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Chemical stability of acetylsalicylic acid in tablets prepared with different commercial brands of dicalcium phosphate dihydrate

M. Landín [a], B. Pérez-Marcos [a], M. Casalderrey [a], R. Martínez-Pacheco [a,*], J.L. Gómez-Amoza [a], C. Souto [a], A. Concheiro [a], R.C. Rowe [b]

[a] *Departamento de Farmacología, Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Santiago, 15706 Santiago de Compostela, Spain,* [b] *ZENECA Pharmaceuticals, Macclesfield, Cheshire, UK*

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Abstract

The chemical stability of acetylsalicylic acid (ASA) in tablets prepared with one of six brands of dicalcium phosphate dihydrate (DCPD, four powder brands and two aggregated brands) was evaluated. The tablets were stored for 6 months at 35°C and 82.9% relative humidity. The stability of ASA varied considerably between tablets prepared with the different brands. This can probably be attributed to between-brand differences in both mean particle size and in intraparticle porosity, as reflected in the close correlation between DCPD specific surface (which itself is a reflection of mean particle size and intraparticle porosity) and percentage of ASA degraded after 6 months storage.

Key words: Dicalcium phosphate dihydrate; Specific surface; Intermanufacturer variability; Acetylsalicylic acid; Chemical stability

In two recent studies (Landín et al., 1994a,b) we characterized a number of brands of dicalcium phosphate dihydrate (DCPD) powder and the two currently available brands of aggregated DCPD for direct compression. We found significant between-brand differences in dehydration behaviour, which we attributed to differences in micromeritic properties and mean particle size. This led us to consider whether the brand of DCPD used for producing solid forms (particularly tablets) might affect the chemical stability of the drug, especially when that drug is readily hydrolysed. We have investigated this question by comparing the chemical stability of acetylsalicylic acid (ASA; Merck, lot 042 K13642985), a drug which is known to be rapidly hydrolysed (Connors et al., 1986) and which has been used as a model in similar studies (Patel et al., 1988), in tablets prepared with one of six brands of DCPD previously characterized (Landín et al., 1994a,b) in our laboratory (Merck, Calipharm, Monsanto, Kyowa, Emcompress and DiTab).

Tablets (350 mg) were obtained by direct compression of a 10:90 w/w mixture (Turbula T2C at 30 rpm for 5 min) of ASA and the corresponding

* Corresponding author.

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Table 1
Specific surfaces, mean particle size and intraparticular porosity of the six DCPD brands tested (Landín et al., 1994a,b), and salicylic acid content (as a percentage of initial acetylsalicylic acid content) after 6 months storage (35°C, 82.9% relative humidity) of tablets produced using each brand

DCPD Brand	Salicylic acid content (% w/w)	Specific surface, (m^2 g^{-1})	Mean particle size (μm)	Intraparticular porosity (cm^3 g^{-1})
DiTab	3.05 (1.39)	0.77	57.22	0.0030
Emcompress	7.83 (2.76)	0.85	57.53	0.0045
Kyowa	27.10 (3.55)	0.98	32.93	0.0040
Calipharm	31.49 (2.39)	1.89	5.09	0.0085
Monsanto	47.29 (1.96)	1.98	4.28	0.0090
Merck	55.80 (1.55)	2.38	4.82	0.0130

Values for salicylic acid content are means (standard deviations) of six determinations.

DCPD. Compression was carried out with an eccentric press (Korsch EKO, fitted with a pressure transducer) with 9 mm diameter flat punches (maximum compression force 10.7 kN). The tablets were stored for 6 months at 35°C and with relative humidity maintained at 82.9% with an aqueous solution of KCl; these storage conditions were selected in view of the results of Rabach and Mielck (1981), and are usual in studies of drug stability in DCPD formulations (Lausier et al., 1977; Vila-Jato et al., 1985). At the end of this period salicylic acid (SA) content in the tablets was determined spectrophotometrically according to the method of Gore et al. (1968) following confirmation of specificity for SA in SA/ASA mixtures. Samples of milled tablets were mixed with boric acid-KCl-NaOH buffer (pH 7.4) by vigorous shaking for 3 min at 0°C. Absorbance at 298 nm was determined, immediately after membrane filtration (Millipore, 0.22 μm pore size) of the supernatant, against a blank obtained by identical treatment of the corresponding DCPD without drug.

Our results (Table 1) reveal that the brand of DCPD used has considerable effects on the rate of ASA degradation. There were no significant correlations between SA content after 6 months storage and DCPD peak heights in thermogravimetric analysis (TGA), for either the 150 or 200°C peak (TGA data from our previous studies). Similarly, there was no significant correlation with mean particle size of the DCPDs; however, specific surface of the DCPDs (as determined by nitrogen adsorption; see Table 1) was significantly and positively correlated with SA content after 6 months storage ($r = 0.9294$).

The strength of this correlation suggests that specific surface is a useful predictor of the rate of loss of lattice water which we consider to be because specific surface reflects a more complex interaction between a number of variables including intraparticle porosity and mean particle size all of which vary considerably among the DCPDs studied. To confirm this hypothesis we have used stepwise multiple regression (Dixon, 1983), with specific surface (SS) as the dependent variable and mean particle size (MPS) and intraparticle porosity (IP) as independent variables. Data for independent variables (Table 1) are from our previous studies. The regression equation obtained ($r = 0.9949$) was as follows:

$$SS = 0.92 - 0.01MPS + 117.90IP$$

This confirms that specific surface is correlated with the variables likely to be most important in determining lattice water loss rate.

The results of this study argue for the adoption of specific surface as one of the criteria to be used in DCPD manufacturing quality control and in the selection of DCPDs as solid form excipient, particularly when dehydration can be expected to affect the stability of the drug or some other component of the formulation.

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