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Formation of formaldehyde in polyethyleneglycol and in poloxamer under stress conditions

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Abstract

Bendroflumethiazide (BFMT) hydrolyses to 5-trifluormethyl-2,4-disulfoamoylaniline (TFSA) and phenylacetaldehyde. In solid dispersions of BFMT in polyethylene glycol 6000 (PEG) and poloxamer 188 (PPEO) an unknown product was detected, isolated and identified as hydroflumethiazide (HFMT). HFMT was produced by the reaction of TFSA with formaldehyde being formed from PEG and from PPEO under stress conditions.

Keywords: Degradation; Polyethylene glycol; Poloxamer; Formaldehyde; Bendroflumethiazide; Hydroflumethiazide

Bendroflumethiazide (BFMT) is a potent, lipophilic diuretic drug, which hydrolyses to 5-trifluoromethyl-2,4-disulfamoyl-aniline (TFSA) and phenylacetaldehyde. Solid dispersions of BFMT in polyethylene glycol 6000 (PEG) were proposed by Corrigan et al. (1979) and Desphande and Agrawal (1982) to enhance the dissolution rate of BFMT in water, however, the chemical stability of such dispersions was not investigated.

We prepared solid dispersions of BFMT in PEG (Lutrol^{TM} E 6000, BASF, Ludwigshafen, Germany, lot no. 65-4593) and in Poloxamer 188 (PPEO, Lutrol F 68, BASF, Ludwigshafen, Germany, lot no. 95-1072), a polyethylene oxide-polypropylene oxide block polymer. Their chemical stability under stress conditions was investigated by HPLC according to a method in the literature (Hassan, 1983). After stressing the dispersions at 60°C and 75% relative humditiy (R.H.), an unknown degradation product was detected by HPLC although the method was not able to separate the peak of TFSA very well from that of the unknown product.

For identification of this product a solid dispersion of BFMT in PEG was prepared by melting both compounds at about 80°C, mixing, and allowing to cool at room temperature. After this procedure only BFMT was detected by HPLC. The solid dispersion was stressed at 70°C and 100% R.H. for 36 days. Firstly, the polymer was separated from BFMT, TFSA and the unknown product by SEC (LKB 2137-system, 650 × 26 mm filled with Sephadex G-15, Mol. Wt cut-off 1500,

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Pharmacia, Freiburg, Germany) using water as eluent. After dissolving the three compounds in methanol/water 1:3, the unknown product was isolated by LC (Lobar A column, 240 × 10 mm, filled with LiChroprep RP 18, E. Merck, Darmstadt, Germany; Büchi 681 pump and UV detector, Büchi AG, Flawil, Switzerland) using water/methanol 95:5 as eluent at a flow rate of 7.8 ml min^{-1}.

This unknown product was identified by elementary analysis, UV, IR, MS, ^{1}H-NMR and ^{13}C-NMR as hydroflumethiazide (HFMT). A comparison with a standard (Sigma Chemicals) confirmed these results (Frontini, 1993). The elementary analysis in addition confirmed that the trifluormethyl group did not undergo hydrolysis, as described by Christoffersen and Christoffersen (1984).

HFMT is the product of a reaction of TFSA with formaldehyde. The latter cannot be formed by degradation of TFSA or of phenylacetaladehyde (Cattaneo, 1934). Since methanol was used as solvent for the separation by LC, an artefact could not be excluded a priori, but reproduction of the experiments with acetonitrile as solvent and as eluent using a new HPLC method (Frontini, 1993) confirmed the existence of HFMT in the solid dispersion. To support the contention that HFMT was produced by the reaction of TFSA and PEG, a solid dispersion of 3% TFSA in PEG was stressed for 27 days at 60°C and 75% R.H. and analysed by HPLC as above. Only TFSA and HFMT were detected. For further quantitative experiments a new HPLC assay was developed and validated (Frontini and Mielck, 1992), which was able to separate all three compounds: BFMT, HFMT and TFSA.

Solid dispersions of 3% BFMT and of 3% TFSA, respectively, both in PEG and in PPEO were tested under different conditions. The results are shown in Table 1.

From these data it is evident that HFMT was not formed and detected below a critical temperature of about 45°C at 0% R.H. and of 40°C at 75% R.H. The amount of detectable HFMT formed above this temperature decreases after about 50 days. Two explanations are given for this decrease: (i) HFMT, like BFMT, hydrolyses to form TFSA until an equilibrium between BFMT, HFMT, and TFSA is established; and (ii) PEG and PPEO both form complexes with BFMT, HFMT, and TFSA (Frontini, 1993). The presence of these complexes cannot be detected by this analytical method as yet, nor has a method for quantitation been found. In addition, the results in Table 1 highlight the importance of water for the formation of HFMT. In spite of the hydrolysis of HFMT to TFSA, high contents of water in the solid dispersions appear to promote the degradation of the polymer to formaldehyde. We postulate an oxidative decomposition of the polyoxyethylene chains which is effective at the higher temperature. This reaction needs water to form ethylene glycol in the first step, which may then be oxidized to formaldehyde. This would also explain the lower contents of HFMT ob-

Table 1
Content of hydroflumethiazide (mol%) in solid dispersions of 3% BFMT and of 3% TFSA in PEG 6000 and in poloxamer 188 after 2 months stress under different conditions

Temperature (°C)	PEG				PPEO			
	0% R.H.		75% R.H.		0% R.H.		75% R.H.	
	BFMT	TFSA	BFMT	TFSA	BFMT	TFSA	BFMT	TFSA
22	0.0	n.i.	0.0	n.i.	0.0	n.i.	0.0	n.i.
35	0.0	n.i.	0.0	n.i.	0.0	0.0	2.4 ± 0.1	3.2 ± 0.2
40	0.0	2.8 ± 0.2	5.8 ± 0.1	7.1 ± 0.3	0.0	n.i.	6.1 ± 0.0	n.i.
45	0.0	n.i.	37.6 ± 2.0	n.i.	0.0	n.i.	18.1 ± 0.0	n.i.
50	1.5 ± 0.1	n.i.	49.6 ± 5.0	n.i.	1.9 ± 0.3	n.i.	19.0 ± 0.8	n.i.
55	7.6 ± 0.5	n.i.	35.8 ± 4.1	n.i.	2.6 ± 0.0	2.7 ± 0.4	24.5 ± 0.4	32.3 ± 4.4
60	n.i.	0.7 ± 0.1	43.2 ± 1.6	36.4 ± 1.4	n.i.	n.i.	n.i.	n.i.

Results are means of two samples ± $R/2$; n.i., not investigated.

served in solid dispersions with PPEO, since the polypropylene blocks af this polymer are not able to form formaldehyde.

From the maximum amount of HFMT determined in solid dispersions of TFSA in PEG, about 2400 ppm of formaldehyde may be calculated, which must have been formed under stress at 60°C and 75% R.H. Further studies are to be conducted in order to elucidate the mechanism of the formation of formaldehyde, and to quantify more closely the critical stress conditions.

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