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DECOMPOSITION AND STABILIZATION OF THE TABLET EXCIPIENT CALCIUM HYDROGENPHOSPHATE DIHYDRATE

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ABSTRACT

Calcium hydrogenphosphate dihydrate is a commonly used filler in solid dosage forms. In the literature it is noticed that drug decomposition reactions can be accelerated by the decomposition of $CaHPO_4.2H_2O$. The present study has been performed to evaluate various types of this commercially available excipient and to elucidate the impact of selected factors on stability.

The influence of both temperature (40, 50 and 60 °C) and environmental humidity (26, 34 and 46 % rel. humidity) on the dehydration of calcium hydrogenphosphate dihydrate was studied for a period of two to three months. Five batches of $CaHPO_4.2H_2O$ were used with different contents of magnesium hydrogenphosphate and sodium pyrophosphate, which are often added to stabilize $CaHPO_4.2H_2O$ in preparations like aqueous dentifrices. Disks of $CaHPO_4.2H_2O$ have been prepared in such a way, that the structure of the disks allowed discrimination between the batches in dehydration kinetics. A relatively low velocity of

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* Correspondence

dehydration was found for the batches containing high levels of sodium pyrophosphate. The effect of environmental humidity on the dehydration velocity appeared not to be straightforward: only at 60 °C an acceleration of the dehydration rate was found for all batches due to the increase of relative humidity. The residues after dehydration were analysed by Diffuse Reflectance Infrared Fourier Transform Spectroscopy (DRIFT), Thermogravimetric Analysis and Differential Scanning Calorimetry.

The results demonstrate that, independent of the storage condition and the type of calcium hydrogenphosphate dihydrate used, the main decomposition product is anhydrous calcium hydrogenphosphate. This contrasts with interpretations in the literature, which include the formation of decomposition products like hydroxyapatite and phosphoric acid.

Although no experiments were performed in the presence of drugs, a hypothesis is proposed on the basis of this study for the mechanism of possible drug decomposition in the presence of calcium hydrogenphosphate dihydrate. The mechanism can be simplified to dissolution of drug in accumulated free water due to dehydration within the drug/excipient system with, possibly, interactions between the drug and calcium hydrogenphosphate dihydrate. Obviously, time, temperature and amount of accumulated free water are important factors in determining the amount of drug decomposed. Accumulation of free water in granulates and tablets containing calcium hydrogenphosphate dihydrate should therefore be avoided or at least limited. This will have implications for e.g. the selection of the quality of calcium hydrogenphosphate dihydrate to be used and for the manufacturing practice of solid dosage forms containing this filler excipient.

INTRODUCTION

Calcium hydrogenphosphate dihydrate is widely used as the abrasive in dentifrices and has for several years been recognized as a filler excipient in tablet formulations. Nowadays $CaHPO_4.2H_2O$ is a commonly used excipient in solid dosage forms, be it less frequently than lactose. When in the development stage of tablet formulations chemical instabilities of drug substances or dosage form are to be expected, as in the classical example of incompatibility between amine drugs and aldehydic lactose, $CaHPO_4.2H_2O$ may become the excipient of choice.

Problems associated with aging of tablets comprising $CaHPO_4.2H_2O$ are unfavourable changes in the physical properties of the dosage forms. Aging of tablets with calcium hydrogenphosphate dihydrate in low and high humidity conditions have been reported to affect both disintegration and dissolution rates (1,2). Horhota et al.(3) found a decrease in dissolution rate without changes in hardness or tablet size under accelerated storage conditions of $CaHPO_4.2H_2O$ containing tablets. The effect on dissolution properties was pointed out to be the result of the loss of hydrated water at high temperature and humidity (4).

The dehydration of calcium hydrogenphosphate dihydrate has been studied for many years (5-7). The course of dehydration at elevated temperatures has been demonstrated to be extremely complicated and dependent on the water-vapour pressure. Rabach and Mielck (8) studied the impact of temperature and humidity on the release kinetics of hydration water from Emcompress tablets. The rate of decomposition increased with temperature, whereas an increase in environmental humidity only resulted in increased decomposition upto a rel. humidity of 34%. They suggested the formation of hydroxyapatite during storage of $CaHPO_4.2H_2O$. This decomposition product might, due to its large surface area, be responsible for some occasional incompatibilities (9).

Addition of (calcium or sodium)pyrophosphate was shown to suppress the rate of dehydration of $CaHPO_4.2H_2O$ in toothpaste (10,11). Phosphates like e.g. magnesium

TABLE 1

Analytical Data of the $CaHPO_4.2H_2O$ Batches

Batch	CODE	Mg* content (%)	Pyrophosph. content (%)	Content** $CaHPO_4.2H_2O$ (%)	Weight loss on ignition at 800 °C
8147/86	1	0.62	< 0.005	100.9	25.8
Stauffer	2	0.23	0.005	-	-
8639/86	3	0.20	0.01	100.2	26.0
8611/87	4	0.51	0.22	98.5	25.6
8754/87	5	0.32	0.40	98.1	25.2

* present as $MgHPO_4.3H_2O$

** according to Ph. Eur. 2 (1981)

\- not determined

hydrogenphosphate are often incorporated in dentifrices to stabilize the thermodynamically unstable $CaHPO_4.2H_2O$ against its transformation into hydroxyapatite (12,13) and to inhibit accumulation of phosphoric acid as decomposition product(14).

The objective of the present study was to determine the effects of both types of stabilizers on the rate of decomposition of calcium hydrogenphosphate dihydrate in tablets under elevated humidity and temperature conditions. Moreover, the study is focussed on a grosso-modo elucidation of the mechanism of the decomposition reaction.

MATERIALS AND METHODS

Samples of calcium hydrogenphosphate dihydrate with the charge numbers 8147/86, 8639/86, 8611/87 and 8754/87 were obtained from Budenheim (FRG). The 'Stauffer sample' (lot no 3050) was provided by Stauffer (USA). Hydroxyapatite was obtained from Merck (FRG) and anhydrous calcium hydrogenphosphate from Aldrich-Chemie (Belg.).

Quantitative analysis of sodium pyrophosphate and magnesium content in the $CaHPO_4.2H_2O$ samples was performed by NMR and Atomic Absorption Spectrometry, respectively. Higher Mg and pyrophosphate contents represented, for the application as tablet excipient, the normal commercial specification for 'stabilised' calcium hydrogenphosphate dihydrate (Table 1).

The Malvern 2600 Particle Sizer was used to characterize the $CaHPO_4.2H_2O$ batches with respect to their specific surface areas and particle size distributions in terms of 10, 50 and 90% of the particles below a measured volume-diameter. The analyses were performed in threefold.

Cylindrical disks of $CaHPO_4.2H_2O$ were prepared on a Courtois tableting press. The disks weighed 350 +/- 3 mg, had a diameter of 12.0 and a height of 1.92 mm. Since the various $CaHPO_4.2H_2O$ batches showed almost equal densities(2.37 g/cm^3, determined with a Beckmann Air Comparison Pycnometer(model 930)), the porosity of all disks was approx. 38%. A crushing-strength of approx. 27 N was determined with a Pharmatest apparatus (Type PTB 301).

Saturated solutions of potassium acetate, magnesium chloride and magnesium nitrate in desiccators were applied to obtain relative humidities of 26, 34 and 46% respectively at temperatures of 40, 50 and 60 °C. Five disks of each batch of $CaHPO_4.2H_2O$ were carefully positioned in a tray to allow complete exposure of the disk surface to environmental vapour.

Differential Scanning Calorimetry was performed with a Perkin Elmer DSC 7 Thermal Analysis System with approx. 5mg of $CaHPO_4.2H_2O$ in open aluminium pans (30 μl). Thermogravimetric Analyses were made on a Perkin Elmer TGA7. The sample size was approx. 7 mg. For both the DSC and TG analyses a heating rate of 6 °C/min was applied. Vapour pressure during analyses, which has been reported to affect the dehydration process(18), was not controlled. Nevertheless, reproducible results were obtained during the study.

A Digilab FTS 15/90 FT-IR spectrometer was applied for IR spectroscopy (Diffuse Reflectance Infrared Fourier Transform (DRIFT)). The DRIFT spectra were obtained from samples in which $CaHPO_4.2H_2O$ was dispersed in KBr.

RESULTS

Effect of the temperature on dehydration

The impact of temperature on the rate of dehydration of calcium hydrogenphosphate dihydrate Batch 1 is shown in Figure 1A. At a relative humidity of 26% the tablets at 40 °C revealed sigmoidally shaped profiles of weight loss in time. After an induction time of about two days, a steadily accelerating velocity of decomposition was found upto a weight loss of approx. 8% (equals 50% decomposition; point of maximum velocity), followed by a decreasing rate towards an equilibrium state of 16% after four weeks. A considerable increase in rate of weight loss is found at 50 °C. Within about 6 days dehydration was completed. At 60 °C only two days were sufficient to decompose the excipient completely. The results clearly demonstrate that at a relative humidity of 26% the chosen storage temperatures do not affect the total amount of weight loss. From the Tables 2, 3 and 4 it can be seen that the time periods required for a decomposition of 50% ($t_{50\%}$) are 7.9 days, 1.8 days and less than one day for the temperatures 40, 50 and 60 °C respectively. Elevation of the temperature resulted in both reduction of the induction period and higher maximum dehydration velocities.

Figures 1B and 1C show the results for Batches 3 and 4 respectively at 26% RH. The impact of temperature on dehydration for these Batches 3 and 4 was comparable with the behaviour shown by Batch 1 in Figure 1A. However, for Batch 3 (Fig. 1B) considerably lower rates of weight loss were found. At a temperature of 40 °C the disks only released 2% of their hydrate water in 53 days at 26% RH.

TABLE 2

Days(storage) at 40°C for 10, 50 and 95% Dehydration

	t_{10} 2)			t_{50}			t_{95}		
RH	26	34	46	26	34	46	26	34	46
BATCH									
1	3.7	1.9	3.8	7.9	4.8	10.0	17.8	12.9	40.5
2	16.5	22.5	- 1)	30	33	-	53	53	-
3	-	48	-	-	-	-	-	-	-
4	42	38	-	-	-	-	-	-	-
5	29	23	32	-	-	-	-	-	-

1) weight loss below limit of 10% in 60 days

2) t_{10}, t_{50} and t_{95} is the time(days) required to attain levels of decomposition of resp. 10, 50 and 95%

TABLE 3

Days(storage) at 50°C for 10, 50 and 95% Dehydration

	t_{10}			t_{50}			t_{95}		
RH	26	34	46	26	34	46	26	34	46
BATCH									
1	0.8	<1	<1	1.8	0.9	1.1	6.1	2.5	4.2
2	2.9	2.9	5	5.2	5.0	8.3	10.3	8.2	12.8
3	13.5	7.5	6.5	18.1	10.7	9.5	26	20	59
4	11.2	6.5	8.1	59	20.5	21.5	-	57	-
5	10.6	4.3	4.1	-	15	12.2	-	41	38

TABLE 4

Days(storage) at 60°C for 10, 50 and 95% Dehydration

	t_{10}			t_{50}			t_{95}		
RH	26	34	46	26	34	46	26	34	46
BATCH									
1	<1	<1	<1	<1	<1	<1	<1	<1	1.7
2	<1	<1	<1	1.3	0.9	1.3	2.5	2.0	2.0
3	2.8	1.5	1.5	4.4	2.5	1.9	6	4	5
4	3.0	1.5	1.8	14.0	5.2	4.0	48	13	14
5	3.0	1.5	1.7	15.8	4.1	3.1	>60	11.0	6.8

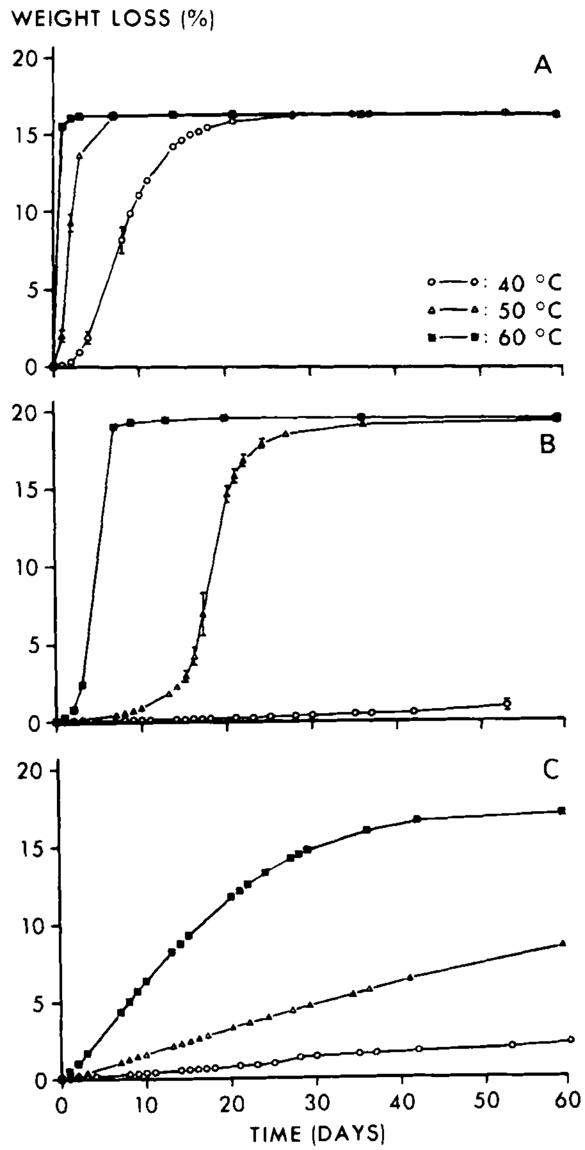

FIGURE 1
Effect of temperature on the loss of weight during storage (RH:26%) of disks prepared from Batch 1 (A), Batch 3 (B) and Batch 4 (C)

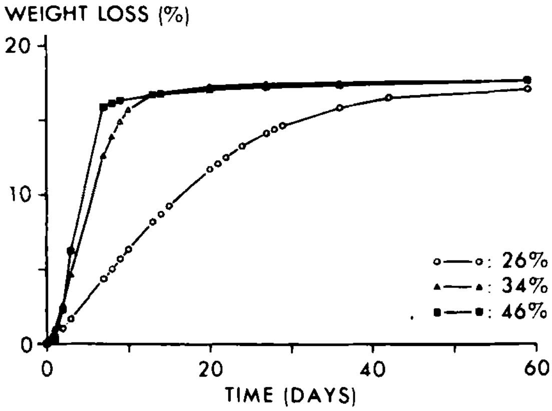

FIGURE 2
Effect of relative humidity (RH) on the loss of weight during storage (60 °C) of disks prepared from Batch 4.

It should be noted that weight variation, indicated by the error bars, was rather low at all time points.

Comparing the results for Batch 4 (Fig. 1C) with the profiles of Batch 3, a sharp decrease in the rate of weight loss at 50°C (t_{50} of 59 days; Table 3) was determined, whereas complete decomposition at 60 °C was hardly reached within 60 days.

Effect of relative humidity on dehydration

Figure 2 reflects the impact of humidity on the kinetics of dehydration at 60 °C of disks from Batch 4. It is remarkable that an increase in humidity results in a faster rate of weight loss (t_{50} of 14.0, 5.2 and 4.0 days for 26%, 34% and 46% RH respectively; Table 4). This rank order relationship is, however, found most pronouncedly for the batches at 60 °C, as demonstrated by Fig. 3 and the Tables 2, 3 and 4. At a temperature of 40 °C, the batches 1, 2, 3 and 4 demonstrated the lowest rate of dehydration at the highest relative humidity (46%), whereas the fastest was mostly found at 34% RH. In the condition of 50 °C, the t_{50} of the profiles found at 46%

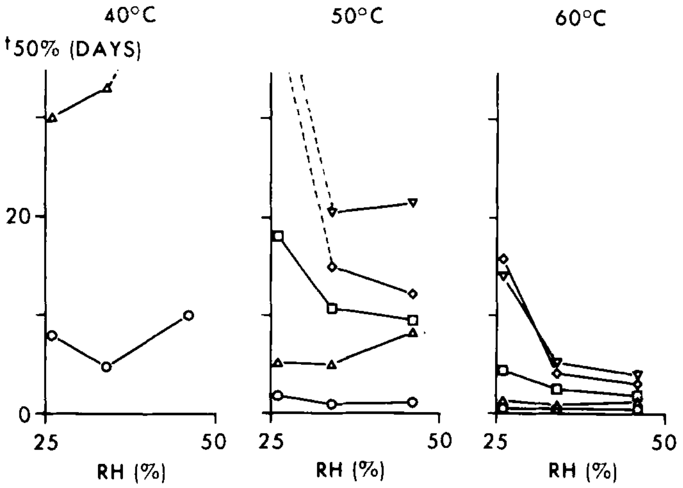

FIGURE 3
Relationship between the humidity and the $t_{50\%}$ at storage temperatures of 40, 50 and 60 °C. Batch 1: ○——○ , Batch 2: ▲——▲ , Batch 3: □——□ , Batch 4: ▼——▼ and Batch 5: ◆——◆ .

RH are mostly equal to or sometimes even smaller than the t_{50} at 34% RH with the exception of Batch 2. At 60 °C the lowest rates for the most of batches was found at 26% RH.

From the Tables 2, 3 and 4 and from Fig. 3 it can be seen that relatively fast velocities of decomposition are found for batches 1, 2 and 3 with sodium pyrophosphate contents of <0.005, 0.005 and 0.01% respectively. Batches 4 and 5 with contents of the stabilizing agent of 0.22 and 0.40% resp. showed lower velocities of weight loss. No clear relationship between the content of magnesium hydrogenphosphate in the batches and the decomposition rate is present.

Temperature and humidity did not affect the total weight loss upon storage per batch, whereas between the batches differences were found (Figs. 1A, B, C and 2).

Table 5 shows the specific surface area and diameters(d_{10}, d_{50} and d_{90}) of the initial particles of

TABLE 5
Size and Size Distribution of the Initial $CaHPO_4.2H_2O$ Particles as supplied

BATCH	S.S.A.[1]	d10%[2]	d50%	d90%
	Mean+/-(SD)	Mean+/-(SD)	Mean+/-(SD)	Mean+/-(SD)
1	0.12 (0.01)	5.9 (0.4)	15.1 (2.0)	36.4 (2.1)
2	0.27 (0.09)	3.7 (0.2)	9.3 (1.3)	21.2 (4.5)
3	0.29 (0.03)	4.3 (0.2)	10.1 (0.7)	20.1 (1.4)
4	0.20 (0.03)	5.6 (0.6)	13.3 (1.3)	27.4 (3.1)
5	0.20 (0.04)	5.2 (0.5)	12.7 (1.1)	28.8 (0.5)

1) Specific Surface Area in m^2/cm^3

2) 10% Of the particles have a volume-diameter below value in the table (μm)

calcium hydrogenphosphate dihydrate, used for preparation of the disks. The data in μm indicate that 10, 50 and 90% of the particles have smaller volume-diameters. The results clearly demonstrate that Batch 1 has larger particles than the other four batches.

Thermal analyses of calcium hydrogenphosphate dihydrate and of the dehydration residues after storage

In Figure 4, the corresponding TGA, DTG and DSC curves of Batch 3 are depicted on the same temperature scale. The DSC curve shows characteristic endotherm peaks at 130 and 185 °C for the dehydration of $CaHPO_4.2H_2O$ in dry nitrogen atmosphere. The TGA curve demonstrates a slight downward step at about 125 °C and a sharp change at about 194°C. Comparing the plots reveals that the temperature points of maximum heat flow correspond with the temperatures at which maximum rates of weight decrease are detected. With the batches of $CaHPO_4.2H_2O$ applied in this study no clear resolution of the endothermic reactions(DSC curves) was found as reported in literature (15). This may be the

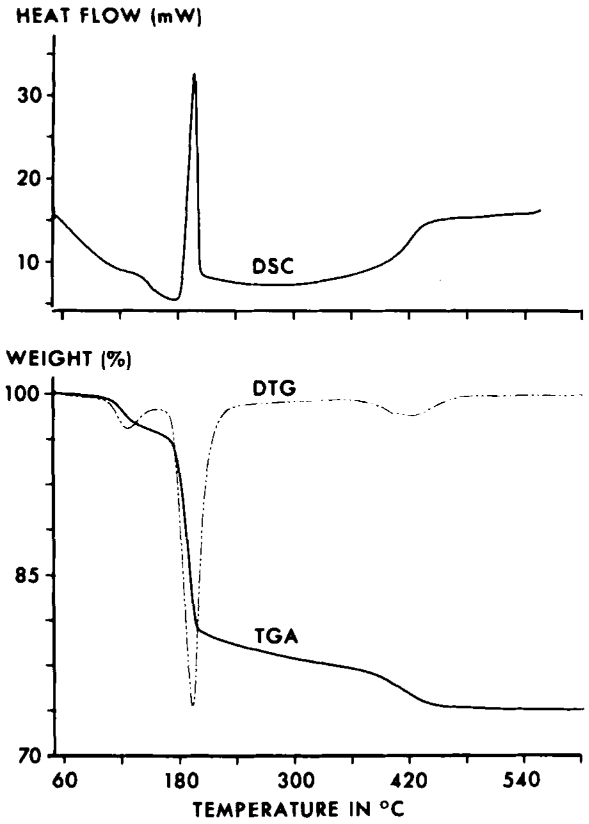

FIGURE 4
The profiles of DSC, TGA and DTG obtained for Batch 3.

effect of the particle size (16). At 430 °C an endotherm deflection is found in the DSC curve, corresponding with a theoretical loss of weight of 5.2 %. Finally, an exothermic peak appears at 530 °C, indicating crystallization of τ-$Ca_2P_2O_7$ (17). The first endotherm deflection at 140 °C coincides with the loss of one mole of water by two moles of CHD:

$$Ca_2(HPO_4)_2 \cdot 4H_2O \longrightarrow Ca_2(HPO_4)_2 \cdot 3H_2O + H_2O(l) \quad (1)$$

It has been argued (17) that the addition of pyrophosphates suppresses the elimination of H_2O (equation 1), thus explaining the use of this compound in the thermal stabilization of calcium hydrogenphosphate dihydrate at relatively low temperatures (10,11). With high resolution a following endotherm peak can be found which is possibly the result of boiling off the water released from the hydrate (equation 2) (18):

$$H_2O(l) \longrightarrow H_2O(g) \qquad (2)$$

The large peak at 185 °C (Fig. 4) indicates the loss of 3 moles of water, initializing the formation of anhydrous calcium hydrogenphosphate (equation 3):

$$Ca_2(HPO_4)_2.3H_2O \longrightarrow Ca_2(HPO_4)_2 + 3\ H_2O \qquad (3)$$

At a temperature of about 430 °C the anhydrous salt is condensated into τ-calcium pyrophosphate (equation 4):

$$Ca_2(HPO_4)_2 \longrightarrow Ca_2P_2O_7 + H_2O \qquad (4)$$

The dehydration rate under dry nitrogen atmospheric conditions, as applied in this study, is lower than under humid conditions (5), probably resulting in poor resolution of the three above steps of loosing hydrate water. Table 6 illustrates for batches 1-5 the loss of water in temperature ranges selected on basis of the distinct reactions on the DSC thermogram.

Before 165 °C most of the batches lost about 1 mole of H_2O per mole of P_2O_5, corresponding to eqs. 1 and 2. Further increase to 215 °C resulted in the formation of anhydrous calcium hydrogenphosphate, i.e. a subsequent loss of three moles of water per mole of P_2O_5 (eq. 3). For Batch 3 this appeared to be a slightly more (3.2 moles H_2O/P_2O_5; Table 6), apparently indicating that the first reaction of the loss of 1 mole of H_2O for this batch of calcium hydrogenphosphate dihydrate did not attain completion at 165 °C. The same phenomenon is found by the weight loss of all batches in the range of 215 to 800 °C: 1.1 to 1.3 moles of water per mole of P_2O_5 were released by the inorganic phosphate, whereas only 1.0 was to be expected for the condensation of anhydrous $CaHPO_4$ to $Ca_2(P_2O_7)$. The total decrease in weight determined with the TGA is in agreement with the results found after ignition at 800 °C to constant weight (Table 1). From

TABLE 6

Results from Thermogravimetric Analyses of the Five Batches of $CaHPO_4.2H_2O$

	Temperature range (°C)					
	50-100	100-165 (T_{max}) 1)	165-215 (T_{max})	215-370	370-500 (T_{max})	50-800
BATCH						
1	0.1 2)	0.8	2.4	0.5	0.7	4.6
		(128)	(192)		(424)	
2	0.1	1.0	2.6	0.5	0.6	5.0
		(120)	(191)		(427)	
3	0.1	0.4	3.2	0.6	0.6	4.9
		(121)	(196)		(428)	
4	0	0.8	2.8	0.5	0.6	4.9
		(128)	(194)		(419)	
5	0.1	0.8	2.9	0.5	0.6	4.9
		(128)	(194)		(422)	

1) temperature point at maximum velocity of weight loss

2) loss of weight in H_2O/P_2O_5 mole ratio

Table 6 it can be seen that the values of the three temperature points of maximum velocity of weight loss (T_{max}) are for all the batches almost the same, i.e. about 125, 193 and 423 °C.

In Figure 5 the TGA and the DTG plots of the residue of Batch 1 after dehydration (60 days; 50 °C/46% RH) are depicted. Two steps of decrease in mass are reflected at 119 and 431 °C with in between a gradual decline in weight. The results of the Thermogravimetric Analyses on the decomposition products of the various batches studied are summarized in Table 7. An important contribution to the differences between the batches in the total weight loss at 500 °C is provided by the effects in the temperature range of 100-165 °C. The largest decrease in weight is found for Batch 1, which is in agreement with

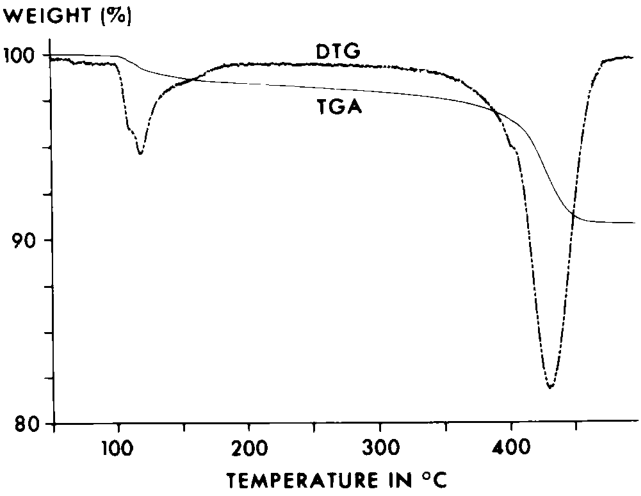

FIGURE 5
TGA and DTG plots of the residue of Batch 1 after decomposition.

the results from the gravimetric analyses of the disks on storage (Fig. 1A): a dehydration of only 16-17% of the initial weight of the disks. For the residues of the other batches, showing less decrease in weight on the TG analyses, a higher degree of dehydration was found in the storage experiments. Nevertheless the batches do not completely dehydrate on storage. Remarkable is the difference in temperature at which the maximum velocity of condensation (T_{max}) of the anhydrous calcium hydrogenphosphate to pyrophosphate is found (Table 7). The temperatures, determined by DTG, appeared to be about 400 °C for the batches 4 and 5 (both containing sodium pyrophosphate), whereas for the batches 1, 2 and 3 temperatures of about 430-440 °C were detected. This difference in behaviour in thermal decomposition of the residues from the various batches is not supported by the results from the thermal decomposition of the hydrates (Table 6).

TABLE 7

Results from Thermogravimetric Analyses of Decomposition Products of $CaHPO_4 \cdot 2H_2O$

		Temperature range (°C)					
	BATCH	50-100	100-165 $(T_{max})^*$	165-215 (T_{max})	215-370	370-500 (T_{max})	50-500
40°C 34%RH	1	0.01**	0.22 (119)	0.03 (-)	0.15	0.99 (435)	1.42
	2	0.01	0.09 (117)	0.02 (-)	0.15	1.01 (441)	1.27
	3	0.03	0.05 (129)	0.02 (-)	0.12	1.01 (430)	1.25
50 °C 46%RH	1	0.03	0.22 (119)	0.04 (-)	0.18	1.03 (431)	1.48
	2	0.03	0.10 (120)	0.02 (-)	0.14	1.05 (448)	1.34
	3	0.02	0.04 (-)	0.03 (-)	0.11	1.05 (437)	1.25
	4	0.05	0.18 (118)	0.06 (184)	0.27	0.89 (401)	1.45
	5	0.04	0.10 (130)	0.05 (-)	0.39	0.77 (399)	1.36
60 °C 34%RH	1	0	0.21 (121)	0.04 (-)	0.17	0.99 (427)	1.42
	3	0.01	0.03 (-)	0.02 (-)	0.11	1.03 (431)	1.19
	4	0.05	0.13 (117)	0.05 (-)	0.16	0.96 (419)	1.35
	5	0.04	0.06 (-)	0.04 (-)	0.20	0.99 (401)	1.36
60 °C 46%RH	2	0.03	0.10 (121)	0.02 (-)	0.13	1.02 (439)	1.30
	4	0.03	0.14 (125)	0.06 (-)	0.22	0.91 (401)	1.36

* temperature point at maximum velocity of weight loss

** weight loss in H_2O/P_2O_5 mole ratio

Fourier transform infrared spectroscopy (FTIR) of the dehydration on residues after storage

The partial infrared spectra of $CaHPO_4.2H_2O$, $CaHPO_4$ and $Ca_5(PO_4)_3.OH$, obtained by diffuse reflectance, are presented in Figure 6. Large differences in spectra between the hydrate and the anhydrate are found in the 3000-4000 cm^{-1} and the 1200-2400 cm^{-1} spectral regions. The water molecules cause absorptions at 3539, 3485, 3280, 1725, 1650, 665 and 635 cm^{-1}. The two forms of calcium hydrogenphosphate (hydrous and anhydrous) have stretching and bending modes of the P-O at 1135, 1072, 990 and 532 cm^{-1} respectively (19,20). Hydroxyapatite shows a very intensive P-O stretching band 1036 cm^{-1} (Fig. 6C) and it is this prominent band that allows identification of hydroxyapatite in mixtures with anhydrous $CaHPO_4$ down to a concentration of about 1-5%. For determination of about one or two percent of hydroxyapatite a computer-subtraction was applied to yield a difference spectrum for identifying the band at 1036 cm^{-1}. Fig. 6D shows such a difference spectrum with the distinctive bands of hydroxyapatite. The spectrum is obtained by subtraction of the spectrum of $CaHPO_4$ from the spectrum of a mixture of $CaHPO_4$ with 1% of hydroxyapatite. Application of the semi-quantitative method of FTIR to the residues after dehydration on storage revealed that, if any, at most 3% of $Ca_5(PO_4)_3.OH$ had been formed during decomposition of $CaHPO_4.2H_2O$ (Table 8). Both the 'non-stabilized' Batch 1 and the 'stabilized' Batch 5 demonstrated hardly a spectral band at 1036 cm^{-1}, independent of humidity and temperature during storage. For that reason the $Ca_5(PO_4)_3.OH$ content, if any, can be considered lower than 3%. Moreover, the spectra indicated (see Table 8) that the reaction of $CaHPO_4.2H_2O$ to the anhydrate was not completed at the pseudo-equilibrium state of dehydration, i.e. characteristic stretch spectral bands were found pointing at the presence of water in the residues. This finding is supported by the TG analyses of the stored samples,

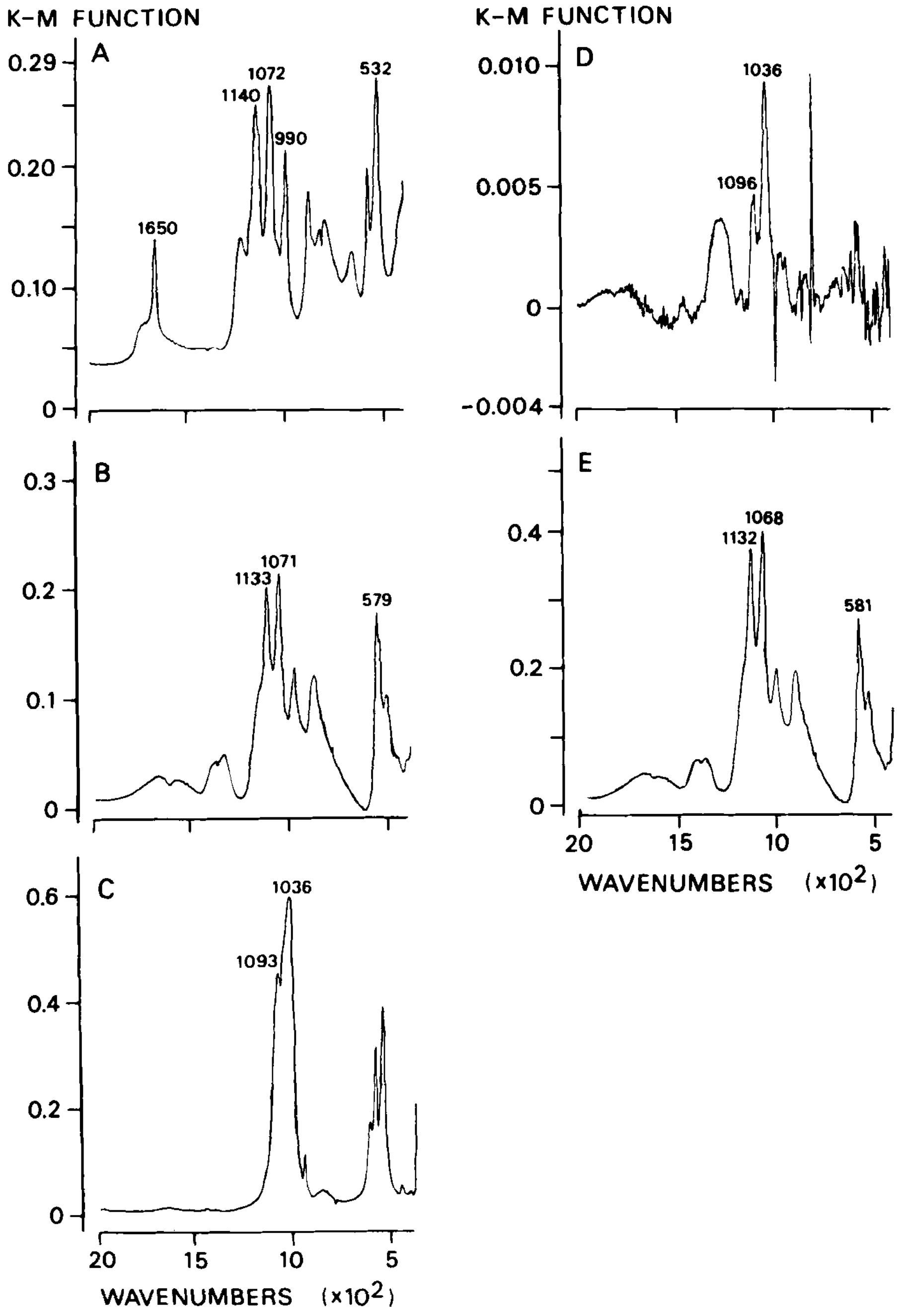

FIGURE 6

DRIFT-spectra of calcium hydrogenphosphate dihydrate (A), calcium hydrogenphosphate anhydrate ($CaHPO_4$) (B), hydroxyapatite ($Ca_5(PO_4)_3 \cdot OH$ (C), a mixture of 1% hydroxyapatite in anhydrous calcium hydrogenphosphate (difference spectrum) (D) and of decomposed Batch 5 (storage condition: 50 °C and 34% RH) (E).

TABLE 8

Results from the IR-Analyses of the residues of Calcium Hydrogenphosphate Dihydrate after Dehydration

Storage condition	BATCH	Content(%) of $Ca_5(PO_4)_3.OH$
40 °C/34%RH	1	1-2*
50 °C/34%RH	1	1-2*
60 °C/34%RH	1	0-2*
50 °C/26%RH	1	0-2*
50 °C/46%RH	1	0-2
40 °C/34%RH	5	0-3*
50 °C/34%RH	5	0-3
60 °C/34%RH	5	0-2
50 °C/26%RH	5	0-3
50 °C/46%RH	5	0-2

* decomposition product probably contaminated with $CaHPO_4.2H_2O$

showing in particular for the decomposition product of Batch 1 a weight loss at about 120 °C (Table 7).

The representative example of the spectra of decomposed $CaHPO_4.2H_2O$ (Fig. 6E) is almost identical with the spectrum of anhydrous $CaHPO_4$ (Fig. 6B).

DISCUSSION

In the literature the decomposition of calcium hydrogenphosphate dihydrate under atmospheric conditions has been described to follow a complex sequence of reaction steps with rates that are dependent of temperature and humidity(5,7,8). In this study the influence of temperature and humidity was determined on weight loss of calcium hydrogenphosphate dihydrate disks. It is assumed that the porous disks of $CaHPO_4.2H_2O$ used give comparable results with respect to the decomposition kinetics and mechanism as the individual particles. This implies that during the weight loss experiments the atmospheric humidity should have been equally distributed within the tablet system, that the migration rate of water should not have become rate limiting due to the physical structure of the reacting system, and that crushing of the initial particles during compression with equal forces should have been comparable for all batches. When transport of water is concerned, it can be stressed that the structure and porosity (approx. 38%) of the disks applied allowed extremely fast rates of weight loss (95% decomposition in less than one day; Table 4). The weight loss profiles of the calcium hydrogenphosphate dihydrate disks are sigmoidal, in agreement with a mechanism of thermal decomposition of solids including an initial, an acceleration and an exhaustion phase (21,24). The reaction is probably initiated on the external surface of the particles in nuclei of relatively low activation energy. Acceleration of the reaction is dependent on the increase of the three dimensional growth of the nuclei and on the increase in number of nuclei e.g. by the formation of small cracks. The decomposition reaction rate decreases after t_{max} (about $t_{50\%}$), at which the rate controlling factor becomes the amount of unreacted material (25).

The effect of temperature increase on the rate of weight loss of calcium hydrogenphosphate dihydrate is straightforward, i.e. shortening of the induction times and enhancement of the acceleration of decomposition, resulting in faster dehydration for all batches. It has been argued that for the dehydration reaction more energy is required at low vapour pressure than at high values for the vapour pressure (15). The dehydration reaction is initiated by adsorption of water(14). In this study the impact of humidity on the velocity of dehydration appeared to be more complicated, as can be concluded from the $t_{50\%}$ values in Figure 3. At 40 °C the batches 1 and 2 lost their bounded water faster at lower humidity conditions, whereas in general for all batches the contrary was found at temperatures of 50 and 60 °C. At these temperatures, the dehydration of the stabilized batches 3, 4 and 5 is sharply enhanced when comparing the $t_{50\%}$ values of 34% with those of 26% RH. Only a slight increase in decomposition rate, particularly at 60 °C, could be detected by increasing the humidity from 34 to 46%. The same conclusion holds for the maximum velocity of decomposition. A comparable phenomenon has been reported by Rabach and Mielck (8). They found no increase in weight loss by increasing humidity from 34 to 45% RH. The results indicate that the 'catalytic effect' of water vapour on dehydration of the dihydrate, as shown by the increase in the relative humidity from 26 to 34%, is not accelerated by further increase to 46%. Apparently the energy required for the reaction causing weight loss of the disks is not lowered by further increase of the relative humidity.

From the Tables 2, 3 and 4 and from Fig. 3 it can be seen that relatively fast velocities of decomposition are found for the Batches 1, 2 and 3 with sodium pyrophosphate contents of <0.005, 0.005 and 0.01% respectively. The batches 4 and 5 show that higher contents of the stabilizing agent(0.22 and 0.40% resp.) result in low velocities of weight loss. For magnesium hydrogenphosphate no such relationship exists between content and stabilizing effect.

Bassett (22) reported that the particle size of calcium hydrogenphosphate dihydrate in suspensions is an important factor in determining the rate of decomposition. The initial particles of Batch 1 have larger sizes than the particles of the other four batches. Considering the compression of $CaHPO_4.2H_2O$ to disks with a porosity of 38% and a crushing strength of 27 N, only little fragmentation of the particles is to be expected. These results suggest that the relatively fast dehydration rate of Batch 1 can not be explained by the factor particle size.

Thermogravimetric Analyses of the decomposition products (Tables 6 and 7) reveal that the largest contribution to the loss of weight is found in the temperature ranges 100-

165 and 215-370 °C. The small DTG peaks in the area of 100-165 °C showed equal and only sometimes lower values for T_{max}. Particularly for Batch 1 the TG analyses demonstrated that the dehydration reaction had not been completed. This impression is supported by the low total percentage of weight loss found in the storage experiment (Fig. 1A). Rabach and Mielck (8) found similar results studying weight loss of Emcompress in various conditions.They suggested two competitive reactions, depending on e.g. humidity. A dehydration reaction,

$$CaHPO_4.2H_2O \longrightarrow CaHPO_4 + 2H_2O \qquad (5)$$

and a polycondensation reaction summarized as:

$$5CaHPO_4 + H_2O \longrightarrow Ca_5(PO_4)_3.OH + 2H_3PO_4 \qquad (6)$$

Carstensen (9) stated that depending on drying conditions for granulations containing calcium hydrogenphosphate dihydrate, hydroxyapatite and other higher phosphates may occur with simultaneously formed phosphoric acid. For calcium hydrogenphosphate dihydrate in aqueous suspensions reaction 6 has been pointed out to be the cause of acidification of toothpaste (13,17,23). Koenig and Wlotzka (14) proposed a series of combined reactions in aqueous medium:

$$4CaHPO_4.2H_2O \longrightarrow Ca(H_2PO_4)_2 + Ca_3(PO_4)_2 + 8H_2O \qquad (7)$$

$$Ca(H_2PO_4)_2 \longrightarrow CaHPO_4 + H_3PO_4 \qquad (8)$$

$$H_3PO_4 + CaHPO_4.2H_2O \longrightarrow Ca(H_2PO_4)_2 + 2H_2O \qquad (9)$$

The function of stabilizing agents such as sodium pyrophosphate ($Na_4P_2O_7$) was suggested to be the immediate transition of the formed phosphoric acid into salts: this'neutralization' inhibits reaction 9. This explanation does not elucidate the mechanism of stabilization by primary and secundary magnesium phosphates in this respect. It was shown (14) that when the decomposition reaction of unstabilized calcium hydrogenphosphate dihydrate was completed, only anhydrous $CaHPO_4$ could be detected by X-ray diffraction.

FT-IR analyses of the residues of the unstable Batch 1 and the stabilized Batch 5, stored in different humidity and temperature conditions, showed that the major part (>97%) of the reaction product is the anhydrous $CaHPO_4$. It appeared from evaluation of the IR-spectra that the content of hydroxyapatite, if any, is probably below 3%. This implies, that reaction 6 does not, or at very low rates, take place during decomposition of the filler excipient in tablets in the studied storage conditions. This finding is of importance, since formation of phosphoric acid(equation 6) may have deleterious effects on the chemical stability of drugs.

The results from the present study suggest that sodium pyrophosphate decelerates the decomposition velocity of calcium hydrogenphosphate dihydrate in storage conditions of high temperature and moderate environmental humidity. The decomposition is presumably based on an overall reaction of dehydration resulting in the anhydrate. This result is in contrast with available literature.Formation of low amounts of phosphoric acid as intermediate reaction product can, however, not be excluded.

Further investigations will be directed on the stability of drugs in the presence of calcium hydrogenphosphate dihydrate. They should elucidate whether e.g. a sharp increase in surface area by the dehydration of calcium hydrogenphosphate dihydrate is responsible for the occasionally accelerated decomposition of drugs (9), whether direct interactions between dissolved drug and calcium hydrogenphosphate dihydrate are responsible, or whether it is just the dissolved drug that decomposes.

The concept of decomposition of drugs as a function of the amount of water in the tablet system available for dissolving the drug (adsorption water on the surface of particles and intra-particulate water) and of the solubility of the drug in water has been discussed in literature (9,26,27). Drugs can dissolve during granulation, drying or storage in available water (granulation water, dehydration water) and may decompose, depending on factors like chemical stability of the drug, temperature, time and amount of accumulated free water within the system. Moreover, dissolved acidic salts of drugs may react with the inorganic salt, forming soluble acidic phosphates or eventually, phosphoric acid. These reaction products may induce/accelerate decomposition reactions, especially when these mixtures are exposed to high temperatures, without control of time.

In this respect stabilized forms of calcium hydrogenphosphate dihydrate might be advantageous: the relatively slow release of hydration water e.g. during storage, even at high temperatures and elevated relative humidity conditions, hinders severe accumulation of free water in the drug containing granulates or tablets. The use of stabilized forms might therefore result in improved physical stability of the tablet and chemical stability of the drug.

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