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Effect of additives on the kinetics of interconversion of sulphamethoxydiazine crystal forms

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The effect of various additives on the rate of transformation of the more energetic sulphamethoxydiazine Form II to the water-stable Form III in aqueous suspension has been studied. Representative structurally related compounds, viscosity imparting agents, surfactants and colouring agents have been used to inhibit the transformation. Significant transformation retarding effects were observed in most cases. The effects vary, however, from slight retardation to almost complete inhibition of the transformation for periods of over a year (e.g. using 1% w/v of polyvinylpyrrolidone). The effect of seeding suspensions of Form II with nuclei of Form III in the presence and absence of additives has also been examined. Accelerated stability testing is shown to be inadequate for the prediction of stability of Form II in aqueous suspension in the presence of acacia or polyvinylpyrrolidone. The use of the results in the formulation of dosage forms containing sulphamethoxydiazine is suggested.

Sulphamethoxydiazine crystal forms (Moustafa, Ebian & others, 1971), their bioavailability (Khalil, Moustafa & others, 1972) as well as the kinetics of their interconversion under standard conditions (Moustafa, Khalil & others, 1972) have recently been described. In these papers, the use of Form II in various dosage forms was suggested because of its higher solubility and greater bioavailability. However, the ease of transformation of Form II during processing or storage stimulated the search for suitable means of stabilizing it, especially in aqueous suspensions. Stabilization of Form II may easily be achieved in the solid state by simply abstracting water from its environment (Moustafa & others, 1972).

The use of various additives to stabilize drug polymorphs was suggested by Higuchi (1958) and Frederick (1961). These additives included, among other substances, structurally related compounds, viscosity imparting materials (hydrocolloids) and surface-active agents. The retardation of solid state transformations by structurally related compounds was demonstrated by the effect of raffinose on sucrose (Albon & Dunning, 1962), sodium cholate on cholesterol (Saad & Higuchi, 1965), chloramphenicol stearate on chloramphenicol palmitate (Aguiar, 1969) and cortisone alcohol on cortisone acetate (Carless, Moustafa & Rapson, 1968). The effect of viscosity-imparting agents, like methylcellulose, algenic acid derivatives and polyvinylpyrrolidone, on the rates of transformation of crystalline drugs has received considerable attention (see for example Mullins & Macek, 1960; Shefter & Higuchi, 1963; Lin, 1971; Carless & Foster, 1966).

We have investigated the effect of some additives, on the retardation of transformations of the more energetic crystal form (Form II) of sulphamethoxydiazine. The

quantitative infrared technique previously described (Moustafa & others, 1972) is used to measure the rates of such transformations.

MATERIALS AND METHODS

Materials and apparatus

Sulphamethoxydiazine Forms II and III were prepared as previously described (Moustafa & others, 1971). The crystals were screened to a particle size of 80–90 μm. Sulphanilamide, sulphadiazine, sulphadimidine, sulphadimethoxine, sulphamethoxypyridazine, *p*-aminobenzoic acid, methylcellulose, sodium carboxymethylcellulose, polyvinylpyrrolidone, acacia, syrup, glycerol, polysorbate 80, sodium lauryl sulphate, dioctyl sodium sulphosuccinate, cetrimide, fluorescein sodium, amaranth and hydrochloric acid, all of B.P. or B.P.C. grade were used. Sulphamerazine (U.S.P.), sulphamethoxypyrazine (Farmitalia, Milan, Italy), yellow No. 4 (Lebensmittel, D.F.G., Germany) and Bordeaux B (B.P.C. 1949) were also used.

Infrared measurements were made using a Perkin-Elmer double beam grating spectrophotometer Model 237-B.

Methods

Aqueous suspensions of sulphamethoxydiazine Form II (1 % w/v), each containing a known quantity of one of the additives, were prepared. The suspensions were kept in a thermostated water-bath at 25° $\pm$ 0·1°. Samples were withdrawn at various time intervals, filtered and the concentration of Form II in the solid phase determined as previously described (Moustafa & others, 1972).

Acceleration of the transformation of sulphamethoxydiazine Form II was, in some instances, carried out. For this purpose, 1 % w/v suspensions of the latter form, containing 1 % w/v of either acacia or polyvinylpyrrolidone as well as a standard suspension containing no additives were kept at 40, 50, 55 and 60° $\pm$ 0·1°. The suspensions were assayed periodically for Form II as before (Moustafa & others, 1972). Similar suspensions were kept on the shelf at room temperature for comparative purposes.

Seeding experiments were made to evaluate the effect of including nuclei of the water-stable sulphamethoxydiazine Form III on the polymorphic transformation as well as the dissolution behaviour of Form II. For this purpose, 5 % w/w of Form III in Form II was used, in place of Form II alone, for the transformation studies in presence and absence of some additives. In a dissolution rate study of Form II, following a procedure similar to that previously described (Moustafa & others, 1971), a seed of Form III corresponding to 10 % by weight of Form II was also introduced at the peak of the dissolution rate curve (15 min from the start of the experiment).

RESULTS AND DISCUSSION

The inhibitory effect of various additives is, in most cases, manifested by the appearance of a lag period during which transformation of sulphamethoxydiazine Form II is very slow (almost negligible). Rate retardation may also be observed. The lag period is probably a measure of the time needed to produce, through transformation of small particles of Form II, an adequate number of nuclei which is presumably a prerequisite for the transformation to take place under steady conditions.

The effect of structurally related compounds on the rate of transformation of sulphamethoxydiazine Form II is shown in Table 1 and Fig. 1. *p*-Aminobenzoic acid,

Table 1. *Effect of additives on the rate of transformation of sulphamethoxydiazine Form II in aqueous suspension.*

Additive	Concentration (% w/v)	Lag time (min)	$K_1 \times 10^3$* (min^{-1})	$K_2 \times 10^2$* (min^{-1})
Standard suspension	—	0	0	4·61
Sulphadiazine	0·1†	15	6·91	2·80
Sulphamerazine	0·1†	30	1·54	0·68
Sulphadimethoxine	0·1†	60	0·27	0·49
Sulphadimidine	0·1†	330	1·32	0·62
Syrup	50‡	1260	0	0·29
Sodium carboxymethylcellulose	0·2	15	1·84	2·09
Glycerol	20‡	5	4·61	3·22
Polysorbate 80	1	60	2·30	1·36
Dioctyl sodium sulphosuccinate	1	1218	0	0·60
Cetrimide	1	40	1·44	1·11
Sodium lauryl sulphate	1	25	7·65	2·39
Fluorescein sodium	0·005	2	0	3·85
Yellow No. 4	0·005	2	0	4·07
Amaranth	0·005	16	0	3·20
Bordeaux B	0·005	15	0	3·28
HCl	0·35	0	0	7·58
HCl	0·035	0	0	6·68
HCl	0·0035	0	0	5·35

* K_1 and K_2 are the rate constants of transformation during and after the initial lag period respectively, † corresponding to 10% by weight of the total solid sulphamethoxydiazine in suspension, ‡ % v/v.

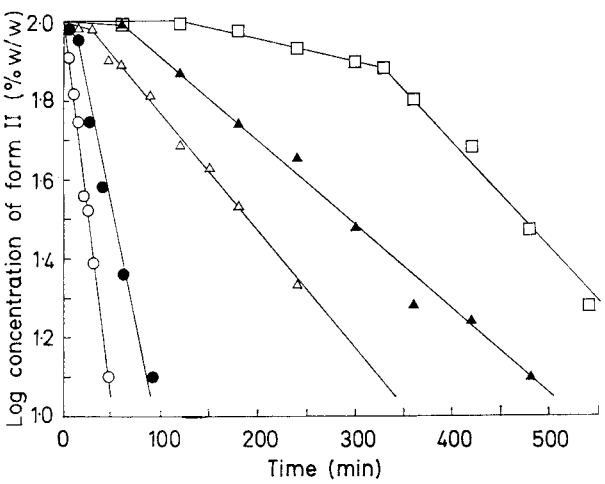

FIG. 1. Effect of structurally related compounds on the rate of transformation of sulphamethoxydiazine Form II. ○——○ standard suspension of Form II, ●——● sulphadiazine, △——△ sulphamerazine, ▲——▲ s ulphadimethoxine, □——□ sulphadimidine.

sulphanilamide, sulphamethoxypyridazine and sulphamethoxypyrazine in 0·10% w/v concentrations showed a lag period of over 15 days during which no transformation could be detected. Smaller molecules (e.g. *p*-aminobenzoic acid and sulphanilamide) seemed to have maximum stabilizing effects on Form II. The ease of fit of these molecules to growing sites on the nuclei of Form III probably explains their effectiveness as transformation retarding agents. Unexpectedly, sulphonamides with

different heterocyclic rings (e.g. sulphamethoxypyridazine and sulphamethoxypyrazine) were more effective in retarding the transformation of Form II than compounds in which the heterocyclic ring, in common with the parent compound (sulphamethoxydiazine), is a pyrimidine ring (e.g. sulphadiazine, sulphamerazine and sulphadimidine). In the latter compounds, substitution of the pyrimidine ring with methyl groups was found to enhance the effect of the compound as a transformation retarding agent. Sulphadimethoxine, with two methoxy groups on the pyrimidine ring, was found to have an intermediate effect. Although differences in solubility of the sulphonamides used are not great, compounds that were relatively more soluble had greater transformation retarding effects. Experience with the use of structurally related compounds, which are also probable impurities in sulphamethoxydiazine, would agree with previous suggestions by Aguiar (1969). He stated that an effective transformation retarding compound should be closely related chemically as well as of favourable spatial configuration to the parent molecule. This might necessitate the presence of an adequate number of free retardant molecules in solution, for in this way they may be able to increase the entropy or energy barrier necessary for nucleation of the thermodynamically stable polymorph as suggested by Aguiar (1969).

The effect of viscosity-imparting materials in retarding the transformation of sulphamethoxydiazine Form II is shown in Table 1 and Fig. 2A. The presence of 1% w/v of acacia, polyvinylpyrrolidone, or 0·2% w/v of methylcellulose produced lag periods of more than 15 days. On the other hand, syrup, sodium carboxymethylcellulose and glycerol showed gradually decreasing transformation retarding effects. The effect of this group of additives is perhaps related to the relatively high viscosity of their aqueous solutions which retards the diffusion controlled processes involved in the

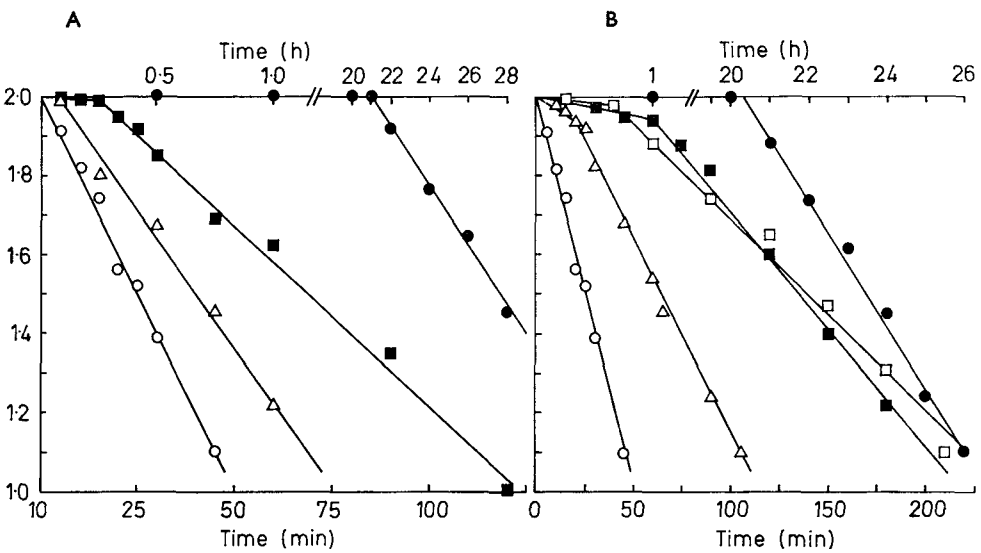

FIG. 2. A. Effect of viscosity imparting agents on the rate of transformation of sulphamethoxydiazine Form II. ○——○ standard suspension of Form II, △——△ glycerol, ■——■ sodium carboxymethylcellulose, ●——● syrup (time in h).

B. Effect of surfactants on the rate of transformation of sulphamethoxydiazine Form II. ○——○ standard suspension of sulphamethoxydiazine Form II, △——△ sodium lauryl sulphate, □——□ cetrimide, ■——■ polysorbate 80, ●——● dioctyl sodium sulphosuccinate (time in h).

Ordinate: log concentration of form II (% w/w).

polymorphic transformation. This, in turn, slows down both nuclei formation and growth rate on the nuclei formed.

Surfactants were also found to have transformation retarding effects (Table 1, Fig. 2B). The cationic surfactant, cetrimide, was found to have better stabilizing effects on sulphamethoxydiazine Form II than the anionic surfactant, sodium lauryl sulphate. This might be attributed to adsorption of the positively charged cetrimide molecules on the normally negatively charged sulphamethoxydiazine nuclei. The formation of some kind of interfacial barrier, as suggested by Higuchi & Lau (1962) and Carless & Foster (1966), might be responsible for the retardation by interfering at the crystal interface and inhibiting the growth of the stable form (Form III). Another interesting aspect of the effect of surfactants is the possibility of incorporation of the formed nuclei within the surfactant micelles (Carless & Foster, 1966). This reduces the number of nuclei available for the transformation process. The latter view might explain the retardation caused by the non-ionic high molecular weight surfactant, polysorbate 80. Dioctyl sodium sulphosuccinate, although anionic like sodium lauryl sulphate, had a greater transformation retarding effect. This is presumably due to the larger micelles formed.

The presence of colouring agents retarded the transformation of sulphamethoxydiazine Form II as shown in Table 1 and Fig. 3. Amaranth and Bordeaux B were more effective retardants than fluorescein sodium or yellow No. 4. The mechanism of action of the colouring agents probably involves preferential adsorption of the dye molecules at the growing crystal surfaces, thus retarding the rate of transformation. A similar mechanism was suggested by Piccolo & Tawashi (1970, 1971) for the inhibited dissolution of drug crystals by certified water-soluble dyes.

Solutions of hydrochloric acid increased the rate of transformation of sulphamethoxydiazine Form II in a manner proportional to the acid concentration (Table 1 and Fig. 3). The increased solubility of sulphamethoxydiazine in acid solutions, might be responsible for the rapid rate of growth on the formed nuclei of Form III.

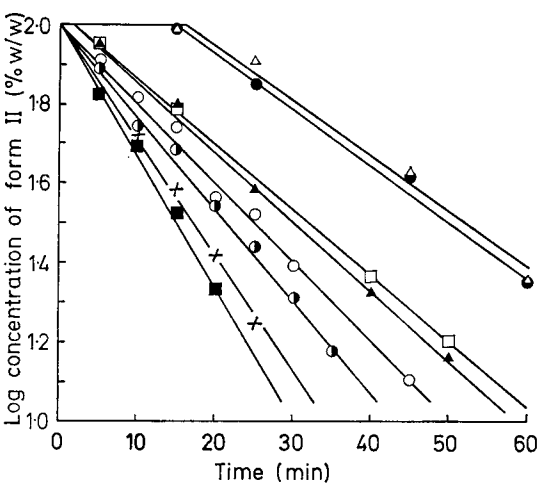

FIG. 3. Effect of colouring agents and hydrochloric acid on the rate of transformation of sulphamethoxydiazine Form II. ■——■ 0·35% w/v HCl, ×——× 0·035% w/v HCl, ◑——◑ 0·0035% w/v HCl, ○——○ standard suspension of Form II, ▲——▲ yellow No. 4, □——□ fluorescein sodium, ●——● Bordeaux B, △——△ amaranth.

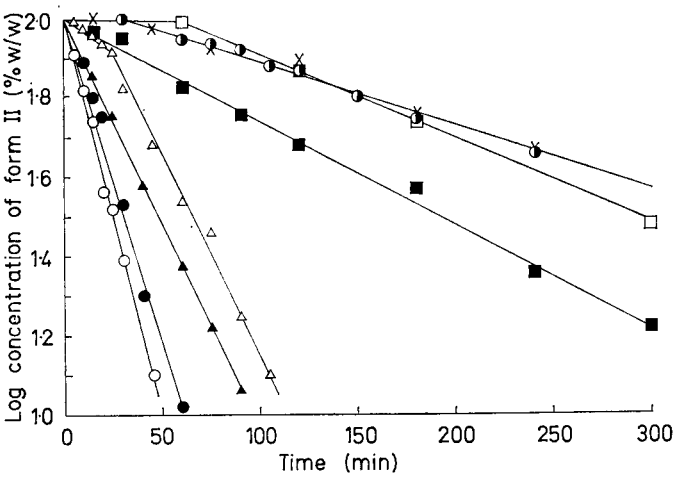

FIG. 4. Effect of seeding with nuclei of Form III on the rate of transformation of sulphamethoxydiazine Form II in the presence of some additives at 25°. ○——○ standard suspension of Form II, ●——● sulphanilamide + Form III seed, ▲——▲ sodium lauryl sulphate + Form III seed, △——△ sodium lauryl sulphate, ■——■ sulphadimethoxine + Form III seed, □——□ sulphadimethoxine, ◑——◑ polyvinylpyrrolidone + Form III seed at 50°, ×——× polyvinylpyrrolidone at 50°.

Representative examples of the effects of seeding with nuclei of Form III on the rate of transformation of sulphamethoxydiazine Form II in presence of various additives are shown in Fig. 4. Seeding effects were found to vary from no change in the rate of transformation to almost complete abolition of the effects of additives. In those cases, e.g. polyvinylpyrrolidone or polysorbate 80, in which seeding with Form III did not produce any measurable change in the rate of transformation of Form II, the interfacial barrier existing is probably so strong as to inhibit the transformation to Form III even in the presence of added nuclei. An intermediate effect is that observed in the presence of sulphadimidine or sodium lauryl sulphate, where seeding eliminated the initial lag period but the rate of transformation which followed was not affected. A third effect of seeding, observed with dioctyl sodium sulphosuccinate or sulphadimethoxine is that where the lag period was eliminated and the rate of transformation was increased about 5 or 12 times respectively. Maximum seeding effects were observed in the presence of sulphanilamide. By providing an adequate number of nuclei, the seed not only eliminated the very long lag period but also enhanced the rate of transformation to a value almost equal to that of the standard suspension containing no additives. The elimination of the lag period, in most instances, by seeding with Form III confirms the previous suggestion that the lag period is a measure of the time necessary to produce an adequate number of nuclei of the water-stable form.

Seeding with Form III was found to have no effect on the rate of transformation of Form II in aqueous suspensions containing no additives. This is probably because the rate of nuclei formation and polymorphic transformation under these conditions is already quite fast. However, seeding with Form III in a dissolution rate experiment of Form II produced a rapid decrease of the concentration of sulphamethoxydiazine in solution, instead of the gradual slow decrease which is observed in the absence of such seeds (Fig. 5). The apparent solubility (peak of the dissolution rate curve) of sulphamethoxydiazine Form II represents a solution which is supersaturated with

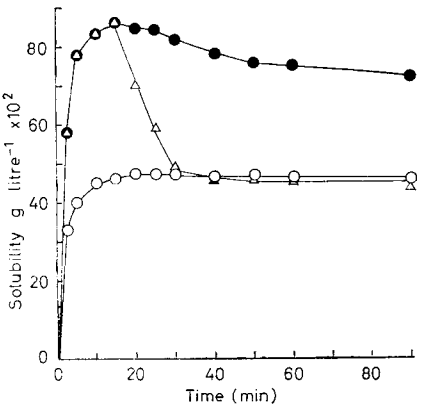

FIG. 5. Effect of seeding with nuclei of Form III on the dissolution behaviour of sulphamethoxydiazine Form II. ●——● Form II, ○——○ Form III, △——△ Form II seeded with Form III at the peak of the dissolution rate curve.

respect to Form III (Moustafa & others, 1971). Once nuclei of Form III are introduced, crystallization of the excess solute takes place resulting in a sharp decrease in the concentration of sulphamethoxydiazine to a level representing the equilibrium apparent solubility of the water-stable Form III.

Attempts to predict stability parameters of Form II in presence of acacia or polyvinylpyrrolidone, the most efficient transformation retardants were made after an accelerated stability test program. The results are shown in Table 2. Although the calculated rate constants and other kinetic parameters were in agreement with the previous findings (Moustafa & others, 1972), the kinetic parameters obtained by extrapolation to room temperature, e.g. half-life values, varied considerably from those found experimentally for suspensions stored on the shelf at room temperature ($\simeq$25°). Contrary to the results in Table 2, storage under room temperature conditions for over a year did not produce any measurable transformation of Form II in suspensions containing 1% w/v of polyvinylpyrrolidone. The discrepancy could be interpreted in the light of loss of consistency of the suspending medium (decreased viscosity) by increasing the temperature, a condition which is not encountered if storage is at room temperature. Accelerated stability testing under similar conditions is, therefore, shown to be inadequate in the prediction of shelf-life of metastable crystal forms.

Table 2. *Kinetic parameters for the transformation of sulphamethoxydiazine Form II in presence and absence of acacia and polyvinylpyrrolidone in aqueous suspension.*

Additive	Rate constant K × 10^2 (min^{-1}) 40°	50°	55°	60°	K × 10^4 (min^{-1}) 25°	$t_{\frac{1}{4}}$ 25° (h)	Ea k cal mol^{-1} (kJ mol^{-1})
Standard suspension of Form II*	—	—	—	—	460·600	0·25	19·0 (79·5)
Acacia (1%)	0·768	3·050	—	14·750	5·955†	19·40	31·0 (129·8)
Polyvinylpyrrolidone (1%)	—	0·370	1·055	3·952	0·033†	3525·00	53·0 (221·9)

* Data from Moustafa & others (1972), † determined by extrapolation.

The present study provides a model of the possible use of additives, many of which are normally used as pharmaceutical adjuvants, to stabilize a metastable polymorph of higher solubility as well as bioavailability. This satisfies the requirements of Higuchi, Lau & others (1963), who drew attention to the need for altering drug availability to the patient through changing the crystal form. Frederick (1961) and Pearson & Varney (1969) also indicated that the formulation of metastable polymorphs in pharmaceutical suspensions might be desirable, provided that adequate measures are taken to keep them in such state for the expected shelf-life of the preparation.

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