SOLUBILITY - DISSOLUTION RATE RELATIONSHIPS FOR A SERIES OF SALTS OF *p*-AMINOSALICYLIC ACID

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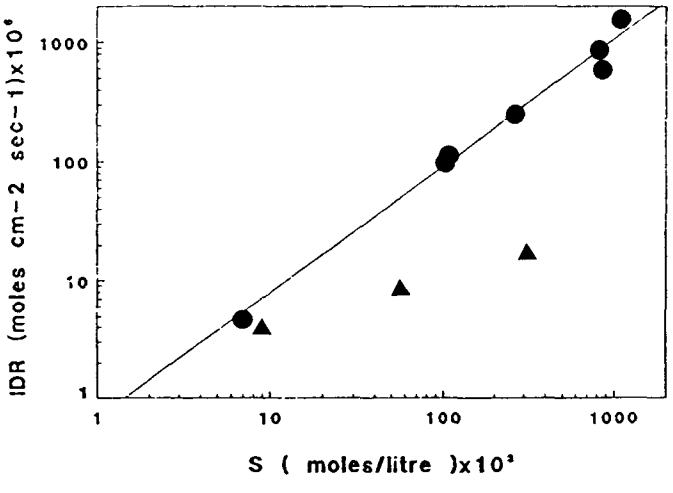
A direct relationship between solubility and intrinsic rates of dissolution of various substances has been reported (Hamlin et al 1965, Nicklasson et al 1981) and used to estimate solubilities where limited amounts of material were available, and to aid salt selection (Nicklasson & Nyqvist 1983). We report the use of this relationship to rank solubility in a series of salts where equilibrium solubility assessment is compromised due to decomposition in solution.

The salts (see Table 1) were synthesized either by metathetical reaction with the sodium salt or by direct reaction with p-aminosalicylic acid (PAS) in a suitable solvent. Synthesis was confirmed by elemental analysis. The intrinsic dissolution rate (IDR) of each salt in water at 10°C was determined spectrophotometrically at 300nm using a static disc method, utilising a USP2 paddle (100rpm) dissolution apparatus. Apparent aqueous solubilities (S) were determined at 10°C after 1 hour equilibration. Table 1 lists the mean values of IDR and S and Fig. 1 shows the data as a log-log plot. A gradient of 1.06 was obtained for the least squares regression line of seven of the salts (●in Fig. 1) conforming to the Noyes-Whitney equation (1897). The three salts - tosylate, mesylate and sulphate (▲in Fig. 1) - which deviated from this line were shown, by examination of the disc surface before and after dissolution using differential scanning calorimetry (DSC) and X-ray diffractometry (XRD), to have reverted to PAS at the surface of the disc.

Table 1 Properties of PAS salts

Salt	IDR $Mcm^{-2}s^{-1}$ x 10^6	S Ml^{-1} x 10^3
PAS (free acid)	5	7
Sodium	888	847
Calciumhydrated	111	107
Calcium	259	268
Magnesium	107	105
Potassium	2673	-
Ethanolamine	595	870
Ammonium	1613	1120
Tosylate	9	56
Mesylate	17	318
Sulphate	4	9
Hydrochloride-	-	25

Fig.1 Relationship between dissolution rate and solubility for PAS salts at 10°C



The use of intrinsic dissolution rates as a means of estimating solubilities in problematic situations of solution instability is thus demonstrated. Since this approach is based on the assumption that no phase transformation occurs on dissolution, it is recommended that supplementary techniques such as DSC and XRD are used.

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