COUNTER-ION EFFECTS ON MOLECULAR PACKING AND HYDRATE PROPERTIES FOR SALTS OF *p*-AMINOSALICYLIC ACID

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Salts are often considered as alternative forms for drug delivery when the physicochemical and/or mechanical characteristics of parent molecules compromise required formulation and processing properties. The rationale for salt selection, however, remains semi-empirical (Wells, 1988). In an attempt to develop a more scientific approach, the propensity for hydrate formation and stability in a model salt series - salts of p-amino salicylic acid (PAS) - was discussed (Forbes et al 1989). This report considers the influence of the counter-ion species on molecular packing and the degree of interaction with water molecules of crystallisation for members of this model salt series.
Powder X-ray diffractograms were obtained (Siemens D-500 Diffractometer) for PAS and the sodium, calcium and magnesium salts of PAS. The salts were shown to be di-, tri- and tetra-hydrates, respectively, using Karl Fischer and elemental analyses (Forbes et al 1989). Data (see representative diffractograms in Figure 1) demonstrate the non isomorphous nature of the PAS and salts, indicating different molecular packing arrangements. Single crystal x-ray diffractometry using Cu-K alpha radiation (Stoe Stadi-4 Diffractometer) was carried out on individual crystals to determine unit cell dimensions and estimate bond lengths between the counter-ion and the oxygen of water of crystallisation.

Table 1 Crystal data for PAS and PAS salts

	PAS[1]	Na-PAS	Ca-PAS
Unit cell dimensions(Å)			
a	7.21	7.00	6.96
b	3.79	14.74	11.15
c	25.11	8.86	21.02
Unit cell angles (°)			
	90.00	90.00	90.00
ß	103.22	97.89	98.68
	90.00	90.00	90.00
No molecules in unit cell	4	4	4
Crystal system	monoclinic	monoclinic	monoclinic

[1] : Lin et al 1978

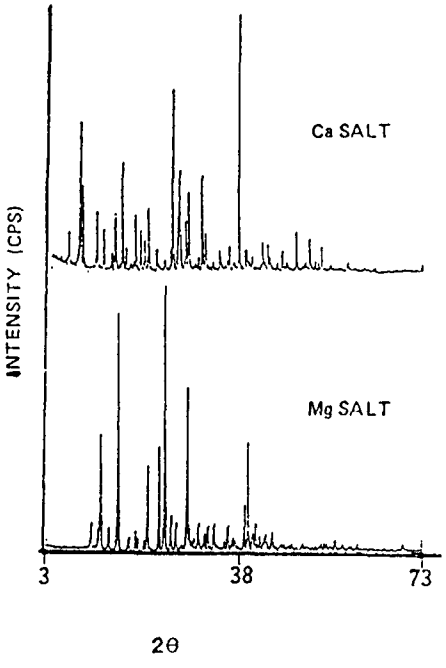

Fig.1 X-ray diffractograms of PAS salts

Data in Table 1 confirm the different molecular packing arrangements of the salts, and variation from the parent PAS. Estimates of the bond lengths between sodium ion and water oxygens were 2.41 and 2.94 Å, whilst those between magnesium ion and water oxygens were all similar within the range 2.08-2.15 Å. As a result of the stronger ion-dipole interaction, dehydration from the magnesium salt would be expected to occur at a higher temperature threshold than the sodium salt. This has been demonstrated using DSC and TGA techniques (Forbes et al 1989). However steric effects and crystal defects will also contribute in determining apparent dehydration threshold temperatures.

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