

Research paper

Interactions between bendroflumethiazide and water-soluble polymers. III. Chemical degradation

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Abstract

Solid dispersions of bendroflumethiazide (BFMT) in polyethylene glycol 6000 (PEG) and Poloxamer 188 were stressed by heating at various temperatures between 22 and 55°C, under either 0 or 75% relative humidity (RH). In solid dispersions at 75% RH as well as in aqueous solution, BFMT hydrolyzed as expected. However, BFMT in the solid dispersions hydrolyzed even at 0% RH. A maximum in hydrolysis was observed at 25 and 13 $\mu\text{mol}\cdot\text{g}^{-1}$ for PEG 6000 and Poloxamer 188, respectively. After a lag time of 10 days, hydroflumethiazide (HFMT) was detected in both solid dispersions of BFMT. HFMT is formed by the reaction of the hydrolysis product of BFMT with formaldehyde, which is a degradation product of the polymers. High humidity promotes this reaction. © 1997 Elsevier Science B.V.

Keywords: Solid dispersion; Hydrolysis; Availability of water; Degradation; Polyethylene glycol; Poloxamer; Bendroflumethiazide; Hydroflumethiazide; Formaldehyde

1. Introduction

Bendroflumethiazide (BFMT, (*RS*)-3-phenylmethyl-3,4-dihydro-6-trifluoromethyl-2*H*-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide [CAS 73-48-3]) hydrolyzes to 5-trifluoromethyl-2,4-disulfoamoyl-aniline (TFSA) and phenylacetaldehyde. Mollica et al. [1,2] already described the reversible hydrolysis for the parent compound hydrochlorothiazide. Frontini and Mielck [3] detected and isolated an unknown product in stressed solid dispersions of BFMT in polyethylene glycol 6000 (PEG 6000) and Poloxamer 188. This product was identified as hydroflumethiazide (HFMT)

which is the condensation product of TFSA with formaldehyde. Formaldehyde must have been generated by the polymers in such a degradation reaction under stress.

The aim of this study was to investigate the kinetics of the hydrolysis of BFMT and of the formation of HFMT in solid dispersions in PEG 6000 and in Poloxamer 188. Based on the results of factorial design studies [4], only those factors relevant for degradation were to be studied, i.e. a drug concentration of 3% (w/w), a series of different temperatures and two highly differing relative humidities, i.e. 0 and 75% RH.

2. Materials and methods

BFMT, PEG 6000 and Poloxamer 188 were supplied as described in Part I of this series of papers [5]. TFSA was obtained as described in Part II [4]. All other reagents were of analytical or HPLC grade.

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HPLC was performed as previously reported [3]. Two different samples of the same solid dispersions were analysed in triplicate.

Karl-Fischer titration was performed with a Radiometer apparatus (ABU 80, TTT 60 and PHM 62, Radiometer, Copenhagen, Denmark) using Hydranal® and Titrant 5 as reagents (Riedel de Haën, Seelze, Germany). Four different samples of the respective polymers were investigated.

Solid dispersions of BFMT and TFSA in each one of the polymers were prepared according to the solution method described in Part I [5] and dried 24 h at < 15 hPa. All solid dispersions were amorphous as determined by X-ray diffraction. To stress the samples climatically, the relative humidity (RH) was kept constant using P₂O₅ for 0% RH, and a saturated NaCl solution with excess salt as described by Nyqvist [6] for 75% RH. The hygrostatic glass chambers were placed into incubators (B 5050 E, Heraeus, Hannover, Germany), which were set to 22, 35 and 45°C and the actual temperatures of which (Table 1) were controlled every 3 days.

Rate constants for first-order kinetics were calculated without weighting, by linear regression of the logarithms of the residual concentrations versus time.

3. Results and discussion

Hydrolysis of BFMT up to about 30 mol%, i.e. 25 $\mu\text{mol} \cdot \text{g}^{-1}$, was observed in solid dispersions in spite of a RH of 0% as shown in Fig. 1 for PEG 6000.

After about 15 days, a steady state was observed. This can be explained by the limited amount of water which may be strongly bound to the polymer considering the drying procedure. By Karl-Fischer titration, we determined for PEG 6000 0.20 ± 0.05 and for Poloxamer 188 $0.16 \pm 0.01\%$ (w/w) water, i.e. 111 ± 28 and $89 \pm 6 \mu\text{mol} \cdot \text{g}^{-1}$, respectively.

Carstensen [7] demonstrated that in a similar system, the quantity of drug hydrolyzed in the steady state depends only on the amount of free water at the start. The temperature may influence the rate of the reaction,

Table 1

Estimated rate constants, 1k [min^{-1}], for the hydrolysis of BFMT in stressed solid dispersions (3% w/w) in PEG 6000 and in Poloxamer 188 at different temperatures and at 75% RH

Temperature		1k constant \pm S.D. [min^{-1}]	
[K]	[°C]	PEG 6000	Poloxamer 188
294.8	21.8	$3.8 \cdot 10^{-6} \pm 0.26 \cdot 10^{-6}$	$2.0 \cdot 10^{-6} \pm 0.21 \cdot 10^{-6}$
308.0	35.0	$1.2 \cdot 10^{-5} \pm 0.071 \cdot 10^{-5}$	$9.0 \cdot 10^{-6} \pm 0.26 \cdot 10^{-6}$
318.0	45.0	$2.5 \cdot 10^{-5} \pm 0.054 \cdot 10^{-5}$	n.i.

n.i., not investigated.

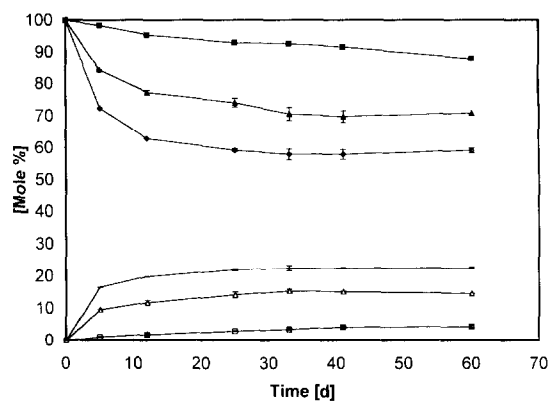


Fig. 1. Hydrolysis of BFMT in solid dispersions in PEG 6000, stressed at different temperatures and 0% RH (P₂O₅), to TFSA. Means of triplicate analyses of two different samples and range of single values. (■) BFMT 22°C, (▲) BFMT 35°C, (◇) BFMT 45°C, (□) TFSA 22°C, (△) TFSA 35°C, (—) TFSA 45°C.

but not the level of the steady state. Fig. 2 shows the results of stressed solid dispersions in PEG 6000 and in Poloxamer 188 at the steady state.

Since the calculated amounts of water consumed by hydrolysis seem to reach a plateau at about 45°C, we conclude that the quantity of free water increases up to that temperature. At higher temperature, apparently no more water can be mobilized, i.e. hydrolysis of the drug is possible up to a maximum of 25 and 13 $\mu\text{mol} \cdot \text{g}^{-1}$ for PEG 6000 and Poloxamer 188, respectively, in spite of only 0% RH.

According to Carstensen [7], Leeson-Mattocks kinetics, i.e. pseudo-zero order kinetics, should be expected in solid dispersions of BFMT since this drug is only slightly soluble in water. However, we did not observe the corresponding time course as shown in Fig. 3 for solid dispersions in PEG 6000.

In spite of the steady state at 0% RH, the hydrolysis of BFMT at 75% RH may be fitted to a first-order kinetic model for the temperatures studied here. The estimated rate constants, 1k , are summarized in Table 1.

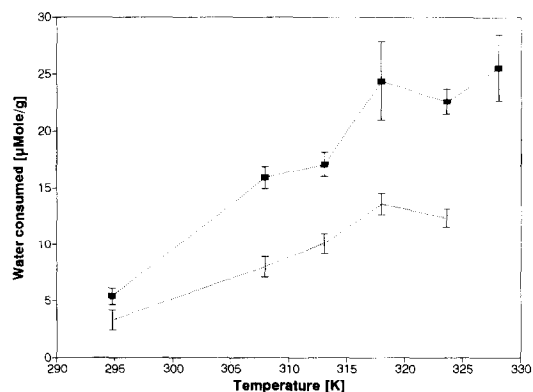


Fig. 2. Amount of water at steady state consumed for the hydrolysis of BFMT in solid dispersions in PEG 6000 and in Poloxamer 188, stressed at different temperatures and 0% RH (P₂O₅). (Means \pm S.D., $n = 4$). (■) PEG 6000, (□) Poloxamer 188.

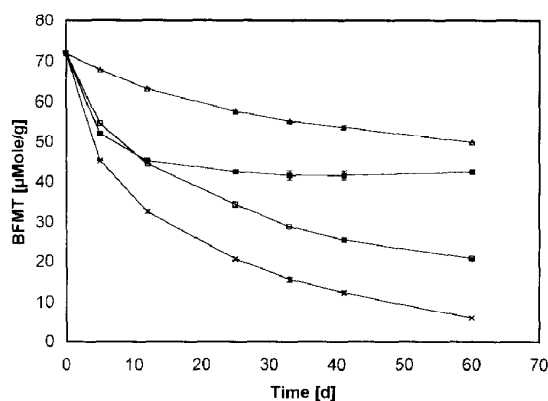


Fig. 3. Hydrolysis of BFMT in solid dispersions in PEG 6000, stressed at different temperatures and relative humidities. Means of triplicate analyses of two different samples and range of single values. (■) 0% RH, 45°C; (☆) 75% RH, 45°C; (□) 75% RH, 35°C; (△) 75% RH, 22°C.

The values of the rate constants are similar to those obtained for a solution of BFMT in water as confirmed by separate trials (results not shown), which in turn correspond to those reported by Mollica et al. [2]. Since BFMT is very stable in the solid state, we can conclude that an increase of the solubility by the solid dispersion is correlated to a decrease of stability by hydrolysis similar to a solution in water. The main hydrolysis product TFSA is able to react with formaldehyde to form hydroflumethiazide (HFMT) as previously reported [8]. Formaldehyde is generated by degradation of the polymers under stress conditions. The kinetics of the reaction we observed in the present study confirm this fact as shown in Fig. 4 for PEG 6000 at 50°C and 75% RH.

Since an appreciable amount of formaldehyde is necessary to react with TFSA, a lag time of about 10 days was observed.

The reaction between formaldehyde and TSFA seems

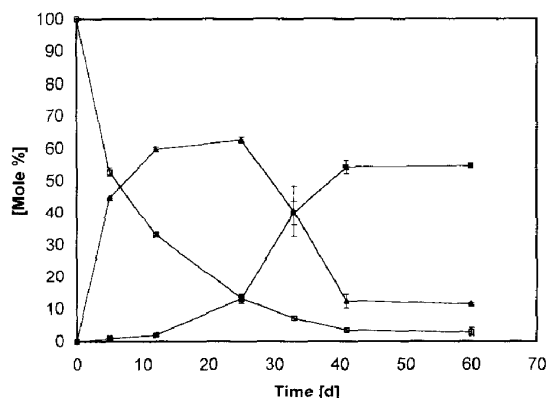


Fig. 4. Hydrolysis of BFMT to TFSA and formation of HFMT in solid dispersions of BFMT in PEG 6000, stressed at 50°C and 75% RH. Means of triplicate analyses of two different samples and range of single values. (□) BFMT, (■) HFMT, (▲) TFSA.

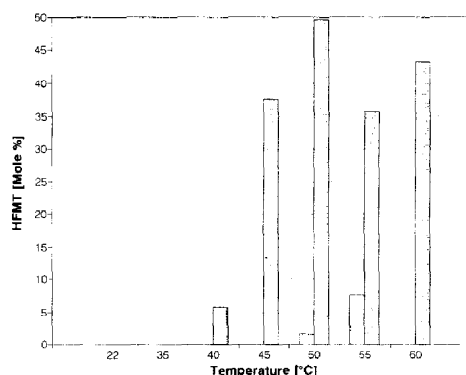


Fig. 5. Amount of HFMT detected in solid dispersions of BFMT in PEG 6000 after 60 days at different stress conditions. Means of triplicate analyses of two different samples. (□) 0% RH, (■) 75% RH.

to be faster than that between the hydrolysis product phenylacetaldehyde and TFSA, since the amount of TFSA decreases rapidly, and that of HFMT correspondingly increases, within 25 and 40 days up to the steady state which should be expected since the reactions are reversible. About 50 mol% HFMT can be formed by this way. A high relative humidity is required for the reaction as shown in Fig. 5 for solid dispersions in PEG 6000 at the steady state.

None or very small amounts of HFMT have been detected at 0% RH in spite of a high temperature. The assumption that water is needed for the hydrolysis of BFMT in the first step to form TFSA cannot be confirmed as the exclusive explanation.

We performed tests with 3% (w/w) solid dispersions of TFSA in PEG 6000 and in Poloxamer 188 and expected a lower amount of HFMT to be formed at 75% RH, since hydrolysis of HFMT should occur at such a high humidity. Fig. 6 illustrates the surprising results.

It is obvious that a high humidity promotes the reaction of TFSA with formaldehyde. This can only be explained by the assumption that water is necessary for

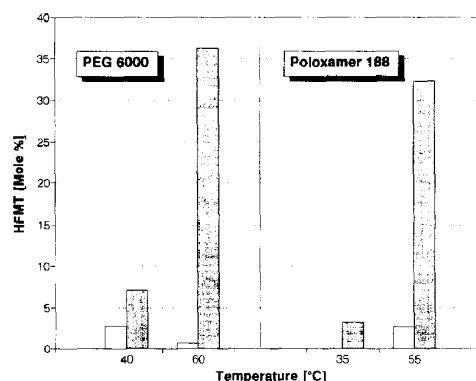


Fig. 6. Amount of HFMT detected in solid dispersions of TFSA after 60 days under different stress conditions. Means of triplicate analyses of two different samples. (□) 0% RH, (■) 75% RH.

the formation of formaldehyde by degradation of the polymers. The high quantity of formaldehyde causes the increase in the amount of HFMT in spite of its hydrolysis. Further studies are required to elucidate the mechanism.

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