DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 14(4), 431-449 (1988)

INTERACTION BETWEEN TRIMETHOPRIM AND SOME SULFA DRUGS

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ABSTRACT

Interaction ability of trimethoprim and sulfa drugs used in pharmaceutical combinations was tested. The preparation of crystalline 1:1 molecular compounds between trimethoprim and sulfametrole, sulfamethoxypyridazine, sulfadimidine is described. Two molecular compounds, with sulfamethoxypyridazine and sulfadimidine, were also isolated as solvates (water and methanol, respectively). No interaction was detected in the case of sulfadiazine, sulfamoxole, and sulfamethopyrazine. Thermal analysis (DSC, TG), X-ray diffractometry, and IR spectroscopy were used for physicochemical characterization. Phase diagrams of each trimethoprim - sulfa drug binary system are reported, comparing experimental to theoretical data from solid-liquid equilibria. The nature of trimethoprim-sulfa drug intermolecular bonding is briefly discussed and the practical consequences of solid molecular compound formation on the pharmaceutical quality of such combinations are outlined.

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INTRODUCTION

Among the physicochemical factors capable of influencing some biopharmaceutical and technological properties of a pharmaceutical solid combination, the possibility of complex formation as a consequence of interaction between the active ingredients is worth considering (1). It is well known that a molecular compound existing in the solid state shows physical characteristics such as particle size and crystal habit, which may influence both surface properties and suspendability (2), dissolution behavior (3), tableting behavior (4), and compatibility (5) of powder materials. These properties often significantly differ from those of the physical mixture of the components. Differences in the thermodynamic properties of a crystalline drug in the free or complexed state can also be observed (6). The equilibrium solubility and dissolution rate, which are often directly related to the physiological activity and availability of the drug, may also be influenced.

Our previous investigations on binary systems involving the antifolate drug trimethoprim, 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine, led to the isolation and characterization of a 1:1 molecular compound with sulfamethoxazole (7), which was also found in commercial and laboratory solid dosage forms (2,8). On the basis of the above considerations, it seemed meaningful to investigate the possible interactions between trimethoprim and the sulfa drugs used in pharmaceutical combinations of therapeutical relevance (9). Thus the present study was designed to explore the behavior of trimethoprim with sulfadiazine, sulfamoxole, sulfametrole, sulfamethopyrazine, sulfamethoxypyridazine and sulfadimidine.

The binary systems of trimethoprim and each of the above sulfonamides were examined mainly by thermal analysis. In order to

properly put into evidence the formation of possible interaction compounds, X-ray diffraction data and IR spectra of the solid phases obtained from trimethoprim and sulfa drug physical mixtures were collected. The possible nature of bonding between trimethoprim and the interacting sulfa drug is also briefly discussed, aiming to focuse some physicochemical and molecular parameters relevant for the interaction. Lastly, some implications of the solid state interaction between the active ingredients on the technological and biopharmaceutical characteristics of solid dosage forms are outlined.

EXPERIMENTAL

Materials - Trimethoprim (TMP) (Poli) was recrystallized three times from water:ethanol 30:70 (form I: mp = 199.4 ± 0.3 °C; ΔHf = 49.4 ± 1.3 kJ/mol) (7). Sulfadiazine (SFD) (Ricerchimica), sulfametrole (SMTR) (Menarini), sulfamethopyrazine (SMP) (Farmitalia - C. Erba), and sulfamethoxypyridazine (SMPD) (Corvi) were used directly. Sulfadimidine (SDMD) (C. Erba), for which different melting points are recorded (10), was twice recrystallized from ethanol and its crystal form and thermodynamic parameters were assessed. Sulfamoxole (SMOS) (Ricerchimica) was twice recrystallized from methanol in order to prepare the high-melting polymorph (11).

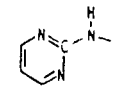
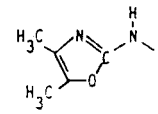
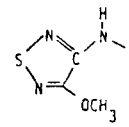
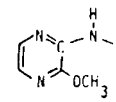
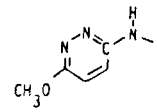
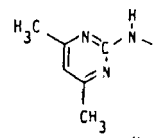
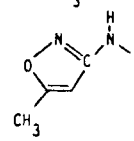
The melting points and heats of fusion of the above sulfonamides and sulfamethoxazole (SMZ), for ease of comparison, are collected in Table 1, together with the respective pK_a values and heterocyclic portions.

The physical mixtures were prepared by mixing lightly and thoroughly the components in a china mortar.

Preparation of molecular compounds - a) 2.88 g of the equimolar physical mixture of SMTR and TMP were recrystallized from 60 ml of

TABLE 1

SOME PHYSICOCHEMICAL AND STRUCTURAL PARAMETERS OF SULFONAMIDES

SULFA DRUG	mp, °C [a]	ΔHf, kJ/mol [a]	pK_a [b]	amino heterocyclic portion [c]
SULFADIAZINE (SFD)	257.6(0.4)	43.7(0.6)	6.4	
SULFAMOXOLE (SMOS)	208.6(0.8)	30.5(1.2)	7.4	
SULFAMETROLE (SMTR)	150.3(0.2)	34.4(0.6)	4.8	
SULFAMETHOPYRAZINE (SMP)	174.6(0.3)	34.2(0.8)	6.1	
SULFAMETHOXYPYRIDAZINE (SMPD)	180.9(0.3)	32.6(0.3) [d]	7.2	
SULFADIMIDINE (SDMD)	197.6(0.1)	36.1(0.3) [e]	7.4	
SULFAMETHOXAZOLE (SMZ)	170.3(0.5)	32.2(0.8) [f]	6.0	

a) (± S.D.), 5 runs. b) From ref. (9). c) For -N=C-N-H bond lengths and angles see refs (12-18). d) In agreement with the value recently assigned to form I (15). e) About 10% higher than the value reported in (19). f) From ref. (7).

95% ethanol. The solid was filtered by suction and dried (drying pistol: 10 mm Hg, 90 °C) to give 2.60 g (90%) of TMP-SMTR ($C_{14}H_{18}N_4O_3.C_9H_{10}N_4O_3S_2$), mp = 180.8 ± 0.3 °C and ΔHf = 80.7 ± 2.5 kJ/mol (5 runs). The same compound could be isolated by recrystallization from methanolic or aqueous solutions and by evaporation of a methanolic solution of the starting mixture, and also from mixtures containing a higher amount of SMTR with respect to TMP (2:1 mol:mol).

- b) 2.85 g of the equimolar physical mixture of SMPD and TMP were recrystallized from 30 ml of 95% ethanol. Following the procedure described in a), were recovered 2.52 g (88%) of TMP-SMPD ($C_{14}H_{18}N_4O_3.C_{11}H_{12}N_4O_3S$), mp = 169.5 ± 0.2 °C and ΔHf = 72.3 ± 0.5 kJ/mol (5 runs). The same compound could be isolated by recrystallization from methanol or by evaporation of a methanolic solution of the starting mixture, and also from mixtures containing a higher amount of SMPD with respect to TMP (2:1 mol:mol). Recrystallizing the starting mixture from distilled water, the hydrate TMP-SMPD.H_2O ($C_{14}H_{18}N_4O_3.C_{11}H_{12}N_4O_3S.H_2O$), was obtained in practically quantitative yield.

- c) 2.84 g of the equimolar physical mixture of SDMD and TMP were recrystallized from 30 ml of ethanol:water 50:50. Following the procedure described in a), were recovered 2.39 g (84%) of TMP-SDMD ($C_{14}H_{18}N_4O_3.C_{12}H_{14}N_4O_2S$), mp = 168.6 ± 0.3 °C and ΔHf = 61.9 ± 2.0 kJ/mol (5 runs). The same compound was also obtained from mixtures containing a higher amount of SDMD with respect to TMP (2:1 mol:mol). The solid obtained by recrystallization of the starting mixture from 100 ml of methanol in a 92% yield was the solvate with one methanol molecule TMP-SDMD.CH_3OH ($C_{14}H_{18}N_4O_3.C_{12}H_{14}N_4O_2S.CH_3OH$). The same product was also isolated

by spontaneous precipitation or by evaporation of a methanolic solution of the mixture.

The elemental analyses of the compounds obtained are in satisfactory agreement (± 0.2% for C, H, N) with the molecular formulas given above in parentheses.

Apparatus and procedures - Calorimetric and thermogravimetric (Mettler TG 50 thermobalance) analyses were performed with a Mettler TA 3000 differential scanning calorimeter. Samples (3-8 mg) sealed in Al containers were scanned between 50 and 300 °C at a heating rate of 5 K/min, using nitrogen as a purge gas. In DSC runs were used physical mixtures containing: 1) TMP and the sulfa drug; 2) equivalent quantities of a single component and the molecular compound, when available. The composition of the mixtures usually ranged from 0.05 to 0.95 sulfa drug mole fractions, with 0.05 increments. The analysis of the phase diagrams of each TMP and sulfa drug binary system was also carried out by theoretical calculations on the solid-liquid equilibria using appropriate models of the melt (20,21). Visual observation of the samples was performed with a hot stage microscope.

X-ray diffraction patterns on powder were obtained with a Philips PW 1050/25 diffractometer, Cu-K_α radiation. IR spectra were taken as Nujol mulls and as KBr pellets on a Perkin-Elmer Mod. 682 spectrophotometer.

RESULTS

Among the sulfonamides considered, SFD, SMOS and SMP did not interact with TMP under the described conditions. The starting mixture of TMP and sulfa drug was recovered in each procedure used to prepare molecular compounds, as proved by IR and X-ray analyses. Thermal analysis of the three binary systems confirmed the absence of interaction between the components and demonstrated

TABLE 2

BINARY SYSTEMS FOR WHICH NO INTERACTION WAS DETECTED

SYSTEM	EUTECTIC TEMPERATURE Te (°C)		EUTECTIC COMPOSITION Xe,sulf. (mole fr.)	
	calc.	exp.(± S.D.)	calc.	exp.
SFD/TMP	189.4	189.5(0.4)	0.23	0.25
SMOS/TMP	171.8	167.6(1.5)	0.54	0.57
SMP/TMP	157.5	152.9(0.2)	0.70	0.68

the occurrence of single eutectic V-type phase diagrams. The theoretical phase diagrams, drawn using thermodynamic parameters of the components, are in agreement with the experimental diagrams, as proved by the eutectic temperature (S.D. from 20 experimental points) and composition values reported in Table 2.

The other sulfa drugs tested, SMTR, SMPD and SDMD, interact with TMP producing the respective 1:1 molecular compound, as in the case of SMZ (7). Moreover two solvated complexes, i.e. TMP-SMPD.H_2O and TMP-SDMD.CH_3OH, were obtained. The molecular ratios of water contained in the hydrate and methanol contained in the methanolate complexes were determined both by weight loss on drying and by thermogravimetry. In both cases, the weight losses (3.3% for the compound with SMPD, theoretical = 3.06%; 5.3% for the compound with SDMD, theoretical = 5.33%) indicate that precisely one mole of crystal water and methanol, respectively, is contained in the solvates (see Fig. 1: curves e, i). TMP-SMPD.H_2O gives the anhydrous complex by washing with absolute ethanol (or methanol) or by heating over 100 °C, while TMP-SDMD.CH_3OH is

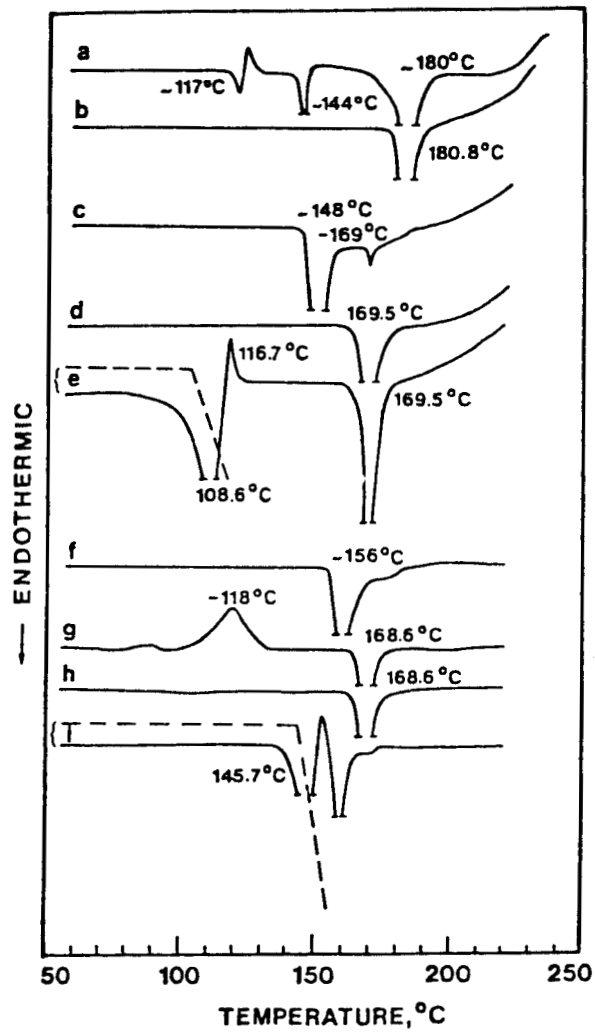


FIGURE 1

DSC (continuous line, 5 K/min) and TG (dotted line, 10 K/min) curves.

Key: a TMP:SMTR 1:1 physical mixture; b TMP-SMTR;
c TMP:SMPD 1:1 physical mixture; d TMP-SMPD;
e TMP-SMPD.H_2O; f TMP:SDMD 1:1 physical mixture;
g rescanning of f; h TMP-SDMD; i TMP-SDMD.CH_3OH.

transformed into TMP-SDMD by washing with an ethanol:water 1:1 solution or by heating over 140 °C.

The thermal behavior of the new solid phases and the physical mixtures used for their preparation is depicted in Fig. 1. Curve a shows the thermal effects associated with the formation of TMP-SMTR during the heating of the mixture of the components and the fusion at about 180 °C followed by decomposition. The fusion of pure crystalline TMP-SMTR is shown by curve b. The small endothermic peak at about 169 °C in curve c is attributable to the fusion of TMP-SMPD formed in the eutectic melt at about 148 °C. The fusion of crystalline TMP-SMPD at 169.5 °C is presented in curve d. TMP-SMPD.H_2O first loses water between 105 and 115 °C giving an amorphous (as proved also by X-ray pattern) which then crystallizes and melts as TMP-SMPD (curves e). The equimolar physical mixture of TMP and SDMD is characterized by an eutectic metastable melting at about 156 °C (curve f). Second scanning on a cooled sample gives curve g: the exothermal effect is attributable to the crystallization of the glassy amorphous solid with a final melting at 168.6 °C, the same mp of crystalline TMP-SDMD (curve h). Curves i show the desolvation of the methanolate and a final melting behavior which resembles that of the physical mixture (see curve f).

X-ray powder analysis of the solid phases prepared as previously described (Fig. 2) and the physical mixtures of the respective components (which correspond to the weighed average of those taken on pure components) provides supporting evidence for arrangements in new crystal structures.

IR spectroscopic data (Fig. 3) also demonstrate the formation of new crystalline entities as a result of interaction. As for

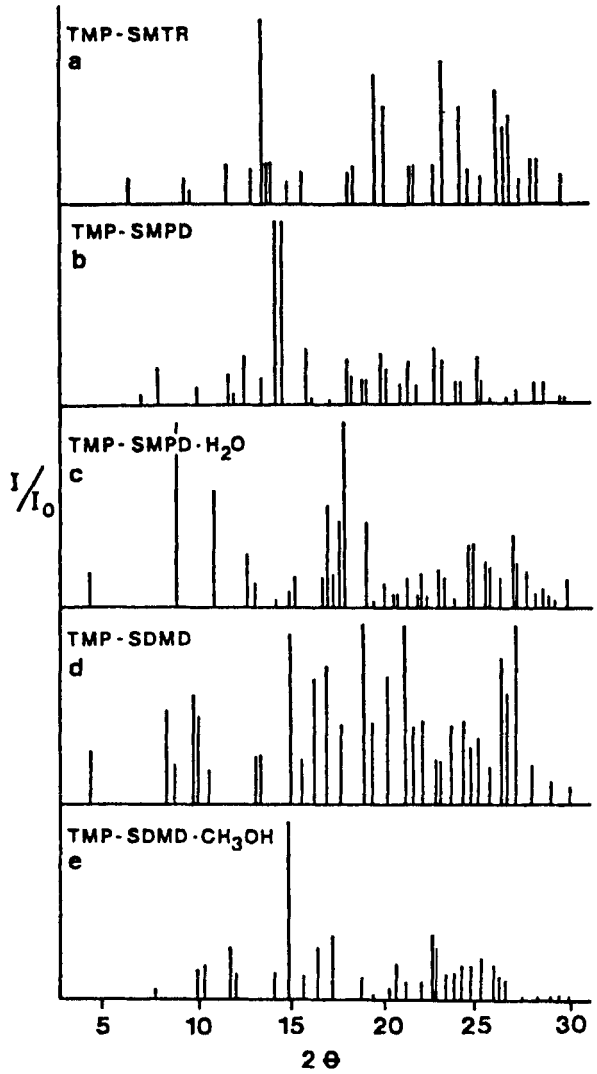


FIGURE 2

X-ray diffraction patterns.

Key: a TMP-SMTR; b TMP-SMPD; c TMP-SMPD.H_2O; d TMP-SDMD; e TMP-SDMD.CH_3OH.

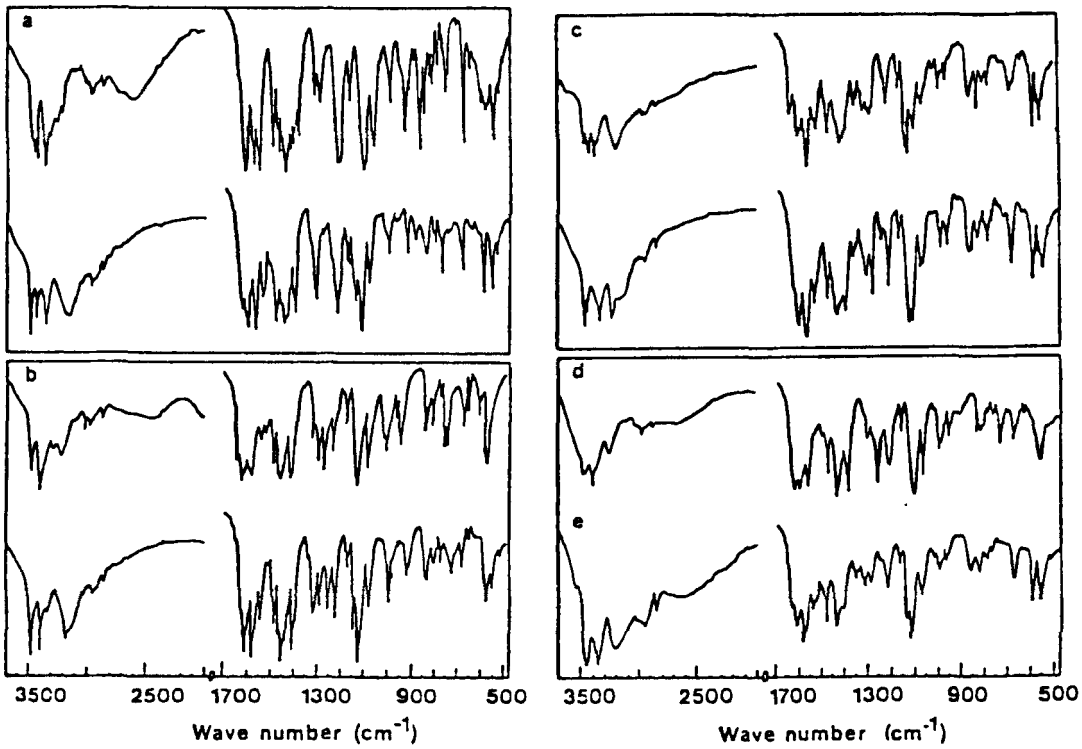


FIGURE 3

IR spectra (KBr pellets) of molecular compounds (a, b, c upper), corresponding physical mixtures (a, b, c, lower), solvates (d, e).

Key: a TMP-SMTR ; b TMP-SMPD ; c TMP-SDMD;
d TMP-SMPD.H_2O ; e TMP-SDMD.CH_3OH.

solvates (spectra d, e), characteristic bands of water and methanol are evident. In the spectra of TMP compounds, peaks corresponding to N-H stretching in the 3500-3000 cm^{-1} region move to lower frequencies of vibrations with respect to TMP alone or physical mixtures. Such a shift is indicative of an increasing of hydrogen bonding, as a consequence of interaction (7,22).

Figures 4, 5 and 6 illustrate the phase diagrams for the systems SMTR/TMP, SMPD/TMP, and SDMD/TMP, respectively. The

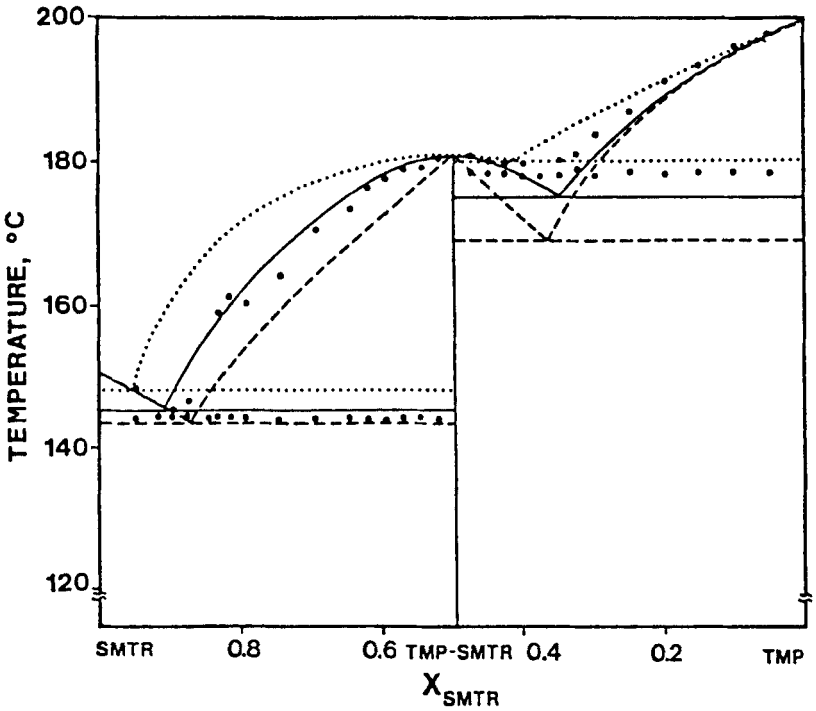


FIGURE 4

Phase diagram of the SMTR/TMP binary system (see Table 3).

Key: Upper curve (dotted line) = calculated from the theoretical model on the assumption of total dissociation of TMP-SMTR in the melt.
Lower curve (dashed line) = calculated from the theoretical model on the assumption of undissociation of TMP-SMTR in the melt.
Continuous line = calculated from the theoretical model on the assumption of partial dissociation of TMP-SMTR in the melt (K(d,a) = 0.1).
(●) Experimental points: endo-exothermal effects associated with the formation of the molecular compound (Fig. 1, curve a) are not represented.

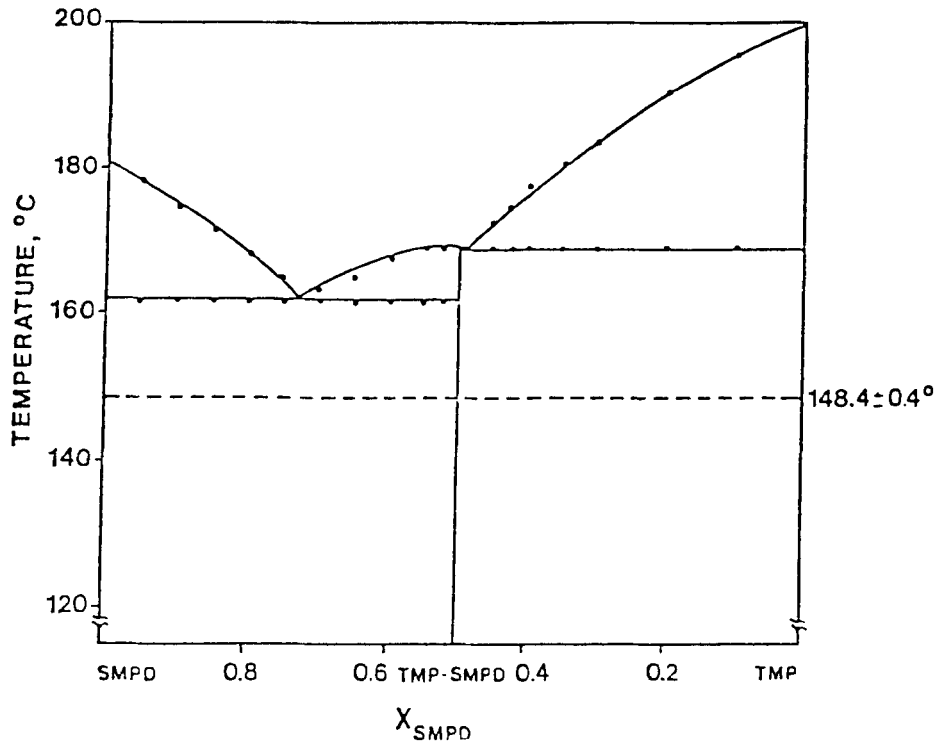


FIGURE 5

Phase diagram of the SMPD/TMP binary system (see Table 3).

Key: Dashed line = eutectic metastable fusion of mixtures of TMP and SMPD.
Continuous line = theoretical curve, calculated on the assumption of TMP-SMPD 50% dissociation in the melt (dissociation equilibrium constant K(d,b) = 1).
(o) Experimental points (from DSC runs on molecular compound and TMP or SMPD mixtures).

experimental data for eutectics agree with the theoretical data calculated assuming partial dissociation of each molecular compound in its components in the melt (Table 3). The K(d)s' values should be taken as merely indicative owing to the uncertainties inherent in the experimental solid-liquid equilibrium points (20).

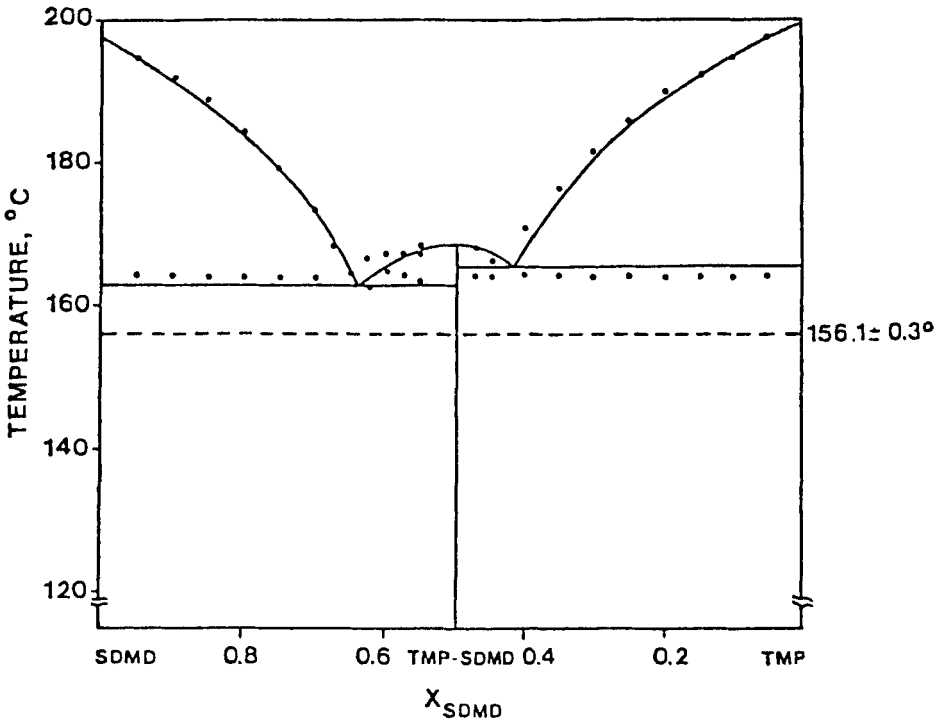


FIGURE 6

Phase diagram of the SDMD/TMP binary system (see Table 3).

Key: Dashed line = eutectic metastable fusion of mixtures of TMP and SDMD.
Continuous line = theoretical curve, calculated on the assumption of a partial dissociation of TMP-SDMD in the melt (dissociation equilibrium constant K(d,a) = 0.1).
(o) Experimental points (from DSC runs on molecular compound and TMP or SDMD mixtures).

DISCUSSION AND CONCLUSIONS

TMP forms 1:1 molecular compounds with SMTR, SMPD, SDMD, and SMZ (7). Some general hints about the binding mode between TMP and sulfa drugs can be derived on the basis of available spectroscopic data and literature data about the crystal structures of sulfonamides (12-18) and various TMP compounds (22-24).

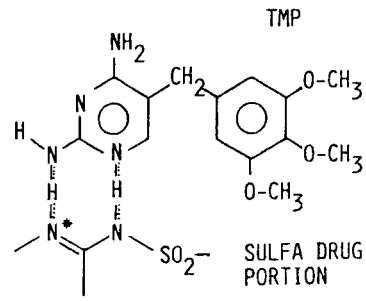


TABLE 3

EXPERIMENTAL AND CALCULATED VALUES (*)
FOR BINARY SYSTEMS FORMING MOLECULAR COMPOUNDS

EUTECTIC E1					EUTECTIC E2				
Te1 (°C)		X1,sulf. (mole fr.)			Te2 (°C)		X2,sulf. (mole fr.)		
calc.	exp. (±S.D.)[e]	calc.	exp.		calc	exp. (±S.D.)[e]	calc.	exp.	
				SMTR/TMP					
148.1[a]		0.95[a]			180.0[a]		0.41[a]		
145.6[b]	144.4 (0.24)	0.91[b]	0.88		175.0[b]	178.7 (0.29)	0.35[b]	0.36	
143.4[c]		0.87[c]				169.2[c]		0.36[c]	
				SMPD/TMP					
162.2[d]	162.0 (0.80)	0.73[d]	0.71		169.3[d]	168.8 (0.50)	0.49[d]	0.49	
				SDMD/TMP					
162.7[b]	163.7 (0.80)	0.64[b]	0.65		165.7[b]	164.5 (0.30)	0.41[b]	0.43	

(*) On the assumption that the molecular compound in the melt is a) totally dissociated; b) partially dissociated, K(d,a) = 0.1; c) undissociated; d) partially dissociated, K(d,b) = 1 (see refs 20, 21). e) At least 10 experimental points.

As a working hypothesis, let us assume that in all the TMP:sulfonamide interactions leading to a crystalline molecular compound the same molecular portions as in TMP-SMZ (22) are involved. This is evidenced in the following scheme.

Four main parameters seem to play a concomitant role: 1) the pK_a of the sulfa drug for the TMP protonation; 2) the basicity of the heterocyclic nitrogen atom N* for hydrogen bonding with NH_2 of TMP; 3) the aromaticity of the heterocycle of the sulfonamide; 4) the geometry (bond lengths and angles) of the atoms involved.

Uptodate it is highly probable that only through the adequate, balanced combination of these parameters, the conditions for a stable linking via hydrogen bonding between TMP and the sulfa drug are reached. As a qualitative observation, it can be said that the presence of a second heteroatom directly linked to N* in the above scheme should enhance its acceptor ability in hydrogen bonding and favours the interaction with TMP.

As for practical implications of these interactions, some of the observed differences in the pharmaceutical quality of solid combinations, e.g. disintegration time and dissolution rate (25,26), might be a consequence of interaction between the active ingredients (27). This interaction can occur depending on the formulation and manufacturing factors. Investigations of the influence of these factors as performed on Co-trimoxazole (28) are also necessary for combinations of TMP with SMTR, SMPD, and SDMD. Further attention should be payed to SMPD and SDMD combinations because of their ability to give solvated molecular compounds.

For example, a powdered mixture of TMP and SMPD is transformed by wetting with water in a clotty mass with poor flow (and dissolution) properties, because of TMP-SMPD.H_2O formation. Thus, in the manufacturing process of solid dosage forms,

incompatibility occurs by contact with aqueous media or even water-containing solvents. This also implies that the dosage forms must be protected from humidity during the shelf time through adequate formulation and storage conditions.

ACKNOWLEDGMENTS

The authors wish to thank Prof. Aldo La Manna for helpful discussion.
The technical assistance of Mrs M.C. Sacchi and Mrs L. Garbuglia is gratefully acknowledged.
This work was partially supported by a grant of Ministero Pubblica Istruzione (Fondi 60%).

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