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Thermoanalytical characterization of pseudopolymorphs of sulphadimidine and sulphadimidine–trimethoprim molecular complexes

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Abstract

In recrystallization experiments of sulphadimidine from water, dioxane and their mixtures aimed at preparing the unstable hydrate, a non-stoichiometric solvate with dioxane $C_{12}H_{14}N_4O_2S \cdot \frac{1}{5}C_4H_8O_2$ and a pseudopolymorph with similar X-ray powder diffraction and infrared absorption properties but different thermal behaviour (DSC, TG) were isolated. In co-crystallization experiments of trimethoprim and sulphadimidine, a monohydrate of the respective 1 : 2 molecular complex and a methanol solvate of the equimolecular complex were obtained from aqueous ethanol and anhydrous methanol, respectively. The thermal stability of both pseudopolymorphic complexes is reflected by the high DSC and TG onset temperatures of solvent escape from the crystal lattice ($T_e \approx 163^\circ C$ and $T_e \approx 144^\circ C$, respectively, for water and methanol) and is consistent with the important role of water in the hydrated crystal packing and the very strong hydrogen-bonding interaction of methanol with a sulphonamido oxygen atom in the methanol solvate crystal. © 1998 Elsevier Science B.V.

Keywords: Differential scanning calorimetry; Evolved gas analysis; Pseudopolymorphism; Sulphadimidine; Sulphadimidine-trimethoprim molecular complex; Thermogravimetry; X-ray diffractometry

1. Introduction

At present, sulphadimidine (N^1-(4,6-dimethyl-2-pyrimidinyl)benzenesulphonamide $C_{12}H_{14}N_4O_2S$, SDMD) is one of the most commonly used sulphonamides for the treatment of coccidiosis in lambs and a sustained-release formulation, able to release the drug during four days after a single oral administration, has been recently developed [1]. SDMD is reported to crystallize from methanol as a methanol solvate [2] and from dioxane–water solutions as an unstable hydrate [3]. However, information on the preparation, identification and physicochemical characterization of the last pseudopolymorph is lacking. On account of the influence of water activity in organic solvents–water mixtures on the nature of the crystallizing drug phase [4], many recrystallization experiments of SDMD from water, dioxane and their mixtures of various compositions were carried out. Thermoanalytical methods, i.e. differential scanning calorimetry (DSC), thermogravimetry (TG) and evolved gas analysis (EGA) were applied to identify and characterize the solid phases isolated. X-ray powder diffractometry (XRD), infrared spectroscopy and dissolution rate profiles were used to complement and support the thermoanalytical data. SDMD is also able to form pseudopolymorphs in the complexed state

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with trimethoprim (2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine, TMP), namely a methanol solvate TMP·SDMD·CH_3OH and a hydrate TMP·$(SDMD)_2$·H_2O [5,6]. Since the crystal structures of both molecular complexes were elucidated recently [7,8], the relevant thermoanalytical properties are herein presented and discussed in connection with crystal packing. A comparison of the thermal and structural characteristics of TMP·SDMD·CH_3OH and the methanol solvate of SDMD in the free state, SDMD·CH_3OH [2,9], is also possible.

2. Experimental

2.1. Materials

Commercial SDMD (C. Erba, Italy) was twice recrystallized from ethanol and the polymorphic modification II [6] (m.p. 197.8±0.3°C, $\Delta_{fus}H$=133.7±3.2 J g^{-1} (n=4)) was obtained and used in the following experiments. Commercial TMP (Poli, Italy) was recrystallized thrice from water : ethanol 3 : 7 (v/v) and the polymorphic modification I [6] (m.p. 199.4±0.3°C, $\Delta_{fus}H$=170.2±4.5 J g^{-1} (n=4)) was isolated and used in the following experiments. Other chemicals used were of analytical grade.

2.2. Preparation of samples

Recrystallization of SDMD from solutions of the compositions reported in Table 1 at the respective boiling points were carried out by spontaneous cooling at room temperature or by abrupt freezing to ca. −15°C. The starting, anhydrous SDMD crystal form II and two SDMD pseudopolymorphs, S1 and S2, with distinct thermal behaviour (see in the following) were isolated (Table 1). Sieved samples (75–150 μm) were used for dissolution tests. Co-crystallization of 1.45 g (5 mmol) TMP and 1.39 g (5 mmol) SDMD from 100 ml of methanol gave a 92% yield of the methanol solvate $C_{14}H_{18}N_4O_3$·$C_{12}H_{14}N_4O_2S$·CH_3OH. Co-crystallization of 1.45 g (5 mmol) TMP and 2.78 g (10 mmol) SDMD from 50 ml of ethanol/water 5/5 (v/v) gave an 84% yield of the hydrate $C_{14}H_{18}N_4O_3$·$(C_{12}H_{14}N_4O_2S)_2$·H_2O.

2.3. Thermal analysis

Differential scanning calorimetry (DSC) and thermogravimetry (TG) were performed with a Mettler TA4000 apparatus equipped with DSC 25 and TG 50 cells. Samples were weighed (Mettler M3 microbalance) in open aluminium pans (DSC, 5–8 mg) or

Table 1
Recrystallization products of sulphadimidine (SDMD) from water (W), dioxane (D) and their mixtures (by volume) by spontaneous cooling at room temperature or abrupt freezing to −15°C

Recrystallization solvent	Solvent per SDMD gram (ml)	Product
Water	180	anhydrous SDMD form II
W/D 8/2	28	SDMD pseudopolymorph S2
W/D 7/3 W/D 6/4	20	SDMD pseudopolymorph S1
W/D 5/5 W/D 4/6	8	both SDMD pseudopolymorph S1 and anhydrous SDMD form II
W/D 3/7 W/D 2/8 W/D 1/9	4	anhydrous SDMD form II
Dioxane	4	anhydrous SDMD form II (by cooling at room temperature) SDMD pseudopolymorph S1 (by abrupt freezing to −15°C)

alumina crucibles (TG, 6–10 mg) and scanned from room temperature to 250°C at a heating rate β=10 K min^{-1} under static air. TG runs were also carried out under a nitrogen atmosphere (flow rate 6 l h^{-1}). Evolved gas analysis (EGA) was carried out by using a Du Pont 916 thermal evolution analyzer (TEA) equipped with a hydrogen–air flame ionization detector which is very sensitive to the organic components and gives no indication of inorganic compounds (water, carbon dioxide). Samples weighing 5 mg were heated (8 K min^{-1}) in open aluminium pans, under a nitrogen atmosphere (flow rate 1.8 l h^{-1}), from room temperature to 200°C.

2.4. X-ray powder diffractometry

X-ray powder diffractometry (XRD) was carried out with a computer controlled Philips PW 1800 apparatus over the $2<2\theta<60^\circ$ range (scan rate $1^\circ(2\theta)$ min^{-1}), using a CuK_α radiation monochromatized with a graphite crystal.

2.5. Infrared spectroscopy

Fourier transform infrared (FT-IR) spectra (Nujol mull) were obtained at room temperature on a Perkin-Elmer Model 1605 apparatus using Fourier transformations of 64 scans (resolution 4 cm^{-1}).

2.6. Dissolution tests

The dissolution rate of SDMD was determined in water at 37±0.5°C by adding 1.88 g of anhydrous SDMD or 2.00 g of either S1 or S2 SDMD pseudo-

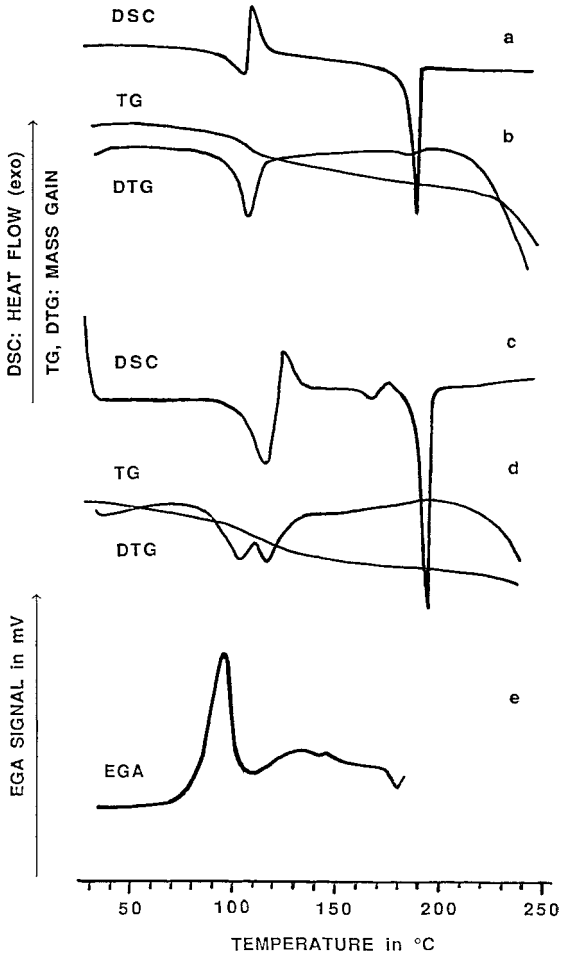

Fig. 1. DSC, TG (under static air) with DTG (1st derivative of TG) and EGA curves of sulphadimidine (SDMD) pseudopolymorphs S1 (from water/dioxane 5/5) and S2 (from water/dioxane 8/2). Key: (a), (b), and (e) S1; (c), and (d) S2.

Table 2
Thermal parameters of sulphadimidine (SDMD) pseudopolymorphs S1 (from water/dioxane 5/5 (v/v) at room temperature) and S2 (from water/dioxane 8/2 (v/v) at −15°C)

Sample	Desolvation endotherm		Crystallization exotherm #1	Fusion endotherm #1		Crystallization exotherm #2	Fusion endotherm #2		
	T_e [a]	T_p [b]	T_p [b]	T_e [a]	T_p [b]	T_p [b]	T_e [a]	T_p [b]	$\Delta_{fus}H$ [c]
S1 [d]	100.1±3.7	113.5±2.7	120.6±4.9				181.2±5.8	192.3±2.2	80±10
S2 [e]	99.8±2.1	115.7±3.4	135.6±9.6	157.9±1.7	168.9±2.7	175.4±4.9		195.0±0.8	87±9

[a] Extrapolated onset temperature (°C).
[b] Peak temperature (°C).
[c] Fusion enthalpy (J g^{-1}).
[d] Mean values±standard deviation (n=12).
[e] Meanvalues±standard deviation (n=5).

polymorph (see Table 1) to 1 l of distilled water in the USP 23 apparatus 2 (paddle stirring element rotated at 100 min^{-1}) [10]. Samples weighing 2.5 ml were withdrawn at appropriate intervals and spectrophotometrically assayed after suitable dilution with distilled water at 262 nm for SDMD content. Each test was performed in triplicate.

3. Results and discussion

The thermal behaviour of S1 (SDMD pseudopolymorph from water/dioxane 5/5 (v/v) at room temperature) and S2 (SDMD pseudopolymorph from water/dioxane 8/2 (v/v) at −15°C) (Table 1) is presented in Fig. 1. The relevant thermal parameters are presented in Table 2. In both cases, desolvation was followed by an exothermal effect which could be ascribed to crystallization of anhydrous SDMD (curves 1a and 1c). The subsequent thermal events, i.e. melting of SDMD form II for S1 (curve 1a) and melting followed by crystallization and melting of SDMD form II for S2 (curve 1c), accounted for the desolvation of S2 to the lower melting SDMD polymorph which, in turn, transformed into SDMD form II. The TG mass losses of S1 (6.8±0.9% as mass fraction (n=7) under static air (curve 1b); 6.1±0.4% as mass fraction (n=4) under nitrogen atmosphere) and S2 (6.1±0.8% as mass fraction (n=4) under static air (curve 1d); 5.1±0.2% as mass fraction (n=4) under nitrogen atmosphere) were, on average, equivalent to the theoretical mass loss associated with dehydration of a presumed SDMD monohydrate $C_{12}H_{14}N_4O_2S{\cdot}H_2O$ (6.1%). The presence of crystal water in S1 and S2 was, however, excluded by Karl Fisher titrimetry. EGA revealed the organic nature of the solvent evolved from S1 (curve 1e) in the temperature range of TG mass loss and the DSC desolvation endotherm. Assuming that dioxane was the unique volatile evolved, a non-stoichiometric dioxane solvate containing ≈0.2 molecules of solvent per SDMD molecule resulted for S1, in agreement with the elemental analysis results for $C_{12}H_{14}N_4O_2S{\cdot}\frac{1}{5}C_4H_8O_2$. XRD distinguished between anhydrous SDMD (Reference Pattern 36-1911 (1995) of the Joint Committee on Powder Diffraction Standards (JCPDS), International Center for Diffraction Data (ICDD) and the SDMD S1 and S2 pseudopolymorphs isolated, and revealed the presence of an anhydrous form in the S1 preparation (Fig. 2).

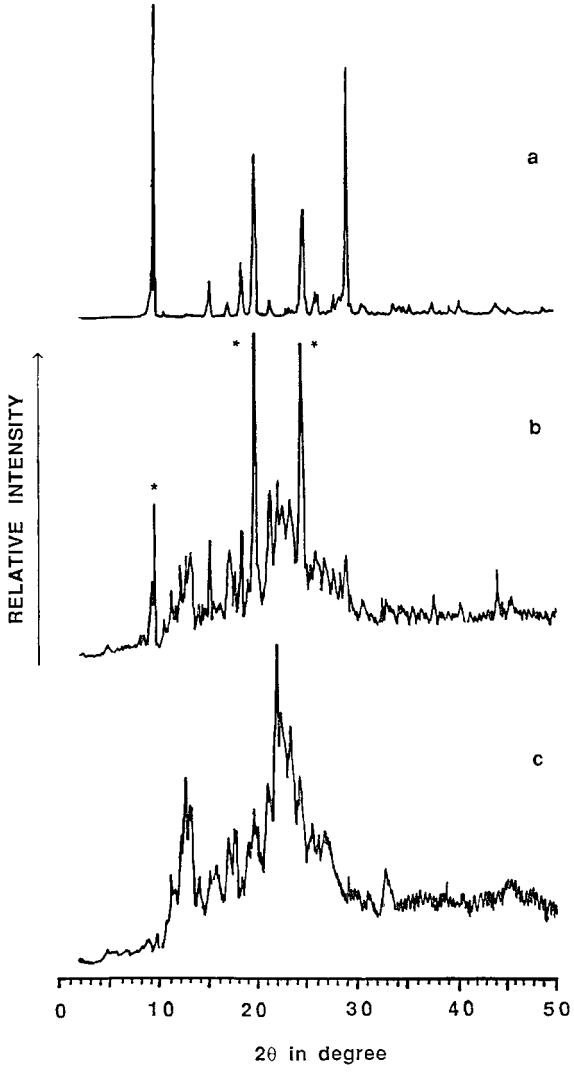

Fig. 2. X-ray powder diffraction patterns of (a) sulphadimidine (SDMD) form II and SDMD pseudopolymorphs (b) S1 (from water/dioxane 5/5) and (c) S2 (from water/dioxane 8/2). The diffraction peaks present in (b) that belong to the anhydrous form (a) are marked with stars.

The partially amorphous character of S1 and S2 preparations accounted for the low fusion enthalpy values of their desolvation products, both composed of SDMD form II (see curves a and c in Figs. 1 and 3 and Table 2). Infrared spectra in the N–H stretch (NH_2+NH) region [11] confirmed the substantial

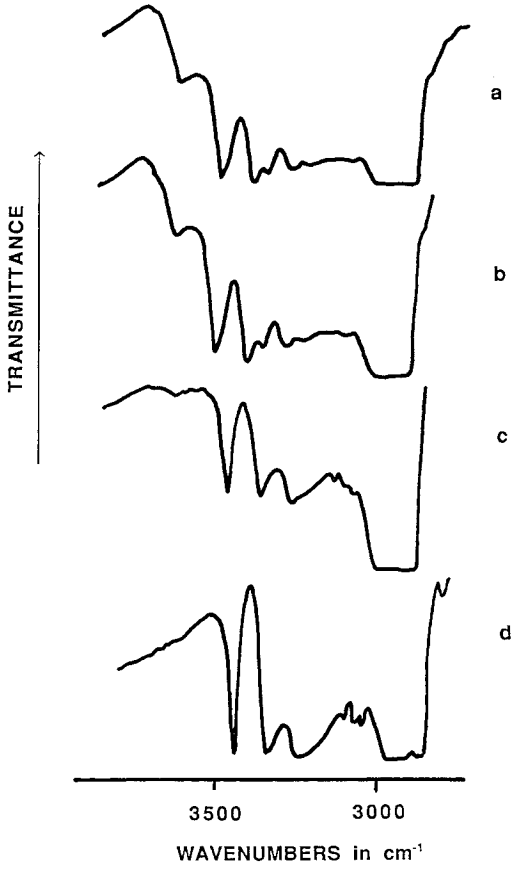

Fig. 3. Infrared spectra (Nujol mull) in the 3800–2900 cm^{-1} region of (d) sulphadimidine (SDMD) form II, SDMD pseudopolymorphs (a) S1 (from water/dioxane 5/5) and (b) S2 (from water/dioxane 8/2), and (c) the desolvation product (in a drying pistol at 150°C and 20 mm Hg for 12 h) of both S1 or S2.

identity of S1 and S2 and the common phase transition to SDMD form II by the heating-induced desolvation (Fig. 3). Dissolution rates of S1 and S2 were markedly faster than that of anhydrous SDMD and confirmed the nature of adducts with water-miscible organic solvents [12], as well as the tendency of SDMD to form supersaturated solutions [3] (Fig. 4). The difference in dissolution rate between S1 and S2 was consistent with the relatively more pronounced amorphous character of S2 relative to S1, as evident from the XRD spectra (see Fig. 2).

The thermal properties of the methanol solvate of the 1 : 1 molecular complex of TMP and SDMD and the hydrate of the 1 : 2 molecular complex of TMP and

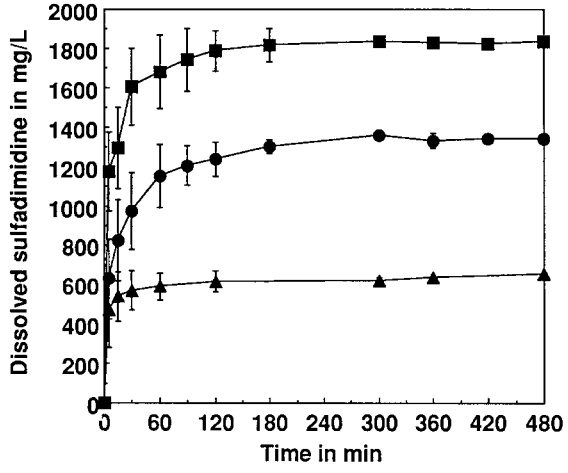

Fig. 4. Dissolution rate profiles in water at 37.0(5) °C of (▲) sulphadimidine (SDMD) form II and (●) SDMD pseudopolymorphs S1 (from water/dioxane 5/5) and (■) S2 (from water/dioxane 8/2). Each point represents the mean of three determinations.

SDMD are presented in Fig. 5. The onset temperature of escape of the solvent from the methanolate complex crystal (T_e=144.2±0.3°C (n=5)) (curves a,b) was distinctly higher than that of the methanolate of SDMD in the free state (T_e≈85°C) [2] and reflected the very strong hydrogen-bonding interaction of methanol with a sulphonamido oxygen atom in the crystal lattice [7] which instead is absent in SDMD·CH_3OH [9]. A similar thermal stability is displayed by the hydrate molecular complex, where the onset temperature of water escape from the crystal lattice (T_e=162.7±0.8°C (n=4)) (curves c and d) was consistent with the important role of the solvent in the stabilization of the crystal structure [8].

4. Conclusions

On recrystallizing SDMD from water-dioxane mixtures, the unstable hydrate reported in the literature [3] was not obtained but a non-stoichiometric dioxane solvate which gives a TG mass loss equivalent to that of the presumed SDMD monohydrate was formed. The possible crystallization of SDMD form II from dioxane confirmed the fast nucleation rate of the anhydrous crystal form [13] which is also displayed in methanolic solution where the SDMD concentra-

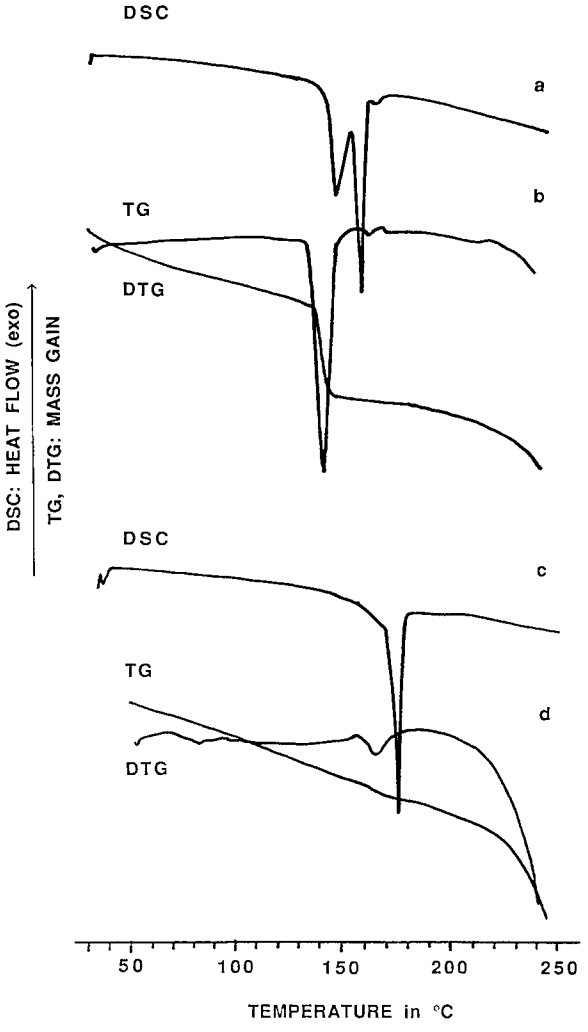

Fig. 5. DSC and TG (under static air) with DTG (1st derivative of TG) of the molecular complexes of (a and b) trimethoprim (TMP) and sulphadimidine (SDMD) methanol solvate TMP·SDMD·CH_3OH and (c and d) TMP·$(SDMD)_2$·H_2O.

tion was a critical factor in driving the crystallization toward anyhdrous SDMD form II rather than SDMD·CH_3OH (very dilute solution). The identity of the physicochemical properties of SDMD recrystallized from ethanol (anhydrous form II) or methanol (supposed to be the methanol solvate, actually the anhydrous form II) reported by Abdel Hadi et al. [14] are hence explained. Other factors are responsible for the differences in bioavalability between the crystal forms tested [14], probably the different crystal habit of anhydrous form II which strongly depends on the recrystallization solvent [2]. SDMD in the complexed state with TMP also forms a methanol solvate TMP·SDMD·CH_3OH [7], where the solvent is involved in much stronger interactions within the crystal lattice than those operating in the SDMD·CH_3OH crystal [9]. Similar strong interactions involving the water of crystallization are present in the monohydrate of the 1 : 2 molecular complex of TMP and SDMD [8] and are evidenced by the rather high temperature of water escape from the crystal lattice.

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References

[1] B. Evrard, L. Delattre, Drug Dev. Ind. Pharm. 22 (1996) 111.
[2] L. Maury, J. Rambaud, B. Pauvert, Y. Lasserre, G. Bergé, M. Audran, J. Pharm. Sci. 74 (1985) 422.
[3] E.H. Northey, The Sulfonamides and Allied Compounds, Reinhold, New York, 1948, p. 31.
[4] H. Zhu, J.W. Grant, Int. J. Pharm. 139 (1996) 33.
[5] L.S. Bernstein, Rev. Infect. Dis. 4 (1982) 411.
[6] G.P. Bettinetti, F. Giordano, Drug Dev. Ind. Pharm. 14 (1988) 431.
[7] G.P. Bettinetti, N. Sardone, Acta Cryst. C53 (1997) 594.
[8] N. Sardone, G.P. Bettinetti, M. Sorrenti, Acta Cryst. C53 (1997) 1295.
[9] J. Rambaud, L. Maury, B. Pauvert, M. Audran, Y. Lasserre, G. Berge, J.-P. Declercq, Acta Cryst. C41 (1985) 133.
[10] The United States Pharmacopeia – The National Formulary, USP 23 – NF 18, Rockville, MD, 1995.
[11] C. Papastephanou, M. Franz, in K. Florey (Ed.), Analytical Profiles of Drug Substances, Vol. 7, Academic Press, USA, 1978, p. 401.
[12] D.J.W. Grant, T. Higuchi, Solubility Behaviour of Organic Compounds, J. Wiley & Sons, New York, 1990, p. 38.
[13] O. Karacsonyi, K. Nikolics, G. Bidlo, Acta Pharm. Hung. 42 (1972) 20.
[14] I. Abdel Hadi, J. Mezosi, G. Kedvessy, J. Morvay, Pharmazie 32 (1977) 791.