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Research Article

Photodegradation and Stabilization of Betamethasone-17 Valerate in Aqueous/Organic Solvents and Topical Formulations

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Abstract. The effects of solvent [acetonitrile, methanol, and acetonitrile/water mixture (20:80, *v*/*v*)], buffer concentration (phosphate buffer, pH7.5), ionic strength and commonly employed adjuvants on the photodegradation of betamethasone-17 valerate in cream and gel formulations have been studied on exposure to UV light (300–400 nm). A validated high-performance liquid chromatography method has been used to determine the parent compound and its photodegraded products. The photodegradation data in the studied solvents showed greater decomposition of the drug in solvents with a lower dielectric constant. A comparatively higher rate of photodegradation was observed in the cream formulation compared to that for the gel formulation. The kinetic treatment of the photodegradation data revealed that the degradation of the drug follows first-order kinetics and the apparent first-order rate constants for the photodegradation reactions, in the media studied, range from 1.62 to $11.30\times10^{-3}\,\mathrm{min}^{-1}$. The values of the rate constants decrease with increasing phosphate concentration and ionic strength which could be due to the deactivation of the excited state and radical quenching. The second-order rate constant (k') for the phosphate ion-inhibited reactions at pH7.5 has been found to be $5.22\times10^{-2}\,\mathrm{M}^{-1}\mathrm{s}^{-1}$. An effective photostabilization of the drug has been achieved in cream and gel formulations with titanium dioxide (33.5–42.5%), vanillin (21.6–28.7%), and butyl hydroxytoluene (18.2–21.6%).

KEY WORDS: betamethasone-17 valerate; creams and gels; kinetics; photodegradation; photostabilization.

INTRODUCTION

Betamethasone-17 valerate (9-floro-11 β, 21-dihydroxy-16β-methyl-3, 20-dioxopregna-1, 4-dien-17-yl pentanoate) is a potent synthetic glucocorticoid used in a variety of allergic and inflammatory skin disorders (1,2). The drug is applied to the skin in the form of cream, gel, ointment, lotion, or solution (3). It has been shown to decompose extensively under UV light (4,5), through a rearrangement of the cyclohexadienone moiety involving a radical mechanism, resulting in lumi, photolumi, and andro derivatives (6) (Fig. 1). The reduction in anti-inflammatory activity of the drug upon exposure to UVB light has also been shown in the same study. It has been established that photodegraded products of the drug are toxic/phototoxic, and the toxicity increases with further irradiation (7). These findings lead to the investigation of the effect of various factors on the rate of photodegradation of the drug in solution and some topical dosage forms and also stabilization of the drug against light in pharmaceutical formulations using photostabilizers. A similar study on the thermal degradation of the compound in methanol, acetonitrile, water, cream, and gel formulations has been reported (8). The compound has shown greater stability in polar media as compared to that of the nonpolar media. Enhanced stability of the compound has also been found in gel formulations as compared to that of the cream formulations. The photostability of drugs has been evaluated with various stabilizers for creams containing ascorbic acid (9) and other drugs (10–12). Steroidal drugs in topical formulations have been stabilized against light using different techniques such as spectral overlay with suitable stabilizers, inclusion into liposomes, and protection with light-blocking agents (4,13–15).

The present work has been carried out to study the effects of the solvent dielectric constant, buffer concentration, ionic strength, and formulation adjuvants on the photodegradation of betamethasone-17 valerate. This information would be useful to the formulators while formulating a particular dosage form of the drug. Efforts have also been made to stabilize the drug against light in cream and gel formulations using photoprotecting agents such as titanium dioxide, vanillin, and butyl hydroxytoluene to minimize the formation of toxic/phototoxic products and to safeguard the patients using the betamethasone formulations for the treatment of skin disorders.

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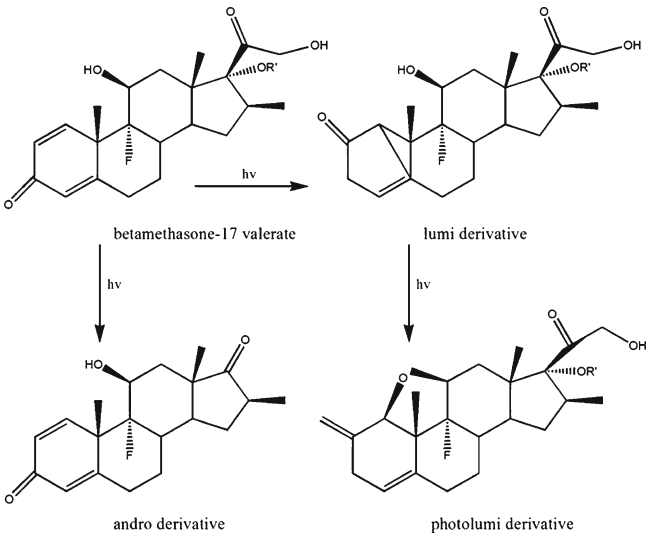

Fig. 1. Phototransformation of betamethasone-17 valerate, R′=CO $[CH_2]_3CH_3$

MATERIALS AND METHODS

Materials

Betamethasone-17 valerate was kindly donated by GSK Pakistan (Pvt.) Ltd. The photodegraded products of betamethasone-17 valerate, i.e., lumi, photolumi, and andro derivatives, were isolated by the method as described by Miolo *et al.* (6). All stabilizers (vanillin, titanium dioxide, and butyl hydroxyltoluene) were obtained from Merck (Germany). Formulation ingredients (carbomer 940, cetostearyl alcohol, hydroxyethyl cellulose, propylene glycol, isopropyl alcohol, and di-isopropanolamine) were obtained from North Chemicals (Columbia), Croda (Japan), Spectrum (USA), Dow Chemicals (Germany), Bio M (Malaysia) and Merck (Germany), respectively. All the solvents used were of spectroscopic grade from Tedia (Japan). The high-performance liquid chromatography (HPLC) grade water used in the mobile phase was purified through a Milli-Q system (Millipore, USA).

Composition and Preparation of Cream and Gel Formulations

The composition of the cream and gel formulations used in this study are given below:

Cream	Percentage (*w*/*w*)	Gel	Percentage (*w*/*w*)
Betamethasone-17 valerate	0.1	Betamethasone-17 valerate	0.1
Carbomer (940)	1.5	Carbomer (940)	0.7
Propylene glycol	8.0	Hydroxyethyl cellulose	0.5
Cetostearyl alcohol	7.0	Propylene glycol	20.0
Isopropyl alcohol	2.0	Di-isopropanolamine	0.5
Ethyl paraben	0.2	Isopropyl alcohol	2.0
Deionized water	81.0	Ethyl paraben	0.2
		Deionized water	75.9

The cream formulation was prepared by soaking carbomer-940 overnight in water. Betamethasone esters dissolved in a small quantity of isopropyl alcohol were added to a mixture of propylene glycol, cetostearyl alcohol, and water and then mixed with the carbomer suspension in a Silverson mixer. The pH of the cream was adjusted with 1 M sodium hydroxide solution under gentle mixing. In the case of gel formulation, the betamethasone ester solution in isopropyl alcohol and carbomer suspension in water were thoroughly mixed with propylene glycol and water in a silver san mixer. Di-isopropanolamine was then added to the mixture under vigorous mixing. The pH of the gel was adjusted with 4 M hydrochloric acid solution.

pH Measurements

All pH measurements were carried out with a WTW pH meter (Model 702, sensitivity±0.01 pH units, Germany). The electrode was standardized with buffer solutions (pH2.0, 4.0, and 7.0) at 25°C. For the determination of pH of the formulated products (cream/gel), a 2 g sample was mixed thoroughly with 30 ml of double distilled water in a beaker and pH of the mixture was determined.

Irradiation of Betamethasone Valerate

Irradiation of the betamethasone-17 valerate was carried out in solution, cream, and gel formulations in a controlled temperature (25±1°C) chamber using a UV lamp (300 W, Ultra-Vitalux, Osram, Germany) emitting in the region of 300–400 nm. The distance of the sample was kept constant, i.e., 30 cm from the radiation source. The intensity of light was measured as 16,000 lx, with a digital illuminance meter (TES-1332A, TES Electrical Corporation, Taiwan). The irradiation was carried out up to 2 h in each case.

Photodegradation of Betamethasone-17 Valerate in Solution

Solutions of betamethasone valerate (1×10^{-4}M) in methanol, acetonitrile, or acetonitrile/water mixture (20:80, *v*/*v*) were aliquoted into six portions and placed into 100 ml plastic capped Pyrex bottles. The samples were exposed to UV radiation for predetermined time intervals. At a selected time, the solutions were filtered through 0.22 μm cellulose acetate filters and analyzed by HPLC. In order to study the effect of buffer concentration on the photodegradation of betamethasone valerate, 10 ml aliquots of the stock solution of betamethasone valerate in acetonitrile (1×10^{-3}M) were mixed with 90 ml of sodium phosphate buffers (pH7.5, μ=0.6 M) and the buffer concentration adjusted to 0.05, 0.1, 0.15, and 0.2 M. For ionic

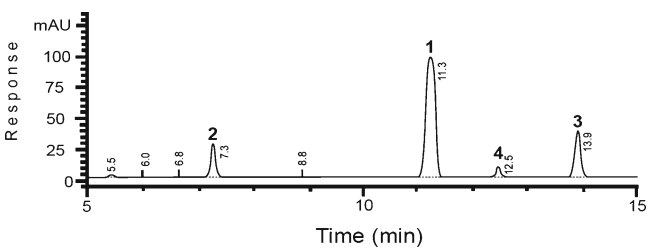

Fig. 2. HPLC chromatogram showing betamethasone-17 valerate, (1) andro derivative, (2) lumi derivative (3), and photolumi derivative (4)

Table I. Photodegradation of Betamethasone-17 Valerate in Different Solvents

Time (min)	Percent degradation±SD		
	Methanol	Acetonitrile	Acetonitrile/water (20:80, *v/v*)
0	100.0±2.31	100.0±1.32	100.0±1.90
30	71.14±1.83	73.01±1.40	75.67±1.48
60	50.10±1.04	53.31±0.95	57.28±0.85
90	35.70±0.91	38.50±2.67	43.31±1.65
120	25.75±0.95	28.03±1.30	32.76±1.12

n=5
In control solutions, there was no change in concentration during the period of 120 min in the dark

strength (μ) effect, sodium phosphate buffers (pH7.5±0.01) of ionic strength 0.3, 0.6, 0.9, 1.2, and 1.5 M were used accordingly.

Photodegradation of Betamethasone-17 Valerate in Cream and Gel Formulations

The cream or gel formulation (1 g) was evenly spread as a 1 mm layer in Petri dishes, placed in a water bath maintained at 25±1°C and irradiated for specified time intervals. At a selected time, the samples were dissolved in methanol, filtered through 0.22 μm cellulose acetate filters and analyzed by HPLC.

Isolation of the Photodegraded Products of Betamethasone-17 Valerate

The Isolation of the photodegraded products was made by the method described by Miolo *et al.* (6). Solutions of betamethasone-17 valerate (1×10^{-2}M) in methanol were irradiated for a specified time and subjected to thin layer chromatography (TLC; Silica gel plates, 0.25 mm thickness, Merck). The elution was made with a mixture of $CHCl_3$: CH_3COCH_3 (5:2, *v/v*). The bands of interest were scrapped off, extracted with methanol, dried *in vacuo*, and stored at room temperature. Identification of the already characterized photodegraded products (6) was confirmed by their respective R_f and t_R values through TLC and HPLC experiments.

HPLC Apparatus and Conditions

The HPLC analysis was carried out on a Shimadzu class-20 A HPLC (Kyoto, Japan) system that consisted of an LC-20AT pump, an SPDM-20A Photodiode-array UV-visible detector and an inbuilt CBM-20A lite communication bus module. Data collection and integration were achieved using Shimadzu LC solution computer software version 1.2 (Kyoto, Japan). All the separations were carried out at ambient temperature on a stainless steel C-18 column (Spherisorb, 250×4.6 mm i.d) packed with ODS 5 μm (water) and attached with a C-18 guard column (10×4.6 mm i.d, packed with ODS, 5 μm). The mobile phase was composed of acetonitrile/water, 50:50 (*v/v*), up to 80:20 (*v/v*) in 20 min. The flow rate was 1 ml/min and the detection was made at 240 nm.

Assay of Betamethasone-17 Valerate and Photodegraded Products

Standard solutions containing beclomethasone dipropionate (50 μg/ml as internal standard) and different concentrations (5–60 μg/ml) of betamethasone-17 valerate spiked with the same concentrations (5–60 μg/ml) of the lumi, photolumi, and andro derivatives (Fig. 1) were prepared in methanol and the calibration curves (peak area ratio of betamethasone-17 valerate or photodegraded products to the internal standard *versus* concentration) were constructed. Test solutions (final concentration, 50 μg/ml) were filtered through 0.22 μm cellulose acetate filters and injected (20 μl) to the liquid chromatography. Quantification of betamethasone-17 valerate and photodegraded products in degraded samples was achieved using calibration curves.

Photostabilization of Betamethasone Valerate in Cream and Gel Formulations

The photostabilization of betamethasone valerate in cream and gel formulations was carried out using excipients (photostabilizers) such as titanium dioxide, vanillin, and butyl hydroxytoluene. A 100 mg (0.1%) quantity of the stabilizer (dissolved/suspended in isopropyl alcohol/water) was mixed with a 100 g sample of the drug in a laboratory scale mixer. The samples were then irradiated for an appropriate time interval as described above and analyzed by HPLC. The control samples were also irradiated under similar conditions.

Table II. Apparent First-Order Rate Constants (k_{obs}) and Half-Lives for the Photodegradation of Betamethasone-17 Valerate in Various Solvents

Solvent system	Dielectric constant (25°C)	$k_{obs}\times10^3$±SD (min^{-1})	Correlation coefficient	*t* 1/2 (min)
Methanol	32.6	11.30±0.83	0.999	61.32
Acetonitrile	40.1	10.65±0.68	0.999	65.07
Acetonitrile/water (20:80, *v/v*)	70.3	9.29±1.04	0.999	74.60

n=5

Table III. Product Distribution at 50% Photodegradation of Betamethasone-17 Valerate in Different Solvents

Solvent system	Percent formation ± SD		
	Lumi derivative	Andro derivative	Photolumi derivative
Methanol	36.5±3.81	9.3±1.10	4.2±0.63
Acetonitrile	40.0±2.12	6.9±0.38	3.1±0.32
Acetonitrile/water (20:80, *v*/*v*)	43.2±3.21	4.8±0.81	2.0±0.19

n=5

Statistical Analysis

The orders of the degradation reactions were determined graphically using the half-life method. The observed degradation rate constants (k_{obs}) were estimated from the slope of the log-linear phase of declining betamethasone-17 valerate concentration *versus* time plots. All first-order plots reported in this study were linear with the square of correlation coefficient (r^2) greater than 0.997. The half-lives were calculated using the half-life equation. The data are expressed as mean of replicate determinations (n=5). The kinetic data were compared using the Student's t test. The statistical significance was defined as the p value <0.05. Computer based Statistical Package for Social Sciences for window XP and Microsoft Excel (version 2003) were used in this work.

RESULTS AND DISCUSSION

Effect of Solvents on Photodegradation

The photodegradation of betamethasone-17 valerate was carried out in methanol, acetonitrile, and acetonitrile/water mixture (20:80, *v*/*v*). Three major photodegraded products of the reaction (lumi, photolumi, and andro) were detected which have already been characterized (6). Under the present chromatographic conditions, the andro derivative was eluted at 7.3 min, lumi derivative at 13.9 min, and photolumi derivative at 12.5 min and betamethasone-17 valerate at 11.3 min (Fig. 2). The assay data on photodegradation of the compound in the solvents studied is given in Table I. The kinetic treatment of the assay data has shown that photodegradation of the compound in the solvents used follows first-order kinetics and the rate of photodegradation is in the order of: methanol>acetonitrile>acetonitrile/buffer mixture, i.e., 11.3, 10.65, and 9.29×10^{-3}min^{-1}, respectively (Table II). These results show that the rate of photodegradation is dependent on solvent characteristics and the values of k_{obs} decrease with an increase in the solvent dielectric constant (Fig. 2). This behavior of the compound suggests the presence of a nonpolar intermediate or transition state in the reaction pathway, controlling the reaction rate. The product distribution data at 50% photodegradation of the compound in different solvents show that lumi derivative (36.5–43.2%) is the main photodegraded product followed by andro derivative (4.8–8.3%) and photolumi derivative (2.0–4.2%), respectively (Table III). The decrease in the values of lumi derivative in methanol (36.5%) and acetonitrile (40.0%) compared to that of the acetonitrile/water (43.2%) is due to the fact that lumi derivative is an intermediate in the degradation pathway of betamethasone-17 valerate and gives rise to photolumi derivative (Fig. 1). The greater loss of lumi derivative in organic solvents is due to its greater conversion to the photolumi derivative.

Effect of Buffer Concentration on Photodegradation

The photodegradation of betamethasone-17 valerate was carried in the presence of varying concentrations (0.05, 0.1, 0.15, and 0.2 M) of phosphate buffer at pH7.5. The kinetic treatment of the assay data on the photodegradation of the compound in phosphate buffer indicates that the k_{obs} of the compound decreases ($12.2–5.1\times10^{-3}$min^{-1}) with an increase in phosphate concentration (0.05–0.2 M; Table IV). This decrease in the rate of photodegradation of the compound with an increase in buffer concentration is statically significant (p<0.05) and may be due to the deactivation of the excited species on an increase in buffer concentration. Such an effect has already been observed with some other glucocorticoids (10). The value of k_0 (rate constant in the absence of buffer) is 1.47×10^{-2}

Table IV. Apparent First-Order Rate Constants (k_{obs}) for the Photodegradation of Betamethasone-17 Valerate at Various Buffer Concentrations

Buffer concentration (M)	$k_{obs}\times10^3\pm$SD (min^{-1})	Correlation coefficient	t[a]
0	14.7±0.54	0.998	–
0.05	12.3±0.93	0.999	5.89
0.10	9.3±0.95	0.996	7.37
0.15	7.0±0.61	0.996	8.43
0.20	4.8±0.73	0.999	6.74

n=5
[a] t calculated>t tabulated (2.78) at 95% confidence interval (p<0.05) for the rate constant at buffer concentration with respect to the previous one

Table V. Apparent First-Order Rate Constants (k_{obs}) for the Photodegradation of Betamethasone-17 Valerate in Solutions at Various Ionic Strengths

Ionic strength (M)	$k_{obs}\times10^3\pm$SD (min^{-1})	Correlation coefficient	t[a]
0	10.2±0	0.999	–
0.3	9.3±0.68	0.996	2.96
0.6	8.1±0.78	0.996	3.45
0.9	7.0±0.57	0.995	4.31
1.2	6.1±0.80	0.998	2.51
1.5	5.4±0.65	0.996	2.40

n=5
[a] t calculated for the ionic strengths 0.3–0.9 M are greater than t tabulated (2.78) at 95% confidence interval ($p<0.05$) for the rate constant with respect to the previous one

min^{-1} when the values of k_{obs} are extrapolated to zero buffer concentration. The second-order rate constant (k') obtained from the slope of the plot of k_{obs} *versus* buffer concentration for the phosphate ion-inhibited reaction is $5.22\times10^{-2}M^{-1}s^{-1}$. A similar effect of borate and citrate ions on the inhibition of the rate of photolysis of riboflavin by deactivation of the excited triplet state has been observed (11,12).

Effect of Ionic Strength on Photodegradation

The effect of ionic strength on the photodegradation of betamethasone-17 valerate was studied using sodium phosphate buffers (pH7.5±0.01) of ionic strength 0.3, 0.6, 0.9, 1.2, and 1.5 M. The kinetic treatment of the assay data on photodegradation of the compound in solutions of varying ionic strength indicated that the rate of photodegradation of the compound also decreases ($9.3–5.4\times10^{-3}min^{-1}$) with an increase in the buffer ionic strength (0.3–1.5 M), under the present experimental conditions (Table V). Similar to the buffer concentration effect, the decrease in the rate of photodegradation with an increase in buffer ionic strength is also statistically significant ($p<0.05$) in the concentration range 0.3–0.9 M; however, the other two values (1.2 and 1.5 M) lie on the linear k_{obs} *versus* ionic strength curve. This decrease in the rate could also be explained on the basis of deactivation of the excited species. The value of k_0 in this case the value is $1.02\times10^{-2}min^{-1}$ as obtained by extrapolation of the value of k_{obs} to zero ionic strength.

Effect of Common Adjuvants of Cream and Gel Formulations on Photodegradation

The assay data on the photodegradation of betamethasone-17 valerate in cream and gel formulations (Table VI) has shown that the degradation of the compound is faster in the cream than in the gel formulation, suggesting the inhibitory role of the formulation ingredients on the photodegradation of the compound. Mechanistically, their role could be explained on the basis of their stabilization or destabilization of the activated species of the compound. The thixotropic properties imparted by a particular excipient to the formulation could also contribute to the shielding effect on the drug during the photodegradation. The difference in the composition of excipients of the cream and gel formulations may cause a difference in degradation rates of the compound in the two formulations. The effect of excipients on the photostability of a formulation has been established in creams containing ascorbic acid (9,16) and a number of other drugs (17–20).

Photostabilization of Betamethasone Valerate in Cream and Gel Formulations

The extensive photodegradation of steroidal drugs has invited a number of workers to study the stabilization of these compounds in different dosage forms. In the present work cream and gel formulations of the betamethasone-17 valerate were stabilized against photodegradation using different

Table VI. Percent Loss, Apparent First-Order Rate Constants (k_{obs}) and Half-Lives (t 1/2) of Photodegradation of Betamethasone-17 Valerate in Cream and Gel Formulation in the Absence and Presence of Various Photostabilizers

	Cream				Gel			
Stabilizer	% Loss±SD	$k_{obs}\times10^3\pm$SD (min^{-1})	Correlation coefficient	t 1/2 (min)	% loss± SD	$k_{obs}\times10^3\pm$SD (min^{-1})	Correlation coefficient	t 1/2 (min)
Control	49.2±0.92	5.661±0.39	0.999	122.4	42.5±1.64	4.613±0.64	0.998	150.2
TiO_2	17.78±1.24	1.637±0.48	0.995	423.3	7.2±0.98	0.6237±0.37	0.999	1111
Vanillin	27.6±1.36	2.69±0.21	0.998	257.6	13.8±1.44	1.237±0.48	0.996	560.2
BHT	31.0±1.22	3.093±0.61	0.999	224	21.9±1.60	2.059±0.73	0.996	336.57

n=5

techniques. Vanillin and butylhydroxy toluene may act as radical scavengers and thus provide stabilization. Titanium oxide exerts a photoprotective effect by light scattering. All the three photostabilizers show promising results in stabilizing the drug against light in the cream and gel formulations, i.e., 33.5–42.5% with titanium dioxide, 21.6–28.7% with vanillin and 18.2–21.6% with butyl hydroxytoluene as compared to unprotected formulations (Table VI). The photostabilization achieved in this investigation is greater than that achieved with 2-phenylbenz-imidazole-5-sulphanic acid and chlorocresol (4,6). This could be attributed to the greater shielding effect of the photostabilizers used in this study and also to the differences in the formulation composition and light source employed.

CONCLUSION

The photodegradation of betamethasone-17 valerate is influenced by factors such as solvent dielectric constant, buffer concentration, ionic strength, formulation characteristics, and adjuvants. The degradation reactions follow first-order kinetics and result in the formation of three major photodegraded products. The rate of photodegradation increases with a decrease in the solvent dielectric constant due to the relatively nonpolar character of the compound and the nature of the excited species involved. On the other hand, an increase in the concentration and ionic strength of phosphate buffer leads to a decrease in the rate of photodegradation probably as a result of the deactivation of the excited species. The compound can be effectively stabilized against UV light in cream and gel formulations by using photostabilizers like titanium dioxide, vanillin, and butyl hydroxytoluene.

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Conflicts of interest The authors declare no conflicts of interest.

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