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Influence of an acetylsalicylic anhydride impurity on the rate of dissolution of acetylsalicylic acid

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The intrinsic dissolution rate of acetylsalicylic acid in 0·1 N hydrochloric acid at 35° has been shown by a rotating disc method to be affected by the presence of acetylsalicylic anhydride in the crystals. At concentrations exceeding 0·25% the impurity decreased the dissolution rate of the acetylsalicylic acid. It is suggested that the previously reported differences in rates of dissolution of various commercial and recrystallized acetylsalicylic acid preparations may be due to differences in content of acetylsalicylic anhydride which is a frequently-occurring impurity in commercial acetylsalicylic acid and is formed on heating solutions of acetylsalicylic acid in various organic solvents.

Since the observation of Mitchell & Saville (1967) that samples of commercial acetylsalicylic acid had different intrinsic dissolution rates and the report of Tawashi (1968) that acetylsalicylic acid recrystallized from 95% ethanol and n-hexane had different dissolution rates, several authors have attempted to explain this difference in dissolution behaviour. The crystals obtained by Tawashi displayed different melting points and heats of fusion and, as differences in infrared absorption spectra and in X-ray diffraction powder patterns also were claimed to exist, Tawashi (1968, 1969) concluded that the crystals were of two polymorphic forms. In contrast, Mitchell & Saville (1969) could not detect any differences in X-ray diffraction powder patterns, infrared spectra, and attenuated total reflectance of infrared of the two commercial acetylsalicylic acid samples which, in their first study, showed the greatest difference in dissolution rate. Using the procedures described by Tawashi (1968), Mitchell, Milaire & others (1971), Schwartzman (1972) as well as Jamali & Mitchell (1973), were unable to produce acetylsalicylic acid crystals exhibiting different optical, spectral, x-ray or dissolution properties. Based upon solution phase transformations and on differences in melting points and densities, Summers, Carless & Enever (1970) claimed to have found six polymorphs of acetylsalicylic acid. No or only minor differences were observed in their x-ray diffraction patterns, however, and Pfeiffer (1971), Mitchell & others (1971) and Jamali & Mitchell (1973) questioned the evidence for the existence of the polymorphs. In a later paper, Summers, Enever & Carless (1973) reported differences in the intrinsic dissolution rates of some of the forms.

Besides polymorphy, several other factors such as crystal habit and size (Pfeiffer, 1971), crystal imperfection (Pfeiffer, 1971; Mitchell & others, 1971), the presence of salicylic acid (Mulley, Rye & Shaw, 1971) and spherulites of acetylsalicylic acid (Tawashi, 1971; Borka, 1972) have been suggested to affect the rate of dissolution of acetylsalicylic acid. Experimental verification or support of these proposals has, however, not been presented and recently Jamali & Mitchell (1973) have repudiated

all the hypotheses advanced. They found that intrinsic dissolution rates were independent of crystal size and habit, crystal growth rate, and thereby the number of crystal imperfections, salicylic acid content (at least up to 3·9%) and the presence of spherulites of acetylsalicylic acid. Jamali & Mitchell concluded that the previously observed differences in the dissolution rates of various samples of commercial acetylsalicylic acid must be due to other factors than those mentioned above, e.g. ageing and ripening of the crystals or poisoning by other impurities besides salicylic acid.

Acetylsalicylic anhydride has recently been found to be a frequently occurring impurity in commercial acetylsalicylic acid preparations (De Weck, 1971; Bundgaard & Bundgaard, 1973) and since the cause for the anomalous dissolution behaviour of acetylsalicylic acid is still unexplained, a study has been made to decide whether this impurity can affect the intrinsic dissolution rate of acetylsalicylic acid.

MATERIALS AND METHODS

Materials

The samples of commercial acetylsalicylic acid conformed in all respects to the requirements of the Pharmacopoeia Nordica (1963). Acetylsalicylic anhydride was synthesized according to the method of Bundgaard & Bundgaard (1973) and recrystallized from ethanol, m.p. 85–86°. All other chemicals and solvents used were of analytical grade.

Preparation of acetylsalicylic acid crystals with varying content of acetylsalicylic anhydride

Experiments (Bundgaard, to be published) have shown that acetylsalicylic acid on heating in various organic solvents (e.g. benzene, acetone, ethyl acetate, n-hexane) is transformed partially into its anhydride (and salicylic acid) and that an equilibrium between the acid and the anhydride is established after heating for a few hours. In benzene the proportion of the equilibrium concentrations of the acid and the anhydride has been found to be approximately 7:1 on a molar basis. According to these experiments it seems likely that acetylsalicylic acid crystals containing varying amounts of the anhydride can be obtained by heating e.g. benzene solutions for various periods and allowing the acetylsalicylic acid to crystallize at various rates.

A commercial preparation of acetylsalicylic acid (50 g) was dissolved in 1300 ml of benzene by heating on a steam bath. The solution was kept at the boiling point and portions were removed at various times over the period 10 min to 3 h. The hot solutions were either cooled rapidly in an ice-water bath or slowly by quiet standing at room temperature. The resulting crystals were collected by filtration and washed with n-hexane. In this manner acetylsalicylic acid crystals containing acetylsalicylic anhydride in amounts ranging from 0·001 to 0·45% were obtained. Crystals containing greater amounts of anhydride were prepared by dissolving 10 g of acetylsalicylic acid and 0·5 or 1 g of acetylsalicylic anhydride in 22 ml of hot 90% v/v ethanol and allowing the solution to stand at 4° for about 5 h. The resulting crystals were thoroughly washed with cold benzene and finally with n-hexane.

Characterization of the acetylsalicylic acid preparations

The various samples of crystalline acetylsalicylic acid were assayed for content of acetylsalicylic anhydride by the spectrophotometric method of Bundgaard & Bundgaard (1973) and for content of salicylic acid by the colorimetric method of DeMarco

& Marcus (1962). By thin-layer chromatographic examination of the samples using various solvent systems, no other impurities including salicylsalicylic acid and acetylsalicylsalicylic acid (Patel, Perrin & Windheuser, 1972; Bundgaard, 1974) could be detected. Infrared spectra were recorded using the potassium bromide disc technique on a Unicam SP200 spectrophotometer. Differential scanning calorimetry was made with a Perkin-Elmer DSC-1, the sample size being approximately 5 mg and the scanning rate 8° min^{-1}.

Measurement of dissolution rate

Intrinsic dissolution rates were measured using the rotating disc method of Nogami, Nagai & Suzuki (1966). Discs of 500 mg and 2·0 cm diameter were prepared by compression of the crystals at about 3000 kg cm^{-2} in a compression punch-die assembly. The dissolution rates were found to be independent of compressional pressure over the range 2000 to 4000 kg cm^{-2}. Whether the crystals were finely ground in a mortar before compression or not was also without influence on the dissolution rates. The dissolution medium was 400 ml of 0·1N hydrochloric acid, the temperature 35°, and the rotation velocity of the disc holder 300 rev min^{-1}. By means of a peristaltic pump (Hiloflow) the dissolution medium was circulated through the 1 cm path-length flow cell of a Perkin-Elmer Model 124 double beam spectrophotometer and the increase in absorption at 278 nm (the isosbestic point for acetylsalicylic acid/salicylic acid in 0·1N hydrochloric acid) was recorded (Servogor S Type RE 54 recorder) to give a continuous plot of amount dissolved *vs* time. Intrinsic dissolution rates in mg cm^{-2} min^{-1} were calculated from the initial slope of an amount dissolved *vs* time curve divided by the surface area of the compressed disc. At least two replicate determinations were made on each acetylsalicylic acid sample, the rate constants obtained therefrom being reproducible to within $\pm 3\%$.

RESULTS AND DISCUSSION

Dissolution curves of some acetylsalicylic acid samples are shown in Fig. 1. While the curves of the samples A–I are linear during the whole measuring period, the linear

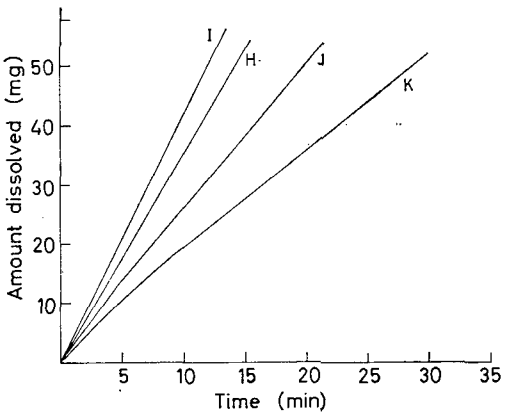

FIG. 1. Dissolution curves of acetylsalicylic acid preparations containing varying amounts of acetylsalicylic anhydride (see Table 1). Rotating disc method at 35° in 0·1N HCl at 300 rev min^{-1}.

parts of the dissolution profiles of samples J and K are preceded by steeper non-linear portions. The dissolution rates of these two samples given in Table 1 are

Table 1. *Methods of preparation and properties of acetylsalicylic acid crystals.*

Method of preparation	Sample nomenclature	Acetylsalicylic anhydride (%)	Salicylic acid (%)	Intrinsic dissolution rate (mg cm^{-2} min^{-1})
Commercial	A	0·0013	0·03	1·32
Commercial	B	0·024	0·04	1·36
Recrystallization from boiling benzene*				
10 min, fast at 0°	C	0·0062	0·05	1·31
40 min, slow at 20°	D	0·049	0·22	1·30
2·5 h, fast at 0°	E	0·048	0·75	1·28
2·5 h, slow at 20°	F	0·12	1·20	1·30
3 h, slow at 20°	G	0·29	1·18	1·16
3 h, slow at 20°	H	0·45	1·30	1·12
Recrystallization from 90% v/v ethanol (22 ml) Preparation A (10 g)	I	0·0010	0·02	1·32
Preparation A (10 g) + acetylsalicylic anhydride (0·5 g)	J	1·54	0·02	0·768
Preparation A (10 g) + acetylsalicylic anhydride (1·0 g)	K	2·76	0·03	0·520

* Acetylsalicylic acid (50 g) in 1300 ml of benzene, heated for the periods stated. Cooling at 0 or 20°.

calculated from the linear part of the curves. As shown in Table 1 the presence of acetylsalicylic anhydride in the acetylsalicylic acid crystals in amounts exceeding 0·29% w/w has an inhibiting effect on the intrinsic dissolution rate. Fig. 2 demon-

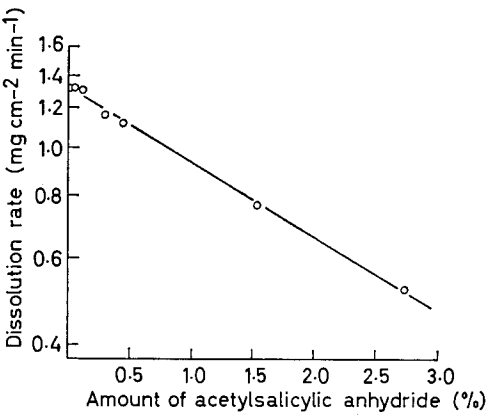

FIG. 2. Variation of intrinsic dissolution rate with amount of acetylsalicylic anhydride in acetylsalicylic acid.

strates that when the logarithm of dissolution rate is plotted against the acetylsalicylic anhydride content a straight line is apparently produced. It is also apparent from Table 1 (compare for example the samples A–F) that the salicylic acid content of the crystals is without any effect on the dissolution rate which agrees with the findings of Jamali & Mitchell (1973). Comparing e.g. samples C and I shows furthermore that the solvent of recrystallization does not affect the dissolution rate of the resulting crystals. The crystal habit and size of samples A, D and I among others differed widely, but as seen from the results in Table 1 the intrinsic dissolution rates are

identical. The independence of intrinsic dissolution rate on differences in crystal habit and size has also been demonstrated by Jamali & Mitchell.

The melting points of some of the samples were determined by differential scanning calorimetry: G 128°; I 132°; J 126°; K 128°. No peaks in the DSC traces were observed at other temperatures. The melting point of acetylsalicylic acid has been found to vary with the starting temperature of the determination and to depend on the crystal habit and size (Jamali & Mitchell, 1973). Since the habit and size of the above samples were not similar, the observed differences may be due to this. Infrared spectroscopy of these samples failed to reveal any differences.

The experiments demonstrate that the presence of acetylsalicylic anhydride in acetylsalicylic acid crystals does have an effect on the intrinsic dissolution rate when the concentration of anhydride exceeds 0·25–0·30%. Above this concentration the dissolution rate decreases with increasing amounts of anhydride (at least up to 2·8%). How then does anhydride produce this effect? An impurity may be captured by the crystal lattice forming solid solutions of various types, it may be adsorbed onto internal or external surfaces or it may be present in the form of separate crystals (Khamskii, 1969). Furthermore, an impurity may cause crystal defects by taking up a normal position in the crystal lattice (Jamali & Mitchell, 1973). It may also decrease dissolution by making the disc more hydrophobic. Of these various possibilities, the occurrence of the anhydride as separate crystals can be ruled out as it has no bearing on the effect observed. The dissolution rate of acetylsalicylic acid from a disc prepared from a physical mixture of finely ground acetylsalicylic acid (97%) and acetylsalicylic anhydride (3%) was 1·06 mg cm^{-2} min^{-1} while sample K, supplied with a similar amount of anhydride through crystallization, had a dissolution rate of 0·520 mg cm^{-2} min^{-1} which suggests that a decrease in solubility of the disc is not a satisfactory explanation in this instance. The solubility and consequently the dissolution rate of acetylsalicylic anhydride in 0·1N hydrochloric acid is approximately 180 times less than that of acetylsalicylic acid (Garrett, 1959) and this may certainly have a bearing on the effect on dissolution rate, particularly if the anhydride occurs as a thin layer adsorbed on the surfaces of the acetylsalicylic acid crystals. It should be remembered that salicylic acid which is without any effect on dissolution rate is only slightly less soluble than acetylsalicylic acid in acidic aqueous solutions.

At present no well-founded explanation of the initial non-linear course of the dissolution curves of the samples containing 1·54 and 2·76% of anhydride (see Fig. 1) can be offered. The break in the usual linear relation between amount dissolved and time is observed only for these samples, and this behaviour is therefore another characteristic property of anhydride-containing acetylsalicylic acid crystals. A similar dissolution profile for the commercial acetylsalicylic acid sample which had the lowest dissolution rate has been described by Mitchell & Saville (1969). The observations described here lead to the conclusion that both the lower dissolution rate and the characteristic dissolution profile of the acetylsalicylic acid sample concerned are due to the presence of an acetylsalicylic anhydride impurity in the crystals. Additional support for this proposal is the observation of Mitchell & Saville (1967, 1969) that the sample in question is a special case among their preparations. Most commercial acetylsalicylic acid preparations contain only small amounts of anhydride (<0·05%) (Bundgaard & Bundgaard, 1973) and therefore, assuming the presence of anhydride to be responsible for the reduced dissolution rate and the initial curvature of the dis-

solution profile, one cannot expect to find many samples containing anhydride in such amounts that the dissolution rate and profile are affected.

The findings of Summers & others (1973) that acetylsalicylic acid recrystallized from n-hexane or n-octane has lower intrinsic dissolution rates than crystals obtained from 96% ethanol may also be explained on the basis of differences in content of anhydride. While heating of acetylsalicylic acid in n-hexane leads to formation of anhydride, no or only little anhydride formation occurs in 96% ethanol (unpublished experiments). Therefore, it is not unlikely that the crystals obtained from n-hexane and n-octane, in contrast to those obtained from 96% ethanol, have been contaminated with acetylsalicylic anhydride. However this cannot be the sole explanation since about 2% of the anhydride would be required in the acetylsalicylic acid recrystallized from n-octane to produce the decrease in dissolution rate observed by Summers & others (1973) and this amount of impurity is unlikely to have arisen from a recrystallization procedure. Moreover the presence of anhydride would not explain the results of Tawashi (1968) in which acetylsalicylic acid recrystallized at room temperature from n-hexane had a faster dissolution rate than acetylsalicylic acid recrystallized from 95% ethanol.

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