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Research article

Interactions between bendroflumethiazide and water soluble polymers. I. Solubility of bendroflumethiazide in water from solid dispersions and formation of associates under climatic stress

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Abstract

Polyvinylpyrrolidone K 25 decreases the solubility of bendroflumethiazide (BFMT) in water at 25°C at concentrations below 2% (w/v) at pH 7.1 and below 1% (w/v) at pH 1.95, and enhances it above these concentrations, while polyethylene glycol 6000 and Poloxamer 188 continuously enhance this solubility in concentrations up to 5% (w/v). Associates are postulated to be formed, when solid dispersions of BFMT in these polymers are stressed climatically. The amount of BFMT bound in such associates is simply and quickly quantified with an acceptable experimental error by HPLC. © 1997 Elsevier Science B.V.

Keywords: Solid dispersion; Associate; Solubility; Polyethylene glycol; Polyvinylpyrrolidone; Poloxamer; Bendroflumethiazide

1. Introduction

Many new therapeutically active compounds are only sparingly soluble in water. One of the various possibilities to enhance both dissolution rate and solubility, the latter at least temporarily, lies in solid dispersions of such compounds in highly hydrophilic polymeric excipients, as already comprehensively reviewed by Chiou and Riegelman [1]. These dispersions are generally prepared with the aim to obtain X-ray-amorphous material.

The polymer used probably in most cases is polyvinylpyrrolidone (PVP) [2], but polyethylene glycols (PEG) have also very frequently been used to prepare solid dispersions.

While many reports deal with the physical stability of such systems, i.e. recrystallisation with subsequent reduction in dissolution rate and in apparent solubility, comparatively little information is available on the chemical stability of drugs in such intimate molecular or colloidal contact with the polymers. Bühler [2] lists favourable as well as unfavourable effects of PVP on the stability of embedded drugs. Craig [3] reports on stability-enhancing effects of PEG.

The formation of complexes between drugs and macromolecules like PVP and PEG is very well known [4]. Molyneux and Frank [5,6] already investigated the interactions between PVP and aromatic compounds in water. These authors emphasized the importance of the reduction of 'icebergs' (clusters) in water by formation of associates. Frank and Evans [7] also concluded that hydrophobic substances like BFMT promote the formation of clusters in water. Ågren and Bäck [8] described the formation of a complex between bendroflumethiazide (BFMT), hydroflumethiazide (HFMT) and human albumin to which the Scatchard

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equation was adapted successfully. Since the term 'complexation' should be used only for clearly reversible and stoichiometrically defined reactions [4], the interactions between BFMT and water soluble polymers would be better described as an 'association'.

More recently, the effect of such polymers and of the concentration of water and the resulting change of their physical state was studied, using reserpine as a model drug [9,10].

Bendroflumethiazide ((*RS*)-3-phenylmethyl-3,4-dihydro-6-trifluoromethyl-2*H*-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide [CAS 73-48-3]) is a potent, lipophilic diuretic drug, which hydrolyzes to 5-trifluoromethyl-2,4-disulfoamoyl-aniline (TFSA) and phenylacetaldeyde.

The solubility of BFMT and its parent drug hydroflumethiazide in solid dispersions of PVP of MW 10 000, and PEG of MW 1000–6000 was already investigated by Corrigan and Timoney [11,12], Corrigan et al. [13], and Corrigan [14]. Solid dispersions of different thiazide derivatives in PEG 6000 have been described by Desphande and Agrawal [15]. In all these systems, the apparent solubility of BFMT was enhanced. As an explanation for the enhanced solubility, these authors proposed an inhibition of the recrystallization of BFMT and the formation of a water-soluble complex between the drug and the polymers. Concurrently, Corrigan and Timoney [12], and Corrigan and Holohan [16] observed a decrease of the apparent solubility of HFMT in the presence of very small concentrations of PVP MW 10 000, but not in the presence of PEG with a MW range of 4000–20 000. However, no explanation for this decrease was offered.

No log k/pH profile has been published for BFMT, but from that for hydrochlothiazide elaborated by Mollica et al. [17,18], a similar profile may be expected, showing one minimum at pH 2–3. The development of a stability-indicating HPLC assay [19] confirmed sufficient stability of BFMT at low pH.

In the present investigation, interactions between the lipophilic drug bendroflumethiazide and different hydrophilic polymers will be studied with respect to 'association' (Parts I and II) and the chemical stability (Part III) in solid dispersions.

2. Materials and methods

Micronized bendroflumethiazide (BFMT, CAS 73-48-3), lot no. BF6916 was supplied by Glaxo (London, UK).

5-Trifluoromethyl-2,4-disulfoamoylaniline (TFSA) was either a reference material (BP-CRS, lot no. 1341) or was prepared by hydrolysis of BFMT as described by Hassan [22] with a purity of 99.6% as determined by using the BP-CRS material.

Polyvinylpyrrolidone, PVP K 25, (Kollidon® 25, lot no. 08-6805) with a molecular weight between 28 000 and 34 000 $g \cdot mol^{-1}$, polyethylene glycol, PEG 6000, (Lutrol® E 6000, lot no. 65-4593) with a molecular weight between 5000 and 7000 $g \cdot mol^{-1}$ and polyethylene oxide/polypropylene oxide block polymer, Poloxamer 188, (Lutrol® F 68, lot no. 95-0172) with a molecular weight of 7910 $g \cdot mol^{-1}$ (ethylene oxide 80.7% w/w) were supplied from BASF (Ludwigshafen, Germany). All other reagents were of analytical or HPLC grade.

Solid dispersions of BFMT and of TFSA were prepared under precisely controlled process conditions according either to the solution method or to the melting method (only PEG and Poloxamer) described by Chiou and Riegelman [1]. In the first method, either BFMT or TFSA and one of the polymers (2–20 g total mass) were dissolved in a mixture of 15 ml methanol and 85 ml dichloromethane. The solvent was removed by evaporating (Büchi RE 121, Büchi, Flawil, Switzerland) at 80 ± 1°C, 100–200 rpm, 600–100 hPa, adjusted depending on the extent of foaming in order to achieve fast evaporation. No methanol was found after drying as measured by GC in the PEG and Poloxamer dispersions. Alternatively the solution of BFMT and PVP K 25 (4.75 g total mass) in a mixture of methanol and water (80 + 20 ml) was freeze dried (Freeze dryer, J.H. Schraden, Göttingen, Germany) as described by Akbuğa et al. [20]. Subsequently, final drying took place in a vacuum oven at 25°C and < 15 hPa; 260 ppm methanol were found after drying as measured by GC.

In the second method, the required amounts of BFMT or TFSA and of the respective polymers were weighed into a 100-ml glass beaker, heated to 80°C on a water bath, and stirred until a clear melt had formed. The melt was poured onto an aluminium foil to obtain a thin layer, and allowed to cool at room temperature. After about 1 h, the solidified dispersions were milled with a pestle and mortar.

The concentrations of BFMT were 3 and 20% in PVP K 25, 3 and 10% in PEG 6000 and Poloxamer 188, those of TFSA were 1, 3, 10 and 15% in PVP K 25 and 3% in PEG 6000. All solid dispersions were analyzed by X-ray diffractometry and were found to be amorphous.

For climatic stressing, samples of solid dispersions were stored in constant humidity chambers, obtained by saturated salt solutions with excess salt [21], located within incubators at the conditions: 60.2°C and 53% RH (NaBr) for dispersions in PVP, and 48.2°C and 53% RH (NaBr) for those in PEG 6000 and in Poloxamer 188. The samples were stressed between 34 and 110 days.

SEC was performed with a LKB 2137 system, 650 × 26 mm filled with Sephadex G-15 (cut-off molecular weight at 1500) using water as eluent (Pharmacia, Freiburg, Germany).

HPLC analysis was performed using a column of Nucleosil® 100 C18, 5 μm (Vertex column 250 × 4 mm, Knauer, Berlin, Germany) kept in a oven at 40°C. The eluent was MeOH/H_2O 1 + 1 at 1.0 ml·min^{-1}. Two methods were used, differing mainly in the hardware. In both methods the samples were dissolved in a mixture of buffer pH 2.0 ± 0.1 containing salicylamide as IS and methanol (500 ml buffer made up to 1000 ml with methanol). The pH of 2.0 is necessary to prevent any degradation of BFMT during the time of analysis [19].

The limits of detection and quantitation were 0.6 and 1.2 μg·ml^{-1} for BFMT and 0.5 and 1.0 μg·ml^{-1} for TFSA, respectively. The accuracy was 99.3 ± 0.8% for BFMT and 102.4 ± 3.7% for TFSA. No significant difference was found between solutions containing polymers or not. The reproducibility was 0.1 μg·ml^{-1} ($n = 6$) for BFMT and 0.3 μg·ml^{-1} ($n = 8$) for TFSA.

Method A was carried out with an HPLC-pump SF 400 (Kratos Analytical, Ramsey, NJ, USA), a UV-detector BT 8200 set at 271 nm (Biotronik, Maintal, Germany) and an integrator SP 4100 (Spectra-Physics, San José, CA, USA).This method was performed according to Hassan [22] with salicylamide as IS. Method B was carried out with a Marathon autosampler (Marathon, Spark Holland, Emmen, The Nederlands), an HPLC-pump SF 400 (Kratos Analytical, Ramsey, NJ, USA), a UV-detector BT 8200 set at 271 nm (Biotronik, Maintal, Germany) and a Siemens PC 16/16 (Siemens, Fürth, Germany) with the software CHROM + 2.04 (Laboratory Technologies, Wilmington, MA, USA).

The solubility of BFMT in the presence of polymers was investigated at pH 7.1 (0.01 M phosphate buffer) and at pH 1.95 (0.02 M KCl/HCl buffer). An excess of BFMT was put into well-closed flasks containing the polymer solution and shaken in a thermostated water bath (Heto 01 TE 623, Heto, Birkeröd, Denmark) at 25 ± 0.02°C for 48 h according to Agrawal and Desphande [23]. Samples were taken in duplicate after 3, 24, and 48 h, and filtered (0.2 μm). Then 5% methanol was added to avoid precipitation of BMFT, and the mixtures were analysed by UV-spectrophotometry at 271 nm (PMQ II, Zeiss, Oberkochen, Germany). The reference was a solution of the polymer, treated by the same procedure.

Dialysis tests were performed at pH 2 (0.02 M KCl/HCl buffer + MeOH 1 + 1) in the diffusion cell of a Sartorius apparatus (Resorptionsmodell SM 16750, Sartorius, Göttingen, Germany) with a membrane of 40 cm^2 providing a cut-off at 12 000 Dalton (Cellulose membrane D-0655, Sigma-Aldrich Chemie, Deisenhofen, Germany). The low pH was chosen to sufficiently suppress hydrolysis of BFMT [17–19], and the high concentration of methanol was indispensable to achieve dissolution of the samples for to the HPLC method above [19]. Donor and acceptor compartments were filled each with 3.0 ml solution. Samples of 50 μl were analyzed by HPLC in triplicate using method B.

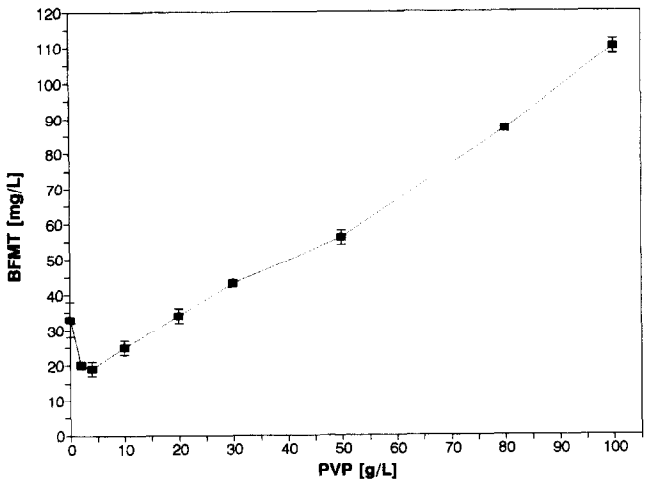

Fig. 1. Influence of PVP K25 on the apparent solubility of BMFT in water at 25°C and pH 7.1 after 3 h. (Means ± S.D., $n = 4$).

UV-differential analysis was performed with a Beckmann Model 35 spectrophotometer (Beckmann Instruments, Fullerton, USA) using the spectra from 190 to 360 nm.

3. Results and discussion

The solubility of micronized BFMT at 25°C and at pH 7.1 was found to be 33 ± 5 mg·l^{-1} ($n = 4$), and at pH 1.95 it was 21 ± 1 mg·l^{-1} after 3 h, and 23 ± 1mg*l^{-1} after 48 h ($n = 4$). These results correspond with those of Agrawal and Desphande [23].

Figs. 1 and 2 show the effect of PVP K 25 on the apparent solubility of BFMT in water at pH 7.1 and at pH 1.95 after 3 h and 48 h, respectively.

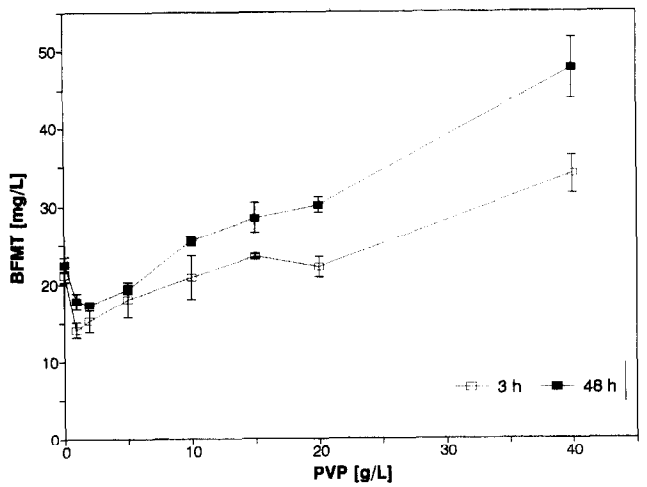

Fig. 2. Influence of PVP K25 on the apparent solubility of BMFT in water at 25°C and pH 1.95 after 3 h (□) and after 48 h (■). (Means ± S.D., $n = 4$).

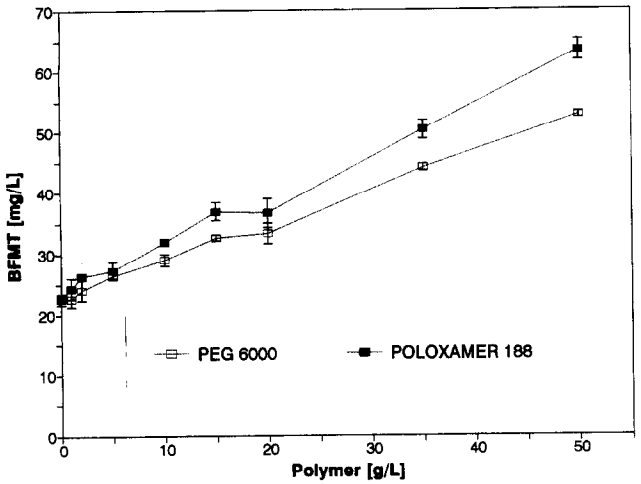

Fig. 3. Influence of PEG 6000 (□) and Poloxamer 188 (■) on the apparent solubility of BMFT in water at 25°C and pH 1.95 after 24 h. (Means ± S.D., $n = 4$).

These results confirm the experimental evidence that PVP (in this case PVP K 25) up to a concentration of about 2% (w/v) reduces the apparent solubility of BFMT, as was observed by Corrigan and Timoney [11] and Corrigan and Holohan [16] for HFMT dispersed in PVP of 10 000 molecular weight. Fig. 2 highlights the fact that this decrease is less distinct after 48 h. Gibaldi and Weintraub [24] already observed a similar profile for the dissolution of salicylic acid in the presence of PVP, which was attributed to a very slow dissolution rate; the depression in solubility had vanished after 336 h, so that the profile became linear. The fast hydrolysis of BFMT, especially at pH 7.1, does not allow such a long test time, but the results after 48 h at pH 1.95 support this explanation.

However, the effects of aromatic compounds and of electrolytes on the coacervation of PVP, as was observed by Sekikawa et al. [25,26], provide a hypothesis for explanation of the decrease of the apparent solubility of BFMT observed for low concentrations of PVP K 25: BFMT as an acidic aromatic compound could promote the coacervation of PVP K 25 in the vicinity of the BFMT particles. This will prevent an equilibrium to be established during the experiment. Such coacervates dissolve slowly at low concentrations of PVP, but rapidly at high ones [26]. This phenomenon explains the reduction in solubility at low concentrations of PVP similar to that reported for salicylic acid. Such a phenomenon was not observed for the systems BFMT/PEG 6000 and BFMT/Poloxamer 188 as shown in Fig. 3.

Poloxamer 188 as a tenside solubilizes BFMT significantly better then PEG 6000. The nearly linear increase in total concentration of BFMT dissolved with increasing concentration of either of these polymers confirms the results of Corrigan and Timoney [12] and suggests the formation of an associate between BFMT and the polymers.

Differential UV-spectrophotometry was not able to detect a complex in solid dispersions of BFMT, but since very small concentrations in solution are requested for this technique, which could promote dissociation of weak associates, the results may not be decisive [4].

However, losses, determined by HPLC, in the molar sum of educt and products after stressing solid dispersions of BFMT in water-soluble polymers at high temperature and humidity led to an indirect confirmation and quantitation of such associates.

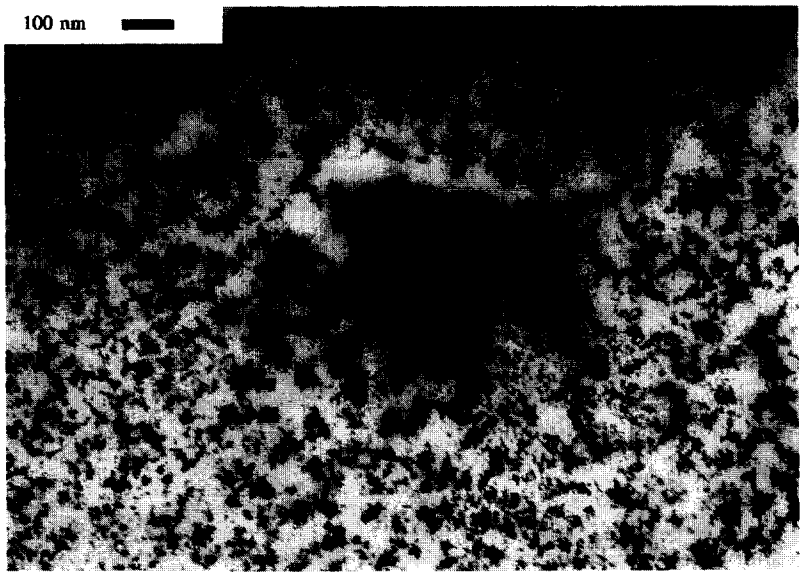

Fig. 4. TEM of the methanol extract from the silica of the HPLC-precolumn after freeze fracturing (110 000 ×).

Table 1
Amount of BFMT and TFSA before and after stressing of solid dispersions in PVP K25 as detected by HPLC

Sample no.	Before stressing			After stressing		
	BFMT [mg·g^{-1}]	TFSA [mg·g^{-1}]	Sum [mol%]	BFMT [mg·g^{-1}]	TFSA [mg·g^{-1}]	Sum [mol%]
1	31.2 ± 0.8	0	103.7	30.1 ± 0.5	0.1 ± 0.0	100.3
2	31.2 ± 0.8	0	103.7	7.8 ± 1.0	5.1 ± 0.4	46.8
3	31.2 ± 0.8	0	103.7	7.8 ± 1.0	5.1 ± 0.4	46.8
4	30.6 ± 0.2	0.4 ± 0.1	103.8	2.3 ± 0.6	9.6 ± 0.3	48.7
5	27.9 ± 0.5	1.6 ± 0.1	99.8	13.6 ± 0.1	7.6 ± 0.2	81.4
6	27.9 ± 0.5	1.6 ± 0.1	99.8	13.6 ± 0.1	7.6 ± 0.2	81.4

Means of triplicate analyses of 4 samples (before stressing) ± S.D. and of two samples (after stressing) ± R

These experiments employing climatic stress had been conducted to investigate the chemical stability of BFMT, which will be reported and discussed in Part III. Although the HPLC-analysis was accurate (see above), the difference between the original amount of BFMT and the molar sum of degradation products in such highly stressed dispersions was significant. Firstly, an unknown product was isolated in solid dispersions prepared by the melting method in PEG 6000 and in Poloxamer 188 by SEC and LC and identified as HFMT [27] but the amount of this product was not sufficient to account for the underestimation. Since during SEC, BFMT and its degradation products were detected by HPLC in the first fraction—i.e. in the fraction eluting the polymer—only in very small amounts, we postulated that the analysis by HPLC was only able to detect the free compounds, but not the associates. The silica material of the HPLC-precolumn was extracted by warm methanol (70°C) and analyzed by UV spectrometry. A strong maximum was seen at 271 nm corresponding to a large amount of BFMT and its degradation products. A direct analysis of this extract by HPLC failed to detect any BFMT or TFSA. The extract was freeze-fractured and photographed by transmission electron microscopy (TEM) at 110 000 × magnification. The picture obtained (Fig. 4) confirmed the macromelecular shape of the associates of BFMT and PVP.

The colloid structures have a diameter between about 20–50 nm. A more exact determination is not possible due to the limit of resolution of the method at about 5 nm, but this diameter corresponds to that of super-helices of PEG as observed by scanning tunneling microscopy (STM) by Yang et al. [28]. This dimension will allow the associates to penetrate into the 60–100 nm pores of the silica and this may explain why HPLC analysis did not detect the associates.

Steady-state dialysis is a good method for separating associates from the free compounds [4]. When the associates in stressed solid dispersions contained within the donor compartment besides free BFMT or TFSA do not dissociate, then after attainment of the steady state the analysis of samples from both donor and acceptor compartment by HPLC should result in the same concentrations of BFMT or TFSA. A plot of concentrations quantified by HPLC in the acceptor versus concentrations in the donor would consequently be a straight line with a slope of 1. Furthermore, no significant differences should be observed between samples with a large difference between the original amount of BFMT and the molar sum of degradation products and those with only a small one.

Table 1 summarizes the amounts determined and the amounts missing in the molar balance for the samples from stressed dispersions of BFMT in PVP. Only solid dispersions in PVP were investigated, because at that time no validated HPLC method was available which could separate TFSA and HFMT, and only in these dispersions in PVP, HFMT was not formed.

Although the balance of some stressed samples differs by up to 55 mol%, Figs. 5 and 6 show for BFMT and TFSA, respectively, that the plot of the concentrations at steady state dialysis is nearly a straight line as predicted.

The slopes are 0.87 ± 0.01 ($r = 0.9997$) for BFMT and 0.94 ± 0.01 ($r = 0.9998$) for TFSA. The difference with the expected slope of 1 may be explained by the fact that HPLC is not an equilibrium system. Particularly at high concentrations, the eluent will set a new equilibrium and consequently higher concentrations will be detected at the donor.

From the results we conclude that after the stressing of solid dispersions, both BFMT and its degradation product TFSA form associates in PVP K 25, PEG 6000 and Poloxamer 188. These associates may be quantified very simply and quickly with an acceptable experimental error by HPLC, as the difference between the molar sum of the detected compounds and the original amount of BFMT.

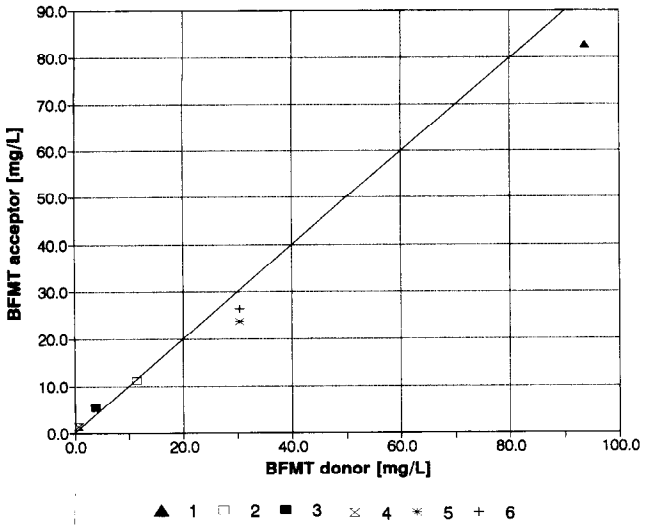

Fig. 5. Steady state dialysis of climatically stressed solid dispersions of BMFT in PVP K25, analyzed by HPLC. Plot of c(BFMT) in the acceptor medium versus c(BFMT) in the donor medium, where the symbols correspond to the sample numbers in Table 1, giving the molar sums of recoverable amounts of BFMT and TFSA by HPLC. Means of triplicate analyses, theoretical straight line with a slope of 1.

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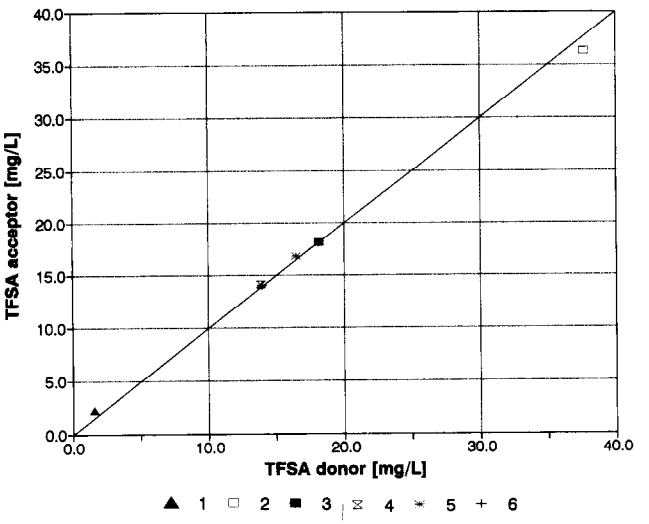

Fig. 6. Steady state dialysis of climatically stressed solid dispersions of TFSA in PVP K25, analyzed by HPLC. Plot of c(TFSA) in the acceptor medium versus c(TFSA) in the donor medium, where the symbols correspond to the sample numbers in Table 1, giving the molar sums of recoverable amounts of BFMT and TFSA by HPLC. Means of triplicate analyses, theoretical straight line with a slope of 1

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