International Journal of Pharmaceutics, 20 (1984) 155–162
Elsevier

IJP 00687

The influence of cyclodextrin complexation on the stability of betamethasone-17-valerate

Finn M. Andersen and Hans Bundgaard

The Royal Danish School of Pharmacy, Department of Pharmaceutical Chemistry AD, DK-2100 Copenhagen (Denmark)

(Received January 17th, 1984)
(Accepted February 28th, 1984)

Summary

The influence of various cyclodextrins on the stability of betamethasone-17-valerate has been investigated in basic aqueous solution at 24°C. The 17-valerate ester undergoes a facile hydroxide ion-catalyzed rearrangement to the less active 21-valerate ester. Whereas α-cyclodextrin did not affect the rate of rearrangement, β-cyclodextrin caused a rate acceleration and γ-cyclodextrin and heptakis-(2,6-di-O-methyl)-β-cyclodextrin resulted in a marked rate retardation. These effects were interpreted in terms of a reaction scheme involving the formation of inclusion complexes with the cyclodextrins and apparent 1:1 complex constants were determined. The reversal in the effects observed for the cyclodextrins is discussed on the basis of microsolvent and conformational effects and it is concluded that inclusion complexation of betamethasone-17-valerate with γ-cyclodextrin or, especially, 2,6-di-O-methylated β-cyclodextrin may be a potentially useful means of increasing the stability of the steroid.

Introduction

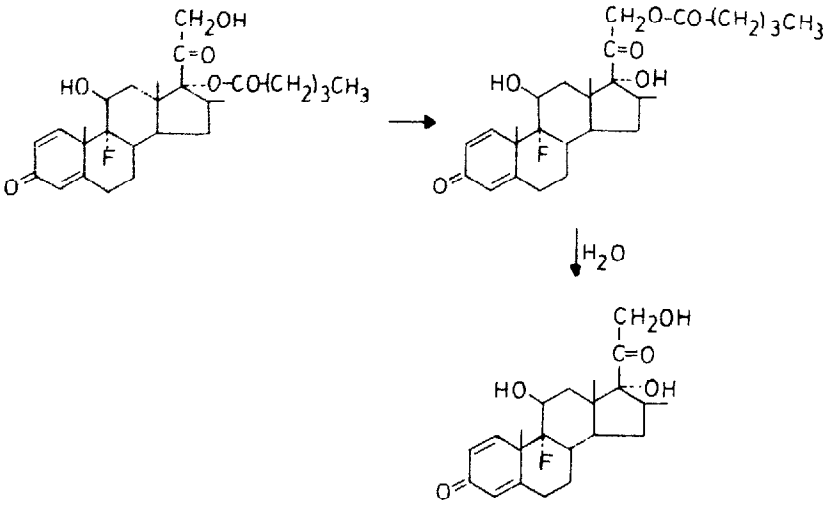
Corticosteroid-17-α-monoesters are unstable and in the presence of acid or base, they may undergo a rearrangement to the corresponding 21-monoesters (Gardi et al., 1963; Vitali and Gardi, 1972; Yip and Li Wan Po, 1979; Bundgaard and Hansen,

Correspondence: H. Bundgaard, Royal Danish School of Pharmacy, Dept. of Pharmaceutical Chemistry AD, 2 Universitetsparken, DK-2100 Copenhagen, Denmark.

1981; Anderson and Taphouse, 1981; Yip et al., 1983). Betamethasone-17-valerate which is available in various formulations for topical application and is several times more active than the 21-isomer (McKenzie and Atkinson, 1964) has recently been subjected to several stability studies. It was shown that in some extemporaneously diluted ointments, the half-life of the 17-valerate may be only a few hours at room temperature (Yip and Li Wan Po, 1979; Ryatt et al., 1982). A basic pH favours the isomerization of the 17-valerate ester to the 21-isomer but the pH does not appear, however, to be the only factor influencing the stability since ointments diluted with Plastibase are highly unstable despite having a pH near that of the more stable undiluted ointment (Yip and Li Wan Po, 1979).

In aqueous solutions of pH 0.5–8 the overall degradation of betamethasone-17-valerate was shown to proceed entirely through an irreversible rearrangement to the 21-valerate ester followed by hydrolysis of the latter to yield betamethasone (Scheme 1) (Bundgaard and Hansen, 1981). The acyl group migration from C_{17} to C_{21} is subject to both specific acid and base catalysis as well as to catalysis by water, the pH–rate profile for the rearrangement showing a minimum at pH 3.5 (Bundgaard and Hansen, 1981).

A recent report has shown that betamethasone-17-valerate as well as other corticosteroids form inclusion complexes with cyclodextrins in water and in the solid state (Uekama et al., 1982). In the present work the influence of various cyclodextrins on the rate of degradation of betamethasone-17-valerate in aqueous solution was investigated with the purpose of exploring the possibility of improving the stability of the steroid by inclusion complexation.



Scheme 1

Materials and Methods

Apparatus

For high-performance liquid chromatography (HPLC) a Waters Model 6000A

pump, a Waters Lambda-Max Model 480 detector and a column (250 mm × 4 mm i.d.) packed with LiChrosorb RP-8 (7 μm particles) (E. Merck, Darmstadt, F.R.G.) were used. Measurements of pH were done at the temperature of study using a Radiometer Type PHM 26 instrument.

Materials

Samples of betamethasone-17-valerate and betamethasone-21-valerate were kindly provided by Glaxo, Middlesex, U.K. Betamethasone and α-cyclodextrin were purchased from Sigma Chemicals, St. Louis; β- and γ-cyclodextrin were gifts from Dumex, Copenhagen. Heptakis-(2,6-di-O-methyl)-β-cyclodextrin was prepared by methylating β-cyclodextrin with dimethyl sulphate as described by Szejtli et al. (1980) and was purified by repeated recrystallization from water.

Kinetic measurements

All rate studies were performed at 24°C in 0.01 M borate buffer solutions of pH 9.00 containing varying concentrations of the cyclodextrins. The reactions were initiated by adding 100 μl of an ethanolic stock solution of betamethasone-17-valerate (about 2.3×10^{-3} M) to 10 ml of the buffer solution. At appropriate intervals samples were taken and analyzed for remaining 17-ester as well as for 21-ester and free betamethasone by the HPLC assay previously described (Bundgaard and Hansen, 1981). Pseudo-first-order rate constants for the disappearance of betamethasone-17-valerate (k_{obs}) were determined from the slopes of linear plots of the logarithm of residual ester against time.

Results and Discussion

Cyclodextrins (CyD) or cycloamyloses are cyclic and toroid-shaped oligosaccharides containing 6(α-CyD), 7(β-CyD) or 8(γ-CyD) α(1,4)-linked glucose units. They are able to form inclusion complexes with various compounds either in the solid phase or in aqueous solution and have recently received considerable attention in the area of pharmaceutical formulation, e.g. for improving aqueous solubility, chemical stability or bioavailability of various drugs (for reviews, see Saenger, 1980; Uekama, 1981; Szejtli, 1982).

To explore the possibility of improving the stability of betamethasone-17-valerate by inclusion complexation with various cyclodextrins the rate of degradation of the steroid was measured in an aqueous borate buffer (pH 9.00) in the presence of varying amounts of the cyclodextrins. For all solutions studied the disappearance of betamethasone-17-valerate displayed strict first-order kinetic behavior. The decrease of betamethasone-17-valerate was in all cases accompanied by the formation of 21-valerate in stoichiometric amounts as revealed by HPLC analysis. Thus, the interaction of the 17-valerate ester with the cyclodextrins does not influence the mechanism of degradation, this being exclusively a 17 → 21 acyl group migration (Scheme 1) as described previously (Bundgaard and Hansen, 1981).

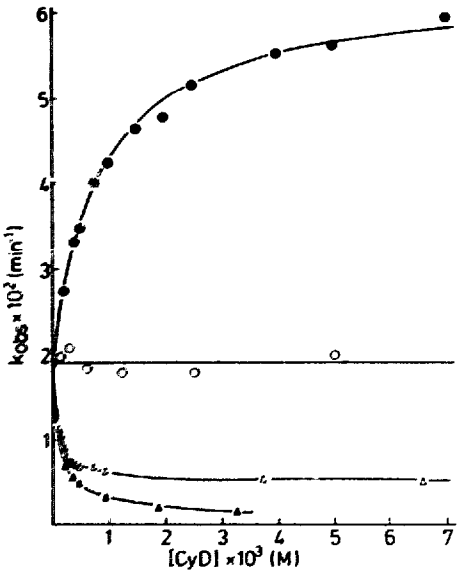


Fig. 1. The effect of various cyclodextrins on the pseudo-first-order rate constant for the degradation of betamethasone-17-valerate in aqueous solution of pH 9.00 at 24 °C. The points are experimental whereas the full lines are constructed from Eqn. 1. Key: ○, α-cyclodextrin; ●, β-cyclodextrin; △, γ-cyclodextrin; ▲, heptakis-(2,6-di-O-methyl)-β-cyclodextrin.

Fig. 1 shows the effect of cyclodextrin concentration on the observed pseudo-first-order rate constants for the loss of betamethasone-17-valerate. It is readily evident that β-CyD accelerates the rate of degradation whereas γ-CyD as well as 2,6-O-dimethylated β-CyD have a pronounced stabilizing effect. In contrast, α-CyD does not exhibit any significant effect on the stability of the steroid. Except in the latter case, k_{obs} is not a linear function of the concentration of added (excess) cyclodextrin, but rather it asymptotically approaches a minimum or maximum value with increasing CyD concentration. This saturation behaviour is characteristic of reactions which proceed through a complex prior to the rate-determining step and may be accommodated by the reaction mechanism illustrated in Scheme 2:

$$\begin{array}{ccc} B_{17} + CyD & \overset{K}{\rightleftharpoons} & B_{17}-CyD \\ \downarrow k_1 & & \downarrow k_2 \\ B_{21} & & B_{21} \end{array}$$

Scheme 2

where B_{17} and B_{21} represent betamethasone-17-valerate and -21-valerate, respectively. B_{17}-CyD the inclusion complex between the drug and the cyclodextrin under the present experimental conditions, k_1 and k_2 are the pseudo-first-order rate constants for the degradation of uncomplexed and complexed 17-valerate, respectively, and K is the apparent formation constant for the complex. From this 1 : 1 complexation scheme the following rate expression may be derived (Griffiths and

Bender, 1973a):

$$k_{obs} = \frac{(k_2 - k_1)[CyD]}{1/K + [CyD]} + k_1 \quad (1)$$

Rearrangement of Eqn. 1 gives:

$$k_{obs} - k_1 = -\frac{(k_{obs} - k_1)}{K[CyD]} + (k_2 - k_1) \quad (2)$$

The rate data of Fig. 1 were plotted according to Eqn. 2 and straight lines were obtained (an example is shown in Fig. 2). From the slope and intercept of those plots values of K and k_2 were obtained. The data are shown in Table 1. The curves shown in Fig. 1 were finally calculated using these data and Eqn. 1 and the good agreement observed between the experimental results and the curves demonstrates that Scheme 2 adequately describes the degradation kinetics.

Based on solubility studies, Uekama et al. (1982) recently determined the apparent 1 : 1 complex formation constants for betamethasone-17-valerate to be 302 (α-CyD), 2990 (β-CyD) and 9850 (γ-CyD) M^{-1} at 25 °C. Apparently, the larger the CyD cavity, the more favorable is the fit of the steroid ester.

The lacking effect of α-CyD on the stability of betamethasone-17-valerate may most likely be ascribed to its poor complexing ability. The strength of the inclusion complexes is, however, not the only factor involved. Thus, the rate effect of β-CyD is quite opposite that of γ-Cyd and the 2,6-di-O-methylated β-CyD derivative. The accelerating (non-covalent catalytic) or decelerating effect observed upon CyD inclusion complexation may arise from a microsolvent effect derived from the relatively apolar properties of the microscopic CyD cavity and/or conformational effects derived from the geometrical requirements of the inclusion process (cf. Griffiths and Bender, 1973a; Bender and Komiyama 1978). To evaluate the importance of the microsolvent effect the rate of degradation of the 17-valerate ester was determined at pH 9 in borate buffers containing varying amounts of 2-propanol. A

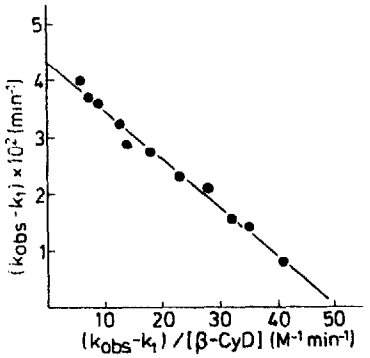


Fig. 2. Plot of the rate data in Fig. 1 for the β-cyclodextrin system according to Eqn. 2.

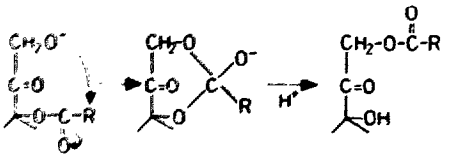
TABLE 1

RATE CONSTANTS AND COMPLEX FORMATION CONSTANTS FOR BETAMETHASONE-17-VALERATE AND VARIOUS CYCLODEXTRINS (AT pH 9.00 AND 24°C) *

Cyclodextrin	K (M^{-1})	k_2 (min^{-1})	k_1/k_2
α-CyD			1.0
β-CyD	1.2×10^3	0.063	0.30
γ-CyD	1.2×10^4	0.0050	3.80
2,6-di-O-methyl β-CyD	7.8×10^3	0.00086	22.1

* $k_1 = 0.019\ min^{-1}$.

seen from Fig. 3, 2-propanol causes a marked rate deceleration. Consequently, a microsolvent effect may be implicated but evidently, this does not explain the reversal in the effect of β-CyD and γ-CyD. A plausible mechanism of the acyl group migration involves a cyclic ortho ester as an intermediate, formed by a nucleophilic attack by a C_{21}-alkoxide ion upon the C_{17}-ester carbonyl moiety (Scheme 3)



Scheme 3

(Bundgaard and Hansen, 1981). From this mechanism a number of different ways can be imagined by which the inclusion complexation may affect the rate of ester rearrangement, e.g. via a conformational effect which fixes the C_{21}-hydroxymethyl group in a position facilitating attack at the C_{17} acyl moiety or, in the case of the rate deceleration, inclusion of the C_{17}-acyl group within the CyD cavity affording protection against the attack from the C_{21}-hydroxyl group. No firm explanation for the different effect of the cyclodextrins can be offered. It is interesting to note,

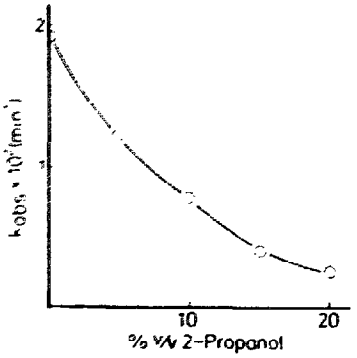
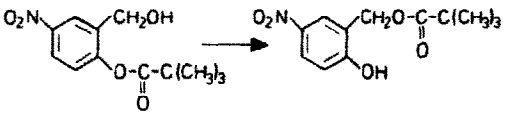


Fig. 3. The effect of 2-propanol concentration on the rate of degradation of betamethasone-17-valerate in aqueous borate buffer solution of pH 9.00 at 24°C.



Scheme 4

however, that in a similar intramolecular transesterification involving 2-hydroxymethyl-4-nitrophenyl trimethylacetate (Scheme 4) α-CyD was found to accelerate the rate of rearrangement whereas β-CyD inhibited the reaction (Griffiths and Bender 1973b). Conformational effects were advanced to explain these observations.

In conclusion, the results obtained demonstrate that the base-catalyzed rearrangement of betamethasone-17-valerate to the 21-valerate ester occurring in aqueous solution can be depressed by γ-CyD and 2,6-di-O-methylated β-CyD. Due to the strong complexes formed with these cyclodextrins the rate-decelerating effect is pronounced even at very low CyD concentrations (cf. Fig. 1). Thus inclusion complexation of betamethasone-17-valerate with these cyclodextrins may be a potentially useful means of increasing the stability of the steroid but further studies are needed to decide whether the effect is also manifestable in the case of topical formulations. In this respect, it is interesting to note that cyclodextrin inclusion complexation of various steroids has been reported to result in enhanced percutaneous absorption (Fujinaga et al., 1982).

References

Anderson, B.D. and Taphouse, V., Initial rate studies of hydrolysis and acyl migration in methylprednisolone-21-hemisuccinate and 17-hemisuccinate. J. Pharm. Sci., 70 (1981) 181–186.

Bender, M.L. and Komiyama, M., Cyclodextrin Chemistry, Springer-Verlag, Berlin and New York, 1978.

Bundgaard, H. and Hansen, J., Studies on the stability of corticosteroids. VI. Kinetics of the rearrangement of betamethasone-17-valerate to the 21-valerate ester in aqueous solution. Int. J. Pharm., 7 (1981) 197–203.

Fujinaga, T., Uemura, Y., Hirayama, F., Otagiri, M. and Uekama, K., Improvements of some pharmaceutical characteristics of various steroidal drugs by cyclodextrin complexation. J. Pharm. Dyn., 5 (1982) s–11.

Gardi, R., Vitali, R. and Ercoli, A., Derivati di condensazione nelle catena laterale di corticosteroidi. Nota III. Preparazione e reazioni dei 17-monoesteri. Gazz. Chim. Ital., 93 (1963) 431–450.

Griffiths, D.W. and Bender, M.L. Cycloamyloses as catalysts. Adv. Catalysis. 23 (1973a) 209–261.

Griffiths, D.W. and Bender, M.L., Orientational catalysis by cyclohexaamylose. J. Am. Chem. Soc., 95 (1973b) 1679–1680.

Ryatt, K.S., Feather, J.W., Mehta, A., Dawson, J.B. Cotterill, J.A. and Swallow, R.S., The stability and blanching efficacy of betamethasone-17-valerate in emulsifying ointment. Br. J. Dermatol., 107 (1982) 71–76.

Saenger, W., Cyclodextrin inclusion compounds in research and industry. Angew. Chem. Int. Edn., 19 (1980) 344–362.

Szejtli, J. (Ed.), Proceedings of the First International Symposium on Cyclodextrins, Budapest, 1981, D. Reidel Publishers, Dordrecht, Holland 1982.

Szejtli, J., Liptak, A., Jodal, I., Fugedi, P., Nanasi, P. and Neszmelyi, A., Synthesis and ^{13}C-NMR spectroscopy of methylated beta-cyclodextrins. Starch, 32 (1980) 165–169.

Uekama, K., Pharmaceutical applications of cyclodextrin complexations. J. Pharm. Soc. Jap., 101 (1981) 857–873.

Uekama, K., Fujinaga, T., Hirayama, F., Otagiri, M. and Yamasaki, M., Inclusion complexations of steroid hormones with cyclodextrins in water and in solid phase. Int. J. Pharm., 10 (1982) 1–15.

Vitali, R. and Gardi, R., Hydrolysis of corticosteroid 17,21-alkylorthoesters in buffered medium. An improved synthesis of 17-monoesters. Il Farmaco, Ed. Sci., 27 (1972) 818–828.

Yip, Y.W. and Li Wan Po, A., The stability of betamethasone-17-valerate in semi-solid bases. J. Pharm. Pharmacol., 31 (1979) 400–402.

Yip, Y.W., Li Wan Po, A. and Irwin, W.J., Kinetics of decomposition and formulation of hydrocortisone butyrate in semiaqueous and gel systems. J. Pharm. Sci., 72 (1983) 776–781.