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Why are aqueous suspensions of the coarse grades of anhydrous calcium hydrogen phosphate acidic?

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The anomalous acidic properties of the coarse grades of anhydrous calcium hydrogen phosphate are commented and a tentative elucidation of this is proposed.

In solid dosage form pharmaceuticals essentially four varieties of calcium hydrogen phosphate are employed, i.e. CaHPO_4 anh. milled (fine powder) and unmilled (coarse) and CaHPO_4 dihydrate milled and unmilled. The coarse grades of anh. CaHPO_4 may be used for direct compression tableting. The principal commercial products (trade names) of these are A-Tab, Di-Cafos AN and Emcompress anhydrous having average particle diameters of approximately 140–180 μm whereas the particle sizes of the powdered qualities of both anh. CaHPO_4 and dihydrate are much smaller or about 9–15 μm (Moreton 2003).

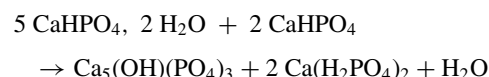
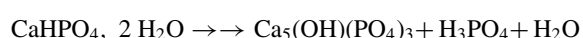
All these varieties of CaHPO_4 are practically insoluble in water. The pHs of 20% aqueous suspensions of the milled versions of both CaHPO_4 anh. and dihydrate as well as the coarse grades of CaHPO_4 dihydrate are typically about 7.4. By contrast, the pHs of aqueous 20% suspensions of anh. CaHPO_4 are about 5.1 (Moreton 2003). For comparison, the pH of a 0.1 M aqueous solution of Na_2HPO_4 is approximately 9.

Theoretically, it would be anticipated that the pHs of aqueous suspensions of all grades of CaHPO_4 were on the slightly alka-

line side (7–8) due to the low solubilities of these compounds. But, unexpectedly, the pHs of the coarse grades of anh. CaHPO_4 stand out as acidic indicating the presence of some unknown impurity/ies. This may have important consequences for drug formulation and indeed instability of bisoprolol fumarate in the presence of coarse anh. CaHPO_4 has been observed (Dulin 1995). It has been shown that the acidic impurity/ies in one of these acidic varieties (A-Tab) can be washed away indicating aqueous solubility of it/them (Dulin 1995).

The author has attempted to contact the three main manufacturers of the coarse grades of anh. CaHPO_4 for information but with little success. Two of them did not respond to the inquiries but one replied by stating that the pH is a result of the processing conditions which are considered to be proprietary.

If coarse anh. CaHPO_4 is prepared by dehydrating CaHPO_4 dihydrate at elevated temperatures the following processes (either of them or both) may conceivably occur:



Both processes result in the formation of insoluble hydroxyapatite and the soluble phosphoric acid (Serajuddin et al. 1999) or the soluble and acidic calcium dihydrogen phosphate (Fulmer and Brown 1998) which may possibly explain the acidic properties of the coarse anh. CaHPO_4 grades.

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