J. Pharm. Pharmacol. 1979, 31: 400–402 Received July 31, 1978

# The stability of betamethasone-17-valerate in semi-solid bases

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The stability of betamethasone-17-valerate in semi-solid bases has been investigated. Emphasis has been placed on the stability problems which could arise upon dilution of proprietary preparations by the use of model systems. Betamethasone-17-valerate has been shown to decompose to betamethasone-21-valerate and betamethasone alcohol. Quantitation of the decomposition was by direct densitometry on thin layer chromatographic plates. The decomposition was found to be an apparent first order process and to depend on the diluent used and its concentration. Attempts were also made to relate the rate of decomposition to the pH of the base used, and to stabilize the products.

Corticosteroid-17-α-monoesters are unstable and in the presence of acid or base, they readily rearrange to the corresponding 21-monoesters (Gardi et al 1963). The resultant products are generally less active than the parent compounds. Betamethasone-21-valerate, for example, has one fifteenth of the activity of the 17-valerate (McKenzie & Atkinson 1964). If conversion to the less active product takes place in formulated products, the change could be of clinical significance for those skin conditions for which the concentration of betamethasone-17-valerate is limiting. We have investigated the stability of betamethasone-17-valerate ointment (Betnovate) after dilution by various ointment bases.

## MATERIALS AND METHODS

Methanol, sodium hydroxide, ethanol, phosphoric acid, hydrochloric acid, chloroform, ethyl acetate and tetrazolium blue were laboratory grade chemicals obtained from British Drug Houses Chemicals Ltd. E. Merck aluminium sheets precoated with silica gel 60 were used throughout (0·25 mm, 20 × 20 cm).

Betamethasone-17-valerate and betamethasone-21-valerate were gifts from Glaxo Ltd., betamethasone alcohol was obtained from the British Pharmacopoeia Commission. 0·1% w/w Betamethasone-17-valerate ointment (Betnovate Ointment, Glaxo Ltd.) was purchased. Other materials were hydrocortisone, emulsifying ointment (Evans), white soft paraffin (Marcarthys Ltd.), Plastibase 50W (Squibb).

### *Preparation of ointments*

The same procedure was used for each ointment. Weighed amounts of betamethasone ointment and the diluent were transferred to a glass plate and thoroughly mixed with a stainless steel spatula. The product was then stored in a constant temperature water bath. To minimize error arising from prolonged temperature equilibration leading to uneven temperature profiles in the ointment bulk, only 3·3 g quantities were stored in each ointment pot.

After transfer to the water bath and 5 min equilibration time, one sample was removed and assayed for the 17-valerate. All subsequent assays were expressed as a percentage of this concentration and storage times were relative to this first sample.

### *Analysis of steroid*

An amount of ointment containing the equivalent of 2·5 mg betamethasone-17-valerate was accurately weighed in a 25 ml glass tube. 10 ml of 1% HCl in 95% ethanol was added and the tube heated in a water bath with intermittent gentle shaking of the contents for 1 min, cooled in an ice bath for at least 1 h, filtered through Whatman No. 42 paper and the filtrate collected in a 20 ml volumetric flask. The residues were returned to the tube and the extraction repeated with more solvent. The filtrates were combined, 0·6 ml of a 0·5% w/v hydrocortisone in acidified ethanol added, and the volume made up to 20 ml using the additional solvent to wash the residues. Extracts if not assayed immediately, were stored in the dark at 4 °C.

A set of six standard solutions containing 0·015% hydrocortisone and betamethasone-17-valerate at concentrations ranging from 0·0025% to 0·0138% were prepared. Twelve solutions (six standard solutions and six test solutions) were applied in 40 μl quantities to separate spots on one thin layer plate and developed over 15 cm in a filter paper lined tank. 200 ml of a 1:1 v/v chloroform–ethyl acetate mixture was used as the mobile phase. Following

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development the plate was air dried and sprayed with alkaline tetrazolium blue reagent B.P.

The colour intensity were measured by densitometry (620 nm) using a Joyce-Loebl Chromoscan. Each spot was integrated 10 times and the average reading taken. The peak ratio of the 17-valerate to the hydrocortisone was calculated for each solution and a calibration curve of peak ratio to concentration of the 17-valerate plotted. Test concentrations were read off the calibration curve which was constructed for each plate.

*pH measurement of the ointments* was obtained by weighing 2 g of ointment into a beaker to which 30 ml of double distilled water was added. The beaker was heated in a water bath and the molten ointment shaken for 10 min, cooled and the pH of the aqueous phase measured. Six replicates were measured for each ointment system.

## RESULTS AND DISCUSSION

Comparison with authentic specimens by thin layer chromatography showed that in the systems studied, betamethasone-17-valerate ($R_F$ 0·219) initially rearranges to betamethasone-21-valerate ($R_F$ 0·454). Subsequently hydrolysis with the formation of betamethasone ($R_F$ 0·129) takes place. The $R_F$ value of hydrocortisone was 0·077.

Any assay method for following the decomposition of betamethasone-17-valerate must therefore be able to discriminate between the three compounds. Colorimetric methods such as those described by Graham et al (1978) are unsuitable without a preliminary separation step. Although the Lewbart-Mattox method described by Chafetz et al (1974) can be used to assay the 17-valerate in the presence of the 21-valerate, the presence of betamethasone alcohol during the decomposition makes the method unsuitable. In our procedure we observed that during the extraction procedure, the use of non-acidified alcohol led to the formation of betamethasone-21-valerate so hydrochloric acid was added which stopped decomposition during the extraction process. Hydrocortisone was a suitable internal standard. There was no interference from ointment bases. With the assay method on betamethasone ointment, a mean recovery (n = 6) of 98·6% of the label claim with s.d. 2·19% was obtained.

In the preparations studied the decomposition of betamethasone-17-valerate followed an apparent first-order process. The temperature dependence of the reaction can be seen in Table 1 which gives the results for the decomposition of the 17-valerate in a system of 3 parts of the 17-valerate ointment and one part emulsifying ointment B.P. A plot of the logarithm of the observed rate constant against the reciprocal of the absolute temperature gave a straight-line showing that the reaction follows the Arrhenius equation. The activation energy as calculated from the regression line by the method of least squares was found to be 94·56 KJ per mol and the pre-exponential or frequency factor was found to be $1{\cdot}07 \times 10^{16}\ h^{-1}$.

Table 1. The effect of temperature on decomposition of betamethasone-17-valerate in a 3:1 mixture of betamethasone ointment and Emulsifying Ointment B.P.

| Temp./°K | Observed rate const ($h^{-1}$) |
|---|---|
| 293·0 | 0·159 |
| 295·5 | 0·221 |
| 298·0 | 0·274 |
| 303·0 | 0·553 |

To study the effect of alteration in diluent ratio on the stability of betamethasone-17-valerate, three dilutions of the ointment with emulsifying ointment B.P. were made at 3:1, 2:1, 1:1 and the observed rate constants ($h^{-1}$) were respectively 0·221, 0·336, 1·016. Thus the higher the amount of emulsifying ointment the more rapid the decomposition. To rationalize this observation, the pH of the ointment systems were measured (see Table 3). Emulsifying ointment is more alkaline than betamethasone ointment, and increasing the ratio of emulsifying ointment raises the pH of the product.

These results indicate that the decomposition of the 17-valerate is base-catalysed, an observation consistent with the fact that acidification of the solvents during extractions stabilized the product. However storage of the acidified solutions at room temperature indicated that the 17-valerate is also subject to acid catalysed hydrolysis but at a rate much smaller than base catalysed hydrolysis. When stored at 4 °C the acidified solutions showed no detectable decomposition after 48 h.

The data using Plastibase as the diluent indicate that a pH near that of the betamethasone-17-valerate ointment in itself does not ensure stability (Tables 2 and 3). A relatively slow rate of decomposition ($3 \times 10^{-3}\ h^{-1}$) was observed using a 3:1 ratio of betamethasone ointment to Plastibase. When the ratio was altered to 1:1, the decomposition rate increased over 150 fold ($4{\cdot}74 \times 10^{-1}\ h^{-1}$) despite a small decrease in temperature, thus indicating a catalytic species in the Plastibase.

When diluted with white soft paraffin B.P., the product showed an acceptable profile (Table 2).

Table 2. The decomposition of betamethasone-17-valerate in various ointment systems.

| Ointment system | Temperature °C | Observed rate constant ($h^{-1}$) |
|---|---|---|
| Betamethasone ointment: Plastibase 3 : 1 | 25 | $3 \times 10^{-3}$ |
| Betamethasone ointment: Plastibase 1 : 1 | 22·5 | $4{\cdot}74 \times 10^{-1}$ |
| Betamethasone ointment: white soft paraffin 1 : 1 | 22·5 | $6{\cdot}13 \times 10^{-5}$ |
| Betamethasone ointment: Emulsifying ointment B.P. 3 : 1 | 22·5 | $2{\cdot}21 \times 10^{-1}$ |
| Betamethasone ointment: Emulsifying ointment B.P. 3 : 1 + phosphoric acid 0·005% | 22·5 | $3{\cdot}85 \times 10^{-3}$ |

Table 3. The half life and the time taken for 10% decomposition for betamethasone-17 valerate in various ointment systems.

| | Ointment system (with pH at 20°) | Temperature °C | $t_{10\%}$ (h) | $t_{\frac{1}{2}}$ (h) |
|---|---|---|---|---|
| A. | Betamethasone Ointment (5·6 ± 0·1) Emulsifying ointment (8·9 ± 0·2) Mixture: 3 : 1 6·7 ± 0·1 | 20·0 | 0·663 | 4·360 |
| B. | " | 22·5 | 0·447 | 3·137 |
| C. | " | 25·0 | 0·385 | 2·530 |
| D. | " | 30·0 | 0·191 | 1·254 |
| E. | Betamethasone ointment Emulsifying ointment B.P. (3 : 1) + Phosphoric acid 0·005% | 22·5 | 27·366 | 180·1 (7·5 days) |
| F. | Betamethasone ointment: Emulsifying ointment B.P. (1 : 1) | 22·5 | 0·1037 | 0·686 |
| G. | Betamethasone ointment: Emulsifying ointment B.P. (2 : 1) | 22·5 | 0·3136 | 2·063 |
| H. | Betamethasone ointment: White soft paraffin (1 : 1) | 22·5 | 1718·769 | 11308·32 (471·2 days) |
| I. | Betamethasone ointment: Plastibase (R) (1 : 1) | 22·5 | 0·222 | 1·462 |
| J. | Betamethasone ointment: Plastibase (R) (3 : 1) | 25·0 | 35·120 | 231·09 (9·63 days) |

pH values: A 6·7 ± 0·1; E. 6·3 ± 0·1; F. 8·4 ± 0·1; H. 5·6 ± 0·1; I. 5·7 ± 0·1; J. 5·8 ± 0·1; Betamethasone ointment 5·6 ± 0·1; Emulsifying ointment 8·9 ± 0·2; White soft paraffin 5·5 ± 0·1; Plastibase 5·8 ± 0·1.

Since the decomposition of the 17-valerate was clearly base-catalysed, an attempt was made to stabilize betamethasone-17-valerate ointment diluted with emulsifying ointment by the addition of an acid. Phosphoric acid was chosen owing to its triple ionization capability. To minimize the concentration of additive, 0·005% phosphoric acid was used. The results (Table 2) clearly demonstrate the effectiveness of the addition. But the acidified product did not show a marked decrease in pH over the non-acidified preparation of A & E; see footnote to Table 3.

Table 3 summarizes the results of this study by expressing the decomposition of betamethasone-17-valerate in the various systems studied, in terms of half lives ($t_{\frac{1}{2}}$) and in terms of time taken for 10% decomposition ($t_{10\%}$). The Table illustrates the practical implications of the results. With the exception of systems (E, H, and J) all the products had a half life of less than a week.

The results with the Plastibase, show that although a 3 : 1 mixture of betamethasone ointment with Plastibase has a half life of 9·63 days, dilution to any other ratio could significantly alter the stability profile since a 1 : 1 ratio had a half life of 1·46 h.

## CONCLUSION

To obtain maximum activity betamethasone is used as the 17-valerate (McKenzie & Atkinson 1964). This readily isomerizes to the 21-valerate. Our results show that acyl migration occurs readily and that, at temperatures close to normal room temperature, most of the diluted products show significant decomposition after a few hours. This suggests that proprietary formulations should not be diluted unless the combination is known to produce a stable product. The acyl rearrangement appears to be much faster than the hydrolysis reaction. Thus in a 3 : 1 mixture of betamethasone ointment and emulsifying ointment B.P. stored at 25 °C, betamethasone alcohol could only be detected by thin layer chromatography after 5 h. At this point using the observed rate constant (Table 3), it can be shown that about 75% of the betamethasone-17-valerate had decomposed.

*Acknowledgement*

We would like to thank Drs W. J. Irwin and J. B. Kayes for helpful advice.

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