solution was calculated using Eq. (2) (Perrin and Dempsey, 1974):

$$\text{Log}[OH^-] = \text{pH} - 12.87 \quad (2)$$

The ionic strength (μ) of the solutions and buffers was adjusted with KCl to 0.60 M unless otherwise stated.

2.4.2. Stability kinetics in aqueous solutions in the presence of EDTA

The presence of EDTA (0.1 and 1 mM) on stability of MF was studied with sodium carbonate buffers (pH 9.55 ± 0.01, μ = 0.60 M).

2.4.3. Stability kinetics in aqueous solutions of different ionic strength

The effect of ionic strength on stability of MF was studied with sodium phosphate buffers (pH 7.38 ± 0.01) of ionic strength 0.30, 0.60, 1.2, and 2.10 M.

2.4.4. Stability kinetics in aqueous solutions of different buffer concentration

The effect of buffer concentration on the stability of MF was studied with sodium phosphate buffers (pH 7.38 ± 0.01, μ = 0.60 M) of buffer concentration of 0.02, 0.05, 0.10, and 0.20 M.

2.4.5. Stability kinetics in simulated biological fluids

Simulated gastric fluid and simulated intestinal fluid were prepared according to US Pharmacopeia XXIII (1995). Simulated lung fluid was prepared as previously described (Kalkwarf, 1983).

2.5. Data analysis

The orders of the degradation reactions were determined graphically using the half-life methods (Martin, 1993). The observed decomposition rate constants (k_{obs}) were estimated from the slope of the log–linear phase of declining MF concentration versus time plots. All pseudo-first-order plots reported in this study were linear with the square of correlation coefficient (r^2) greater than 0.9. The half-lives were calculated using the following equation: $t_{1/2} = 0.693/k_{obs}$ (Kostenbauder and Bogardus, 1990; Martin, 1993). Data are expressed as the mean ± S.D. of replicate determinations ($n \geq 3$) or the mean ± S.E.M. for duplicates.

Statistical analyses were performed using Microsoft Excel (version 97) or Statistical Package for Social Sciences (SPSS) (Spss Inc., IL). Hypothesis analysis of data from one sample was conducted using one-sample *t*-test. Significance of difference in means of paired samples was assessed using paired-sample *t*-test. Analysis of variance of two or more groups of data was performed using analysis of variance (ANOVA). All values of *P* were based on two-tailed tests and *P* values of less than 0.05 were considered as statistically significant.

Kinetic analysis of the parent drug disappearance and product formation data was undertaken using SCIENTIST™ version 2.0 (Micromath® Scientific Software, Salt Lake City, UT). Model development in simulation of the metabolic and degradation kinetics was also performed with SCIENTIST™. Selection of the models was assessed based on correlation, randomness of the residuals, the S.D. of the parameter estimates (<10%), and model selection criterion (MSC) which is defined as:

$$\text{MSC} = \ln\left(\frac{\sum_{i=1}^{n} w_i(Y_{\text{obs},i} - \bar{Y}_{\text{obs}})^2}{\sum_{i=1}^{n} w_i(Y_{\text{obs},i} - Y_{\text{cal}})^2}\right) - \frac{2p}{n} \quad (3)$$

where n is number of points, w_i is weight applied to each point, Y_{obs} is weighted mean of the observed data, Y_{cal} is weighted mean of the calculated data based on the equation, p is number of parameters estimated in the equation fitted. MSC is a modified Akaike information criterion (AIC), a commonly used criterion for selecting pharmacokinetic multiexponential equations (Imbimbo et al., 1991; Ludden et al., 1994). MSC has been normalized so that it is independent of the scaling of the data points, providing the same rankings between models as the AIC. The most appropriate model would be that with the largest MSC.

3. Results

3.1. Degradation in aqueous solutions

The pH values of aqueous solutions did not vary more than 0.14 pH unit during the incubations. In the

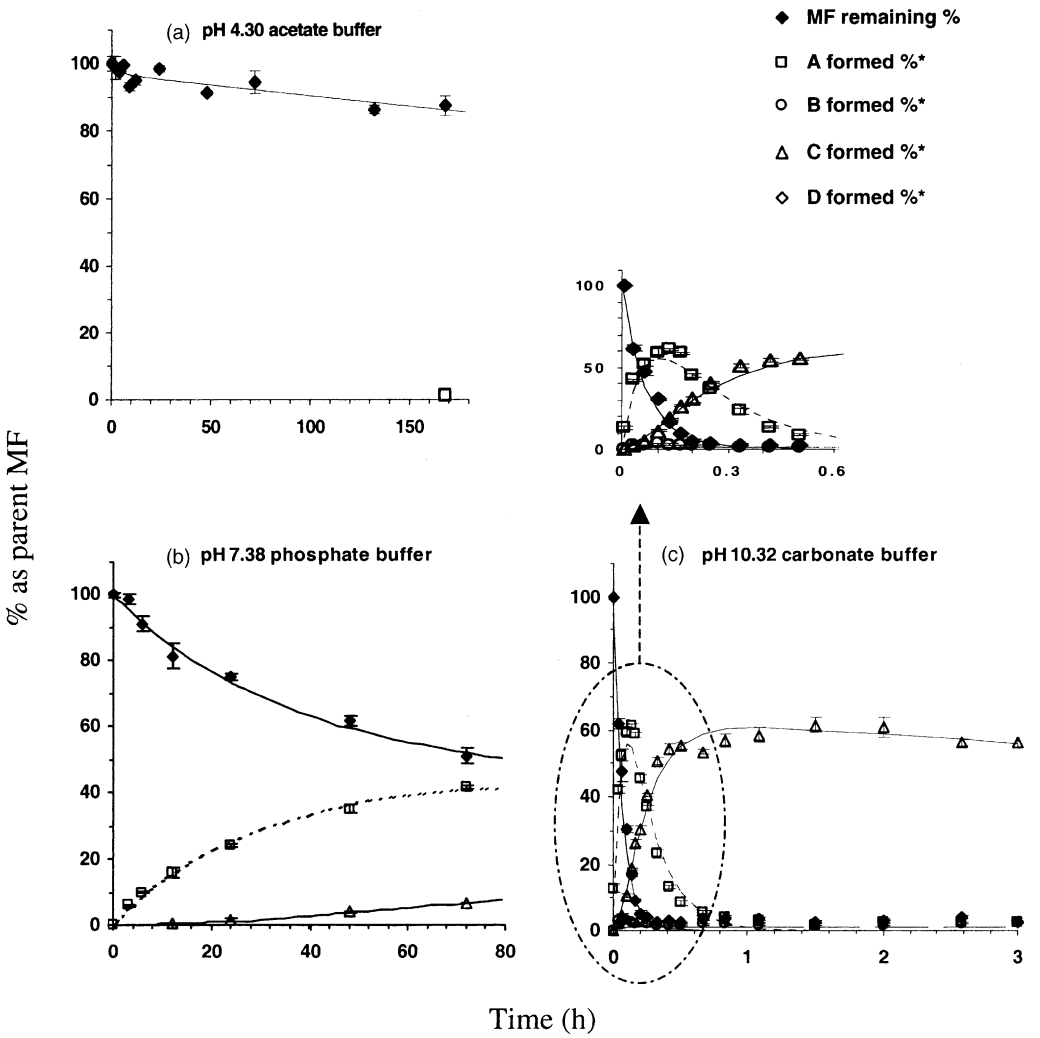

Fig. 3. Typical time-course for MF ($C_0 = 2\,\mu g/ml$) and its degradation products in 0.2 M buffers of pH 4.30, 7.38, and 10.32. (∗) The product formation at various times is expressed as percent in relation to the initial MF determined by HPLC. Each symbol represents the mean value, the vertical bars indicate the S.D. ($n = 3$), and the lines are simulated data using Eqs. (6)–(10).

buffers or solutions tested at pH < 4, no significant decomposition of MF ($C_0 = 2\,\mu g/ml$) was evident, following incubation at 37 °C for 7 days. In weak acidic buffers of pH 4.3, 5.26, and 5.32, little degradation of MF was detected during 1-week incubation, with a small amount of product A found after a lag-time of a few hours (Figs. 1 and 3). In buffers of pH 6.73, 7.38, and 7.98, relatively faster degradation was observed with MF, and three major products, A–C being detected during the incubation period (Figs. 1 and 3). In aqueous solutions of pH ≥ 8.67, MF decomposed rapidly with the formation of four major products, A–D (Figs. 1 and 3).

The observed rate of MF degradation followed pseudo-first-order kinetics over at least three half-lives of the reaction in aqueous media of pH > 6.73. The effect of pH on the degradation rate constant (k_{obs}) of MF at 37 °C is shown in Fig. 4. An almost pH-independent plateau was observed between pH 1.7 and 4. The observed degradation rate constants in the initial pH range of 1.72–5.32 were not significantly different from zero ($n = 3$, $P > 0.05$). The

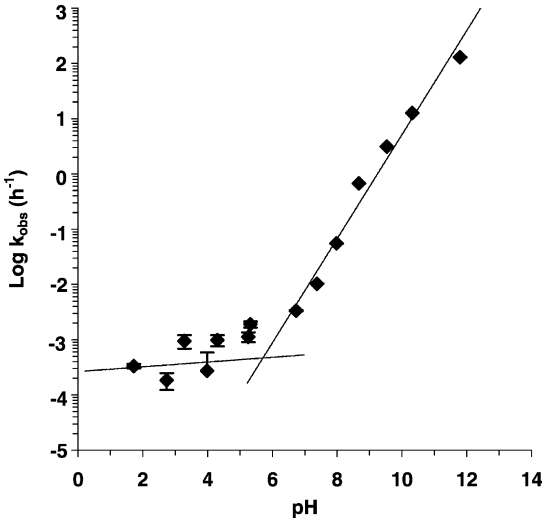

Fig. 4. pH-rate profile for the degradation of MF ($C_0 = 2\,\mu g/ml$) in aqueous solution. Each symbol represents the mean value ($n = 3$).

$\log k_{obs}$, however, was found to increase with the increase in pH from 6.73 to 11.79, demonstrated by the straight-line portion with a slope of 0.94. This profile suggests that the degradation of MF in aqueous solution is base catalysed. The kinetic data obtained in the range of pH 1.72–11.79 could be described by Eq. (4):

$$k_{obs} = k_0 + k_{OH}[OH^-] \quad (4)$$

where k_{obs} is the observed pseudo-first-order rate constant for the overall degradation of MF, k_0 is a first-order rate constant for spontaneous degradation, and k_{OH} is the second-order rate constant for specific base catalysis. Applying Eq. (4) to the experimental data, the values of k_0 and k_{OH} were estimated to be $0.84\,h^{-1}$ and $1590\,M^{-1}\,h^{-1}$, respectively, for MF ($C_0 = 2\,\mu g/ml$) degradation in aqueous solution.

In new methods for the synthesis of MF, product A has been reported as a synthetic intermediate, which can be converted to MF when treated with hydrogen chloride gas in dichloromethane (Draper et al., 1998) or with concentrated HCl in acetic acid (Draper et al., 1999). Thus, the conversion between MF and product A appears to be reversible under certain conditions and the direction of the reaction may be governed by the presence of hydrogen ion and chloride ion as well as pH. Due to the pivotal role of product A in the degradation pathway of MF, pH and the presence of hydrogen and chloride ions will be important factors determining stability of MF. This supports the present finding that MF appears to be stable in HCl solution and acidic solutions of pH < 4, including simulated gastric fluid.

To test if the presence of trace metal ions catalyzes the degradation of MF in aqueous system, EDTA-2Na was added to the incubation buffer. The presence of 0.1 or 1 mM EDTA-2Na did not significantly change the observed degradation rate constant of MF in 0.2 M sodium carbonate buffer (pH 9.55, $\mu = 0.60$ M; $n = 3$, $\alpha = 0.05$, $P > 0.05$, single-factor ANOVA).

It appeared that the k_{obs} of MF decreased slightly with an increase in ionic strength from 0.3 to 2.1 M, in pH 7.38 sodium phosphate buffer (0.10 M; Fig. 5a), implying that the degradation of MF involved reaction between ions. This is consistent with the proposed mechanism for the conversion of MF to product A, the major reaction in aqueous solution. However, the slope of the line was only approximately 0.4, which is lower than the expected value from the Debye–Hückel Equation (Eq. (5); Martin, 1993). This could be due to that high ionic strength and temperature used in this study, whereas the assumption of Debye–Hückel Equation is that the reaction involving ions is in a diluted aqueous solution ($\mu < 0.01$) at 25 °C. In the present investigation, however, it was necessary to keep the concentration of buffering agent sufficiently high to maintain constant pH values during incubation, resulting in a higher ionic strength.

$$\log k_{obs} = \log k_0 - 1.02\, z_a z_b \sqrt{\mu} \quad (5)$$

Moreover, in pH 7.38, sodium phosphate buffer of constant ionic strength (0.60 M), the observed degradation rate constant of MF appeared to decrease with the increase in buffer concentration from 0.02 to 0.20 M (Fig. 5b). There may be significant contribution of buffer. The k_{obs} was $0.17\,h^{-1}$ when the observed rate constant was extrapolated to zero buffer concentration.

These results indicate that some differences are expected in the degradation rate constant in simulated biological fluids (following section) in addition to the pH dependent effects because of other differences in composition.

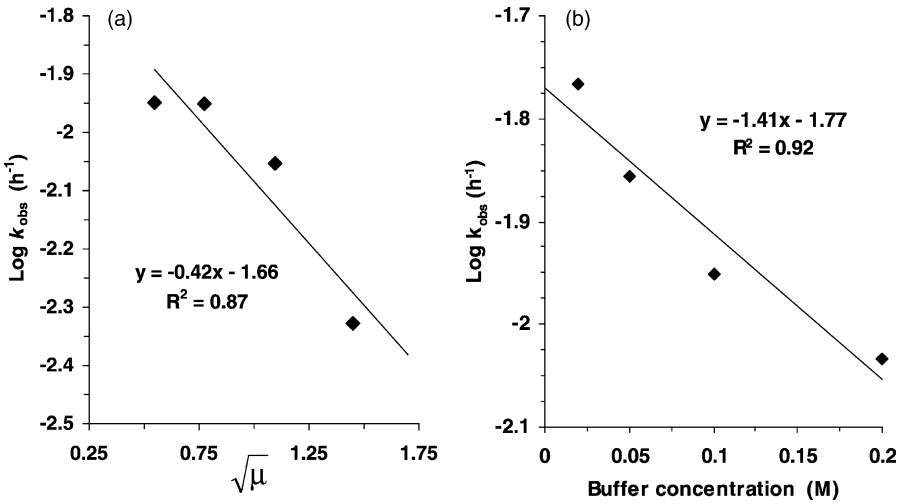

Fig. 5. The effect of (a) ionic strength and (b) buffer concentration on the overall rate of the degradation of MF ($C_0 = 2\,\mu$g/ml) in sodium phosphate buffers of pH 7.38 at 37 °C. Each symbol represents the mean value ($n = 3$).

3.2. Degradation in simulated biological fluids

In simulated gastric fluid, no significant degradation was detected when MF ($C_0 = 10\,\mu$g/ml) was incubated over 7 days at 37 °C. The degradation rate constant of MF obtained in simulated gastric fluid ($0.0001 \pm 0.0002\,h^{-1}$, $n = 4$) was not significantly different from zero ($P > 0.05$). In simulated intestinal fluid and simulated lung fluid, MF ($C_0 = 10\,\mu$g/ml) degraded into, respectively, three (A–C) and four (A–D) products during the incubation. The half-lives of MF degradation observed were 47.3 ± 8.3 h ($n = 4$) and 4.5 ± 0.2 h ($n = 4$) in simulated intestinal fluid and simulated lung fluid, respectively.

3.3. Major degradation pathways

In alkaline solutions of pH > 8 (Fig. 3), product A was formed rapidly and primarily at the beginning and then subsequently declined. Product B was observed in a small amount but formed with no obvious lag-time. The production of B also declined during prolonged incubation time. Marked initial lag-time was found in the formation of products C and D, implying that these two products could be yielded from intermediate(s). The formation of C also declined at longer incubation times. Thus, it is proposed that MF degrades into A and B; product C was formed from products A and B, and product D was from A (Fig. 1). Support for the kinetic scheme for degradation of MF was obtained by data from incubation of the isolated products A, B, and C. In a pH 8 aqueous solution at 60 °C, isolated product A was found to decompose to C primarily, D minimally and some substances in more polar regions of the HPLC chromatogram. When isolated product B was incubated likewise, it was readily converted to product C. In contrast, little degradation was observed with product C under similar incubation conditions.

When MF was incubated at high pH conditions, some chromatographically more polar compounds were detected apart from products A–D. Some of them presented similar UV absorption spectra to MF with maxima at 244–252 nm while some exhibited UV absorption maximum of 202 nm and did not have the UV absorption property raised from 1,4-diene-3-keto conjugation of ring-A. They could be further uncharacterized breakdown products of MF, demonstrating the complexity of transformation pathways of MF.

3.4. Kinetic model for decomposition of MF

According to the understanding of degradation pathways of MF, together with the information on synthesis of MF from product A (Draper et al., 1998, 1999), a kinetic scheme (Fig. 6) to describe the overall reaction sequence was proposed and tested. In this scheme,

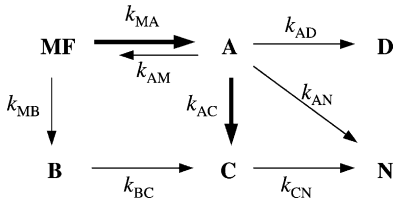

Fig. 6. Kinetic scheme for the reaction sequence of MF in aqueous media.

MF degrades in parallel to A and B, followed by consecutive degradation of both A and B to form C. Product A also converts to D in alkaline conditions and to MF in acidic conditions. In addition, products A and C degrade into some unidentified further breakdown products which are all indicated as N.

In the scheme, k_{MA}, k_{MB}, k_{AM}, k_{AC}, k_{AD}, k_{BC}, k_{AN}, and k_{CN} are the rate constants of corresponding reactions. Thus, the disappearance of parent MF, formation, and disappearance of products A, B, and C, and formation of D can be described by differential Eqs. (6)–(10). As no data were available for N, no differential equation was included for these supposed products.

$$[\mathrm{MF}]' = -(k_{MA} + k_{MB})[\mathrm{MF}] + k_{AM}[\mathrm{A}] \quad (6)$$

$$[\mathrm{A}]' = k_{MA}[\mathrm{MF}] - (k_{AC} + k_{AD} + k_{AN} + k_{AM})[\mathrm{A}] \quad (7)$$

$$[\mathrm{B}]' = k_{MB}[\mathrm{MF}] - k_{BC}[\mathrm{B}] \quad (8)$$

$$[\mathrm{C}]' = k_{AC}[\mathrm{A}] + k_{BC}[\mathrm{B}] - k_{CN}[\mathrm{C}] \quad (9)$$

$$[\mathrm{D}]' = k_{AD}[\mathrm{A}] \quad (10)$$

Characters in brackets represent the percentage of parent drug or formed products at time t, while $[\mathrm{X}]'$ represents the derivative of X with respect to t.

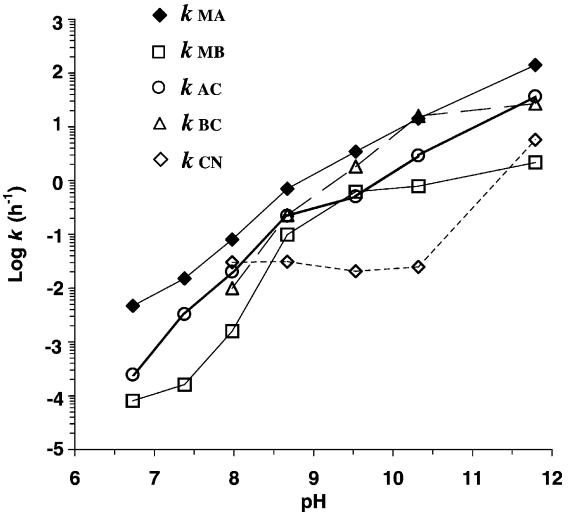

Fig. 7. pH-rate profile for the degradation major reactions of MF in aqueous solution. Each symbol represents the rate constant of the major reactions involved in the degradation of MF in aqueous solutions (shown schematically in Fig. 6) of varying pH, estimated using Eqs. (6)–(10).

Good correlation ($r^2 > 0.99$, MSC > 3) was obtained between the observed and the predicted values, when Eqs. (6)–(10) were fitted by fitting the time-course profiles of MF in aqueous systems (Fig. 3). Based on this model and experimental data, the estimated rate constants for the major reactions involved in the degradation of MF, k_{MA}, k_{MB}, k_{AC}, and k_{BC}, displayed significant pH dependence in the range of pH 6.73–11.79 (Fig. 7). The log–linear relationships between the values of pH and the apparent rate constants, for the total disappearance of MF and the major degradation reactions, are presented in Table 1.

Table 1
The log–linear relationships between the pH value of the aqueous reaction medium and the rate constant, for the total disappearance of MF and the formation of degradation products, A–C

Reaction	Relationship in pH 6.73–11.79	r^2	P (two-tailed)[a]
Total loss of MF	$\mathrm{Log}\,k_{obs} = 0.9422 \times [\mathrm{pH}] - 8.71$ or $k_{obs} = 1.95 \times 10^{-9} \times 10^{0.9422 \times [\mathrm{pH}]}$	0.9794	0.043
MF → A	$\mathrm{Log}\,k_{MA} = 0.9133 \times [\mathrm{pH}] - 8.3645$ or $k_{obs} = 4.32 \times 10^{-9} \times 10^{0.9133 \times [\mathrm{pH}]}$	0.9841	0.043
MF → B	$\mathrm{Log}\,k_{MB} = 0.9808 \times [\mathrm{pH}] - 0.411$ or $k_{obs} = 3.88 \times 10^{-11} \times 10^{0.9808 \times [\mathrm{pH}]}$	0.8661	0.004
A → C	$\mathrm{Log}\,k_{AC} = 0.9849 \times [\mathrm{pH}] - 0.7398$ or $k_{obs} = 1.82 \times 10^{-10} \times 10^{0.9849 \times [\mathrm{pH}]}$	0.9639	0.048
B → C	$\mathrm{Log}\,k_{BC} = 0.8859 \times [\mathrm{pH}] - 0.5066$ or $k_{obs} = 3.12 \times 10^{-9} \times 10^{0.8859 \times [\mathrm{pH}]}$	0.8693	0.008

[a] The correlation between rate constant and pH value was evaluated by two-tailed test, with $P < 0.05$ considered to be significantly correlated.

In addition, the rates of A and B formation were, respectively, ~91 and 6% of that of total degradation of MF in aqueous solutions of pH 6.73–11.97. The remainder of MF loss (~3%) could be due to other degradation pathways, such as C-17 ester-bond hydrolysis and 21-Cl substitution.

4. Discussion

In previous studies, various factors influencing the stability of a number of corticosteroids in aqueous suspensions and solutions have been investigated. Findings from the present study were in good agreement with the previous experiences that corticosteroids of similar structure to prednisolone should not be exposed to materials capable of producing an elevated pH during formulation (Chulski and Forist, 1958). In aqueous solutions, stability of MF was found to reduce with an increase in pH. Thus, a higher pH should be avoided in formulating MF, as well as in choosing a diluting agent when dilution is needed in clinical use and in extemporaneous pharmaceutical compounding.

The composition of the simulated gastric fluid is similar to that of the pH 1.72 HCl solution tested, apart from the addition of pepsin in the former. Although the pH of simulated gastric fluid increased from 1.2 to 2.3 during incubation, it was still in the range over which MF appeared to be stable, with no evidence of significant degradation of MF. A similar finding demonstrating stability in simulated gastric fluid over a 3-h incubation period has previously been reported for beclomethasone dipropionate (Würthwein and Rohdewald, 1990). The k_{obs} ($0.015 \pm 0.003\,h^{-1}$, $n = 4$) of MF in the simulated intestinal fluid (pH 7.45, $\mu = 0.07$ M (calculated from inorganic ions present)) was in the right order in the pH-rate profile (Fig. 4). It appears that the existence of pancreatin does not significantly modulate the degradation processes of MF. However, the degradation profile of MF in simulated lung fluid (pH 7.35, $\mu = 0.324$, $k_{obs} = 0.129 \pm 0.014\,h^{-1}$, $n = 4$) was significantly higher than those in pH 7.38 buffer solutions ($P < 0.01$). This is most likely due to the fact that pH value of simulated lung fluid increased from 7.35 to 8.10 within 30-min incubation at 37 °C. The degradation of the drug would then be accelerated due to the increase of pH. Attempts to maintain a constant pH were not successful without changing ionic strength/components of the simulated lung fluid. In humans, the pH of lung fluid is kept at a proper physiological level by the buffering capacity of other components (e.g. proteins), but this pH can also change in various disease states of the lungs.

In previous studies, steroids have been found to degrade via different pathways depending on their chemical structure and the reaction environment. Many corticosteroids are unstable in acidic solutions. MF is a C-17 esterified 21-chlorinated steroid, having a C-17 side-chain different from mibolerone and C-17 dihydroxyacetone steroids (e.g. hydrocortisone, prednisolone, and dexamethasone). This could result in different degradation pathway(s) for MF from those observed with mibolerone and C-17 dihydroxyacetone steroids. In acidic conditions, the reactions involving Wagner–Meerwein rearrangement, C-17 dehydroxylatoin and C-21 dehydration, are not likely to happen with MF. In fact, in the present study, no degradation of MF was evident in acidic solutions of pH < 4. In alkaline conditions, like other steroids, stability of MF decreased with an increase in pH. Product A was the major direct degradation product yielded via loss of HCl on ring-C from MF. This reaction was also observed in alkaline conditions (with product A formed) during synthesis of mometasone furoate-3-(*O*-carboxymethyl)oxime (Wang et al., 1992). In addition, the authors indicated that product A had not been found in vivo by the time their work was done. This reaction route has been previously documented with other 9α-halo-11β-hydroxy steroids in non-biological media (Fried et al., 1955; Oliveto et al., 1958; Annen et al., 1982) and in plasma in vitro (Foe et al., 1998). The mechanism of the reaction has been proposed by Foe et al. (1998). It involves a stereospecific nucleophilic attack of the 11β-hydroxyl on C-9 from the β face on departure of the 9-halogen, leading to the formation of 9β,11β-epoxide derivative.

The involvement of metal ions in catalyzing the degradation of corticosteroids has been previous reported in the literature. EDTA has been demonstrated to effectively inhibit oxidation of hydrocortisone to its 21-dehydro derivative (Monder, 1968; Hansen and Bundgaard, 1980). In alkaline sultions, EDTA also inhibits degradation of prednisolone (Oesterling and Guttman, 1964). However, for a 9-fluoro steroid, desoximetasone, EDTA has been found to block the reaction involving C-17 side-chain but not that involving

loss of HF around C-9 (Dekker and Buijs, 1980). Consistent with the later, in the present study, EDTA did not inhibit the formation of product A that formed via loss of HCl from MF, a 9-chloro steroid, in alkaline buffer. This is due to the loss of HCl or HF is not a redox reaction and does not involve radical spices. Because of the 'rate-determining' role of A formation in degradation of MF, the overall degradation of this drug would not be altered significantly by EDTA. These results together with the previous finding of Dekker and Buijs (1980) suggest that different behavior of EDTA on degradation of steroids may be due to the difference in chemical structures of the steroids and the nature of the degradation reactions.

Additionally, product B could be formed through a rearrangement and dehydration on the C-17 side-chains of MF. In the present investigation, hydrolysis of the C-17 furoate group was not found to be a predominant event in decomposition of MF in all the aqueous media tested. Other C-17 steroidal esters, such as betamethasone 17-valerate (Bundgaard and Hansen, 1981) and hydrocortisone butyrate (Yip et al., 1983), have previously been demonstrated to undergo reversible ester group migration to form their C-21 steroidal esters in non-biological systems. This ester migration between C-17 and C-21 of steroids has also been shown in biological systems, such as between beclomethasone 17-propionate and beclomethasone 21-propionate (Foe et al., 1998). The C-21 ester isomers then degrade to the corresponding steroidal alcohols through hydrolysis. These findings suggest that the C-17 ester is relatively less prone to hydrolysis than the corresponding C-21 ester. Although MF is a C-17 steroidal ester, the reversible rearrangement of C-17 furoate group to C-21 might not be favored due to the presence of C-21 chlorine. It has been previously demonstrated that the substitution of the 21-acyl by chlorine increases the resistance of this drug to degradation by esterases in the epidermis (Mori et al., 1994; Prakash and Benfield, 1998). Thus, MF was not expected to undergo extensive hydrolysis under the conditions studied.

5. Conclusion

The chemical stability of MF in aqueous system was significantly dependent on pH. MF appeared to be stable at pH < 4 but degraded to four products, A–D, at higher pH. The degradation of MF in aqueous solutions follows pseudo-first-order kinetics and involved a series of parallel and consecutive reactions. The turnover of MF and its products appears to be catalyzed by the hydroxide ion. The pH dependence of these reactions should be considered when formulating or extemporaneously compounding MF formulations. An optimal pH of stability was below pH 4. The changes in pH, however, do not appear to be the only factor of importance, since an increase in ionic strength and buffer concentration displayed a stabilizing effect on this glucocorticoid in the buffers tested. It may be of interest to further test if individual metal ions influence MF stability. In addition, other factors, such as temperature and light also needed to be considered in further delineating the factors influencing the decomposition of MF.

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