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PARTICLE MORPHOLOGY OF AMORPHOUS ALUMINUM HYDROXYCARBONATE AND ITS EFFECT ON TABLET PRODUCTION

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ABSTRACT

The particle morphology of amorphous aluminum hydroxycarbonate was studied by disaggregation induced by phosphate adsorption and direct observation by high resolution transmission electron microscopy. The primary particles are sheet-like and have equivalent diameters of 55A or less. The primary particles are believed to correspond to planar polymers comprised of six-membered rings of aluminum ions joined by double hydroxide bridges. Secondary particles form by attractive interaction of primary particles. The size of the primary particles affects the porosity of the secondary particles. The granulating and tableting properties of two spray dried amorphous aluminum hydroxycarbonates were shown to be related to the size of the primary particles and the porosity of the secondary particles.

INTRODUCTION

Particle morphology influences many physical properties of drugs and their dosage forms but it has been less frequently studied than chemical properties[1]. The particle morphology of amorphous aluminum hydroxycarbonate is of interest because of some apparently anomalous behavior. For example, numerous studies have concluded that specifically adsorbed carbonate only substitutes for hydroxyl at surface sites and is not contained within the interior of the particle[2]. Furthermore, the carbonate to aluminum ratio of samples exhibiting good antacid properties is usually between 0.2 and 0.5[3]. These two facts can only be reconciled if the particle size is very small. Furthermore, the kinetics of acid neutralization by amorphous aluminum hydroxycarbonate are different from other antacid compounds. Sodium bicarbonate, calcium carbonate, magnesium hydroxide and hydrotalcite all exhibit a linear rate of acid neutralization under pH-stat conditions[4,5]. In contrast, the pH-stat titrigram of amorphous aluminum hydroxycarbonate contains three phases rather than the linear rate of acid neutralization expected for an acid-base titration[6]. The pH-stat titrigram has been recently interpreted based on the hypothesis that three types of particles exist: primary particles, secondary particles and aggregates[7]. Primary particles were proposed to be platy crystallites composed of fused six-membered rings of aluminum joined by double hydroxide bridges. Secondary particles form from primary particles due to the cohesive strength of van der Waals forces. Aggregates, composed of secondary particles, are formed in response to the balance of attractive and repulsive forces described by the Derjaguin, Landau, Vervey, Overbeek theory[8]. Finally, it has also been observed that the physical appearance of a chloride-containing aluminum hydroxide suspension changed during aging from a milky dispersion which exhibited sedimentation to a translucent dispersion which did not settle[9]. This change in physical appearance suggests that the surface charge increased during aging causing dispersal into a system of very small particles. In order to obtain more evidence, the particle morphology of amorphous aluminum hydroxycarbonate was studied by disaggregation induced by phosphate adsorption and direct observation by high resolution transmission electron microscopy.

EXPERIMENTAL

For the first series of experiments, an amorphous aluminum hydroxycarbonate gel (Reheis) was used to study disaggregation by phosphate adsorption. The equivalent aluminum oxide content was determined by chelatometric titration[10]. The carbonate content was determined by gasometric displacement[11]. Adsorption isotherms were obtained by using the heteropoly blue method[12] to determine the amount of phosphorus in solution after the supernatant liquid was separated by centrifugation. The effect of time on phosphate adsorption and the fraction of phosphate which was exchanged for carbonate, hydroxyl and aquo surface groups was determined by adjusting suspensions containing 15.5 mmol of aluminum and 10 mmol KCl to pH 6.6 with an automated titrator (Radiometer, Copenhagen, Denmark). After the pH was adjusted to 6.6, a solution containing 26.9 mmol NaH_2PO_4 at pH 6.6 was added and the volume adjusted to 100 ml with distilled water. The pH was maintained at 6.6 and 25°C for the desired time period with constant stirring by the automated titrator and the amount of 1 N HCl added was recorded. At the end of the time period, 25 ml of the suspension was used to determine the carbonate content and the remaining sample was centrifuged at 15,000 rpm (27,000 g) for

30 min. to obtain a sample of the supernatant liquid which was analyzed for phosphorus and carbonate. The quantity of phosphate adsorbed and carbonate desorbed were determined by difference. A blank composed of a phosphate-free system was used to confirm the experimental procedures. Disaggregation of amorphous aluminum hydroxycarbonate was studied by use of fiber optic Doppler anemometry[13] (SIRA).

For the second series of experiments, two samples of spray dried amorphous aluminum hydroxycarbonate (Barcroft and Kyowa) were examined by high resolution electron microscopy (Joel 200 KV). Samples were prepared by drying micro-drops of a dilute suspension onto carbon films supported by copper grids. Several particles were examined in each sample and the particles shown are representative. Micrographs were made at magnifications of 21,000, 90,000 and 450,000. The photomicrographs shown were photographically enlarged 2X.

The granulation and tableting characteristics of Barcroft and Kyowa spray dried amorphous aluminum hydroxide were evaluated by incorporating the sample into a standard formula for an antacid tablet. The tablets were compressed to a hardness of 8 Kg using 11/16 inch flat face beveled edge punches.

RESULTS AND DISCUSSION

The adsorption of phosphate by aluminum hydroxide has been extensively studied because of the widespread use of phosphate

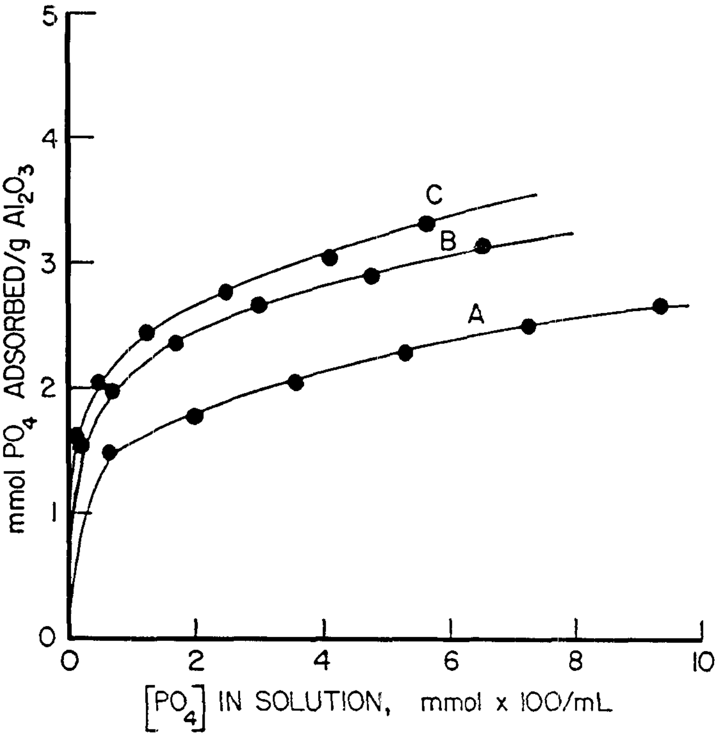


FIGURE 1

Effect of exposure time on the adsorption isotherm of phosphate by amorphous aluminum hydroxycarbonate at pH 6.6, 25^{o}C. Key: A, 30 min., B, 3 hours; C, 4.5 hours.

fertilizers[14-21]. The adsorption of phosphate by amorphous aluminum hydroxycarbonate is shown in Figure 1. Adsorption follows the Freundlich equation as evidenced by R^2 values of 0.9854, 0.9992 and 0.9994, respectively, at 0.5, 3 and 4.5 hours. However, phosphate adsorption increased over the 4.5 hour exposure period. The increase in adsorption with time is seen more clearly in Figure 2 where an amorphous aluminum

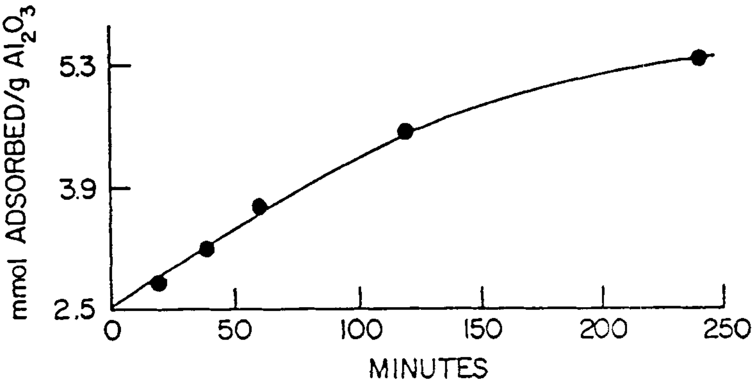


FIGURE 2

Effect of time on the adsorption of phosphate by amorphous aluminum hydroxycarbonate at pH 6.6, 25°C.

hydroxycarbonate suspension containing 15.5 mmol aluminum was exposed to 26.9 mmol NaH_2PO_4 and monitored for 4 h. The time dependency of phosphate adsorption is believed to be due to the diffusion of phosphate ions into a porous secondary particle such as was recently proposed for amorphous aluminum hydroxycarbonate[22]. The adsorption of phosphate may facilitate diffusion by inducing disaggregation of the secondary particle into its constituent primary particles.

The point of zero charge is defined as the pH where the net surface charge from the potential determining ions and the specifically adsorbed ions is zero[23]. The point of zero charge is related to the isoelectric point. However, the isoelectric point is the pH where the net surface charge from only the potential determining ions is zero. Thus, the point of zero charge and the isoelectric point are the same only in the absence of specifically adsorbed ions. This is not the case in this study because phosphate anion is specifically adsorbed by aluminum hydroxide[14-16]. The aggregation state of suspensions is controlled by the interparticle forces described in the Derjaguin, Landau, Vervey, Overbeek theory[8]. According to this theory, the total surface charge, arising from either potential determining ions or specifically adsorbed ions, is important because it gives rise to the electrostatic repulsive interparticle force. Thus, the point of zero charge was used to characterize the surface charge in this study. The point of zero charge of the amorphous aluminum hydroxycarbonate gel was 6.8 but phosphate adsorption decreases the point of zero charge[14-16]. Thus, at pH 6.6 under the pH-stat conditions of the experiment, the surface charge is initially slightly positive but it will become increasingly negative as phosphate adsorption occurs and the point of zero charge is decreased. This increase in negative surface charge will cause disaggregation, thereby facilitating diffusion and further adsorption of phosphate.

The fraction of adsorbed phosphate which exchanges for hydroxyl, carbonate and aquo groups when an amorphous aluminum hydroxycarbonate suspension containing 15.5 mmol aluminum was exposed to 26.9 mmol NaH_2PO_4 was determined from the amount of

TABLE 1

Effect of Exposure time on the Fraction of Phosphate Adsorption Occurring by Exchange with Hydroxyl, Carbonate and Aquo Surface Groups

Exposure Time, min.	Phosphate Adsorbed, mmol.	Fraction of Phosphate Adsorption Occurring by Exchange with Hydroxyl	Carbonate	Aquo
30	7.0	0.52	0.31	0.17
60	8.8	0.50	0.32	0.19
120	10.9	0.53	0.32	0.15
240	13.5	0.58	0.28	0.14

phosphate adsorbed, the change in the carbonate content due to adsorption and the proton consumption during adsorption. Table 1 shows that even though phosphate adsorption increased over a 4 hour exposure period, the contribution by each type of exchange group remained essentially constant at approximately 53% hydroxyl, 31% carbonate and 16% aquo. The relatively constant exchange ratio over the 4 hour exposure period suggests that new surface, composed of the same surface groups, is becoming accessible during phosphate adsorption rather than a differential rate of exchange for each type of surface group. Thus, the time dependency of phosphate adsorption appears to be due to the diffusion of phosphate ions into a porous particle.

The disaggregation effect of phosphate adsorption on amorphous aluminum hydroxycarbonate was tested by exposing a sample containing 3.74 mmol aluminum to various phosphate concentrations ranging from 0 to 25 mmol. The apparent hydrodynamic radius was determined by fiber optic Doppler anemometry[13] after a 60 min. exposure period. The point of zero charge of the sample was 6.8. As seen in Figure 3, the addition of 2.5 mmol phosphate caused an increase in apparent particle size. This probably occurs because adsorption of a small amount of phosphate lowers the point of zero charge until it is identical to the pH of the suspension, resulting in a reduction in surface charge. The particles undergo attractive particle interactions more readily and the apparent particle size increases. Phosphate levels of greater than 2.5 mmol caused a further decrease in the point of zero charge causing the surface charge to become increasingly negative under pH-stat conditions. The increased negative surface charge results in disaggregation which is indicated by the minimum apparent particle size at 5 mmol phosphate. Higher concentrations of sodium phosphate exceed the adsorptive capacity and the added ions remain in solution reducing the Debye length. This compression of the diffuse double layer leads to flocculation and an increase in apparent particle size occurred. The behavior seen in Figure 3 is consistent with classical aggregation-disaggregation theory.

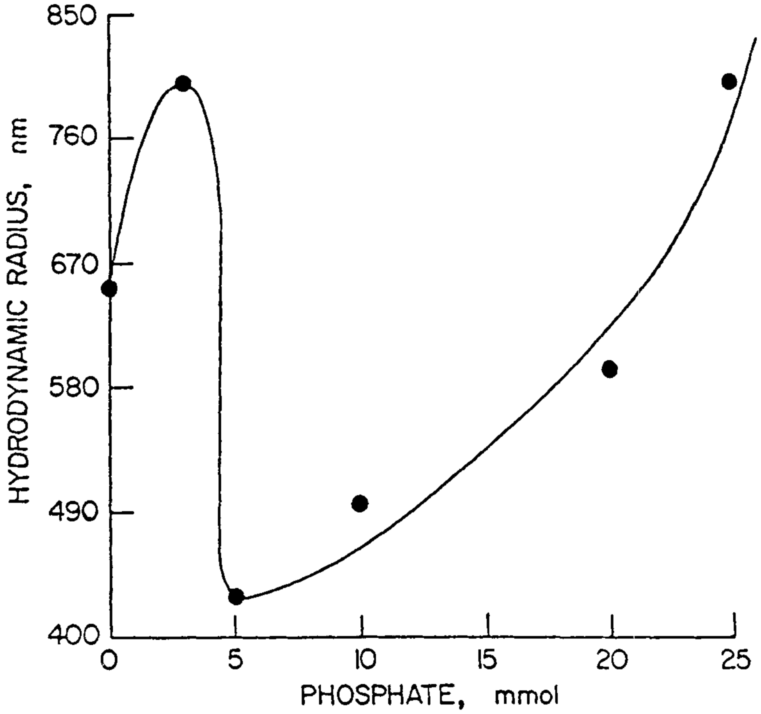


FIGURE 3

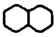
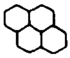
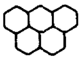
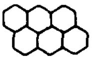
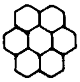
Effect of phosphate on the apparent particle size of amorphous aluminum hydroxycarbonate at pH 6.6 measured by fiber optic Doppler anemometry.

The basic structural unit of amorphous aluminum hydroxycarbonate is a six-membered ring of aluminum ions joined by double hydroxide bridges[24]. These six-membered rings polymerize to form sheet-like structures[25] such as are shown in Table II. These platy polymers may be the primary particles whose existence was hypothesized in previous studies[6,22]. The equivalent diameter of these polymers in the amorphous aluminum hydroxycarbonate gel studied can be estimated from the fact that the carbonate to aluminum ratio was 0.40 and the observation that 31% of the phosphate adsorption was due to exchange with carbonate (Table 1.) Because aluminum ions in aluminum hydroxycarbonate are in octahedral coordination, each edge aluminum has two coordination sites. These coordination sites represent the available adsorption sites. The number of coordinated carbonate ions in each structure was calculated from the carbonate to aluminum ratio (0.40) and the total number of aluminum ions in the polymer. When the ratio of coordinated carbonate to total adsorption sites was calculated for polymers of increasing size, the results in Table 2 were obtained.

Examination of Table 2 reveals that a polymer consisting of 4 fused rings has a ratio of coordinated carbonate to total adsorption sites of 0.32. This agrees very well with the experimentally determined fraction of phosphate adsorption which occurred through exchange with carbonate (Table 1). Thus, a planar polymer of 4 fused rings fits the experimentally determined surface properties of the primary particle of the amorphous aluminum hydroxycarbonate under study. Since the equivalent diameter of the polymers shown in Table 2 which contain between 4 and 7 rings is approximately 20 A[26,27], it is believed that the primary particle has an equivalent diameter of approximately 20 A.

TABLE 2

Potential Structures for the Primary Particle of Amorphous Aluminum Hydroxycarbonate Having a Carbonate to Aluminum Ratio of 0.40.

# of Rings	Structure	Total Alum. Ions	Edge Alum. Ions	Total Adsorption Sites	Co-Ordinated Carbonate	Co-Ordinated Carbonate/ Total Adsorption Sites
1		6	6	12	2.4	0.20
2		10	8	16	4.0	0.25
3		13	9	18	5.2	0.29
4		16	10	20	6.4	0.32
5		19	11	22	7.6	0.35
6		22	12	24	8.8	0.40
7		24	12	24	9.6	0.40

In a second series of experiments, the particle morphology of two samples of spray dried amorphous aluminum hydroxycarbonate was examined by high resolution transmission electron microscopy. Figures 4 and 5 show a particle from the samples produced by Barcroft and Kyowa, respectively. The spray dried particle in Figure 4 is spherical with a diameter of approximately 14,500 A while the particle in Figure 5 has a diameter of 27,000 A. However, the photomicrographs suggest

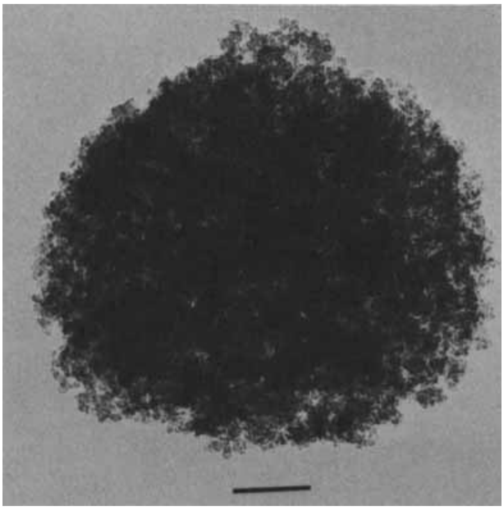


FIGURE 4

High resolution transmission electron photomicrograph of spray dried amorphous aluminum hydroxycarbonate (Barcroft) at a magnification of 42,000. The bar represents 2380 A.

that the particles observed are composed of even smaller particles. Examination of the sample produced by Barcroft at a higher magnification (Fig. 6) clearly shows that the 14,500 A particle is composed of primary particles as small as 55 A. Thus, the hypothesis that amorphous aluminum hydroxycarbonate is composed of very small primary particles is substantiated. The size of the primary particles seen in Figure 6 is similar to the calculated size of the primary particles of the amorphous aluminum hydroxycarbonate (Table 2). The 14,500 and 27,000 A particles seen in Figures 4 and 5 correspond to the

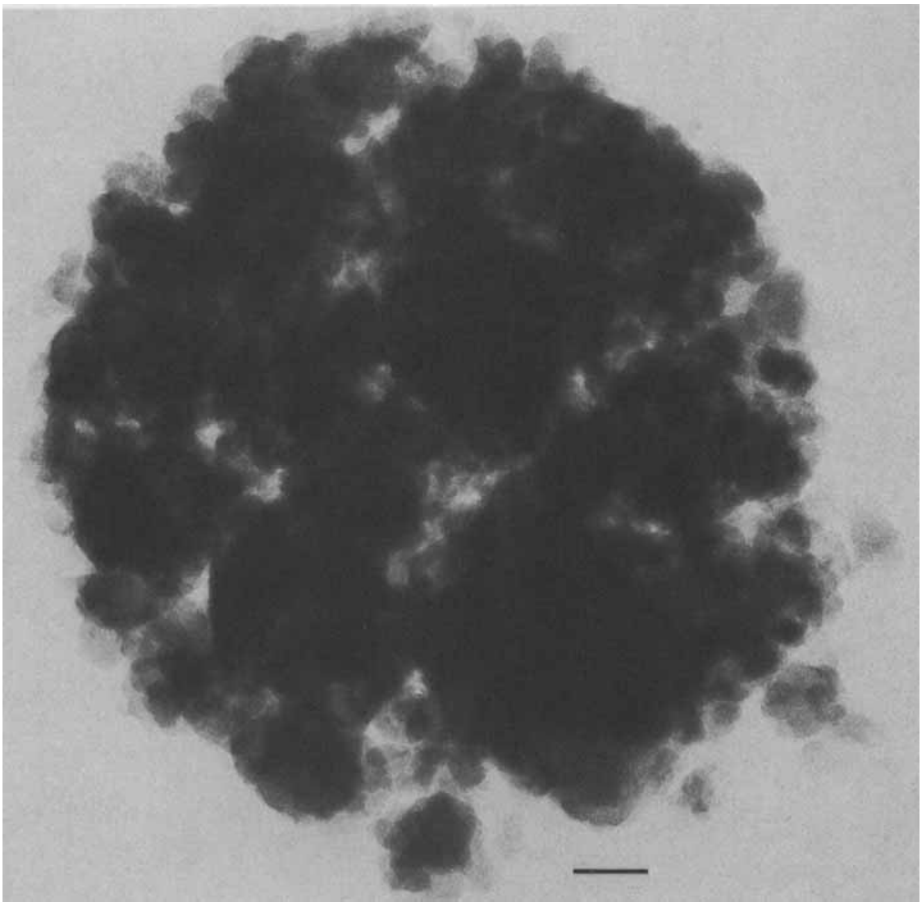


FIGURE 5

High resolution transmission electron photomicrograph of spray dried amorphous aluminum hydroxycarbonate (Kyowa) at a magnification of 42,000. The bar represents 2380 A.

hypothesized secondary particles. Figure 7 reveals that the sample produced by Kyowa has the same particle morphology, except that the primary particles are larger, 110 to 270 A. These results are supported by previous electron microscope

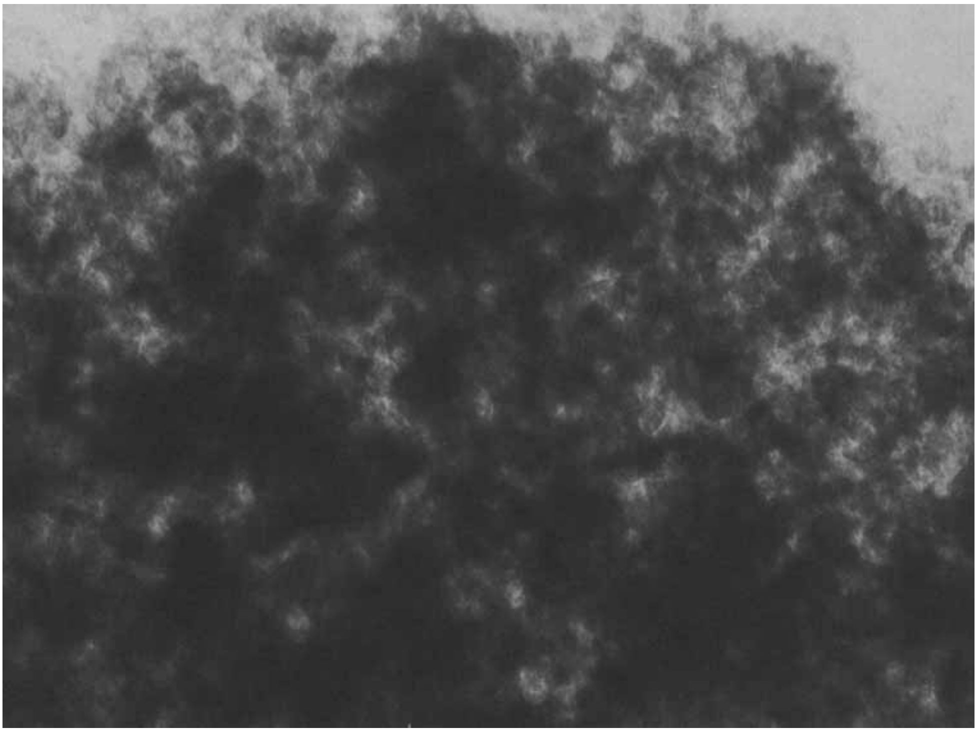


FIGURE 6

High resolution transmission electron photomicrograph of spray dried amorphous aluminum hydroxycarbonate (Barcroft) at a magnification of 180,000. The bar represents 550 A.

studies of aluminum hydroxide[28-30] and fibrous alumina[31] which have revealed primary particles ranging from 25 to 3700 A.

The platy nature of the primary particles was seen when the Kyowa sample was examined at a magnification of 900,000 (Fig. 8). The primary particle in the center of Figure 8 has an

FIGURE 7

High resolution transmission electron photomicrograph of spray dried amorphous aluminum hydroxycarbonate (Kyowa) at a magnification of 180,000. The bar represents 550 A.

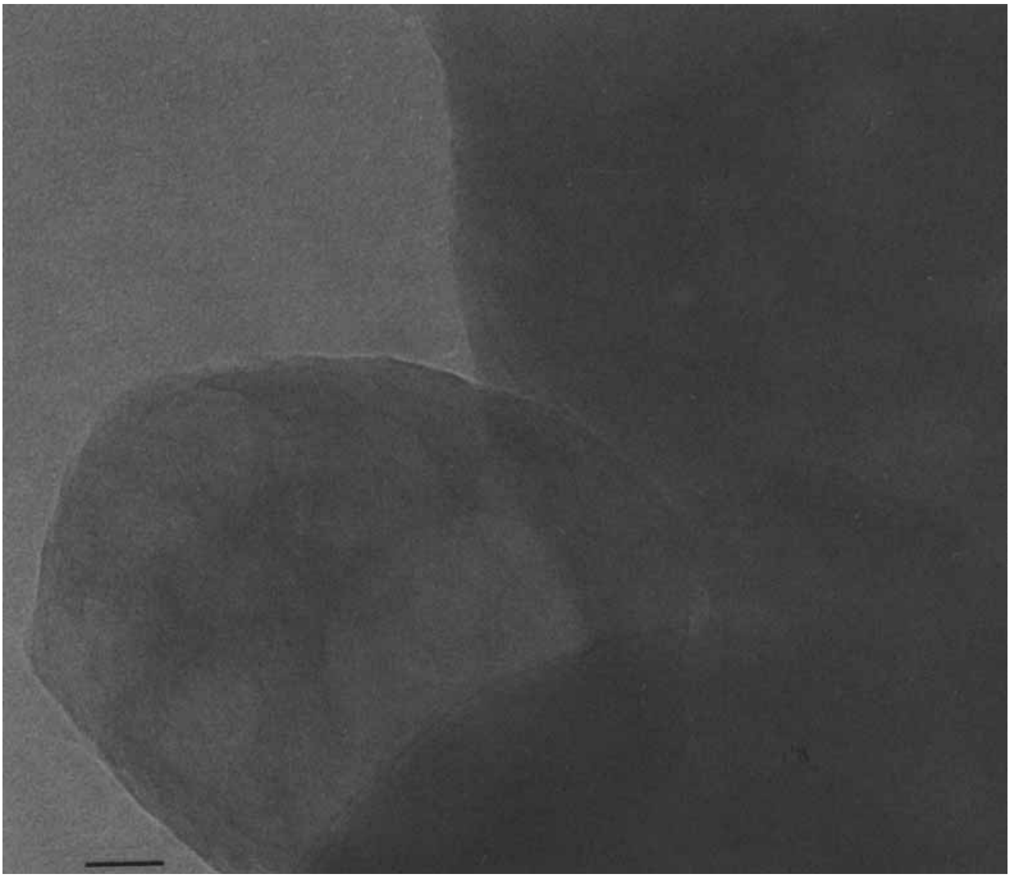


FIGURE 8

High resolution transmission electron photomicrograph of spray dried amorphous aluminum hydroxycarbonate (Kyowa) at a magnification of 900,000. The bar represents 110 A.

equivalent diameter of 880 A. It is especially interesting to note the over-lapping of the sheet-like primary particles seen in the lower center of Figure 8. Thus, the understanding that amorphous aluminum hydroxycarbonate is composed of sheets of fused six-membered rings was also confirmed by direct examination.

The disaggregation and high resolution transmission electron microscopy studies resolve the anomalous results described in the Introduction by revealing that the primary particles in amorphous aluminum hydroxycarbonate are platy and may be smaller than 55 A. Thus, the dimensions of the primary particle are responsible for the high surface area, the unique pH-stat titrigram and the conversion from a milky to a translucent dispersion upon aging.

A full understanding of the particle morphology of amorphous aluminum hydroxycarbonate gives valuable insights into the formulation and production of antacid dosage forms. For example, different samples of spray dried amorphous aluminum hydroxycarbonate behave quite differently when used to prepare aluminum hydroxycarbonate-magnesium hydroxide antacid tablets (Table 3). The lower apparent density of the Barcroft sample in comparison to the Kyowa sample reflects the smaller primary particles and more porous secondary particles of the Barcroft sample seen in Figures 4 to 7. Wet granulation of the powders when they were incorporated into a standard formulation required 50% more water for the granulation containing the Barcroft sample. This is also explained by the smaller primary particle size of the Barcroft spray dried amorphous aluminum hydroxycarbonate . The moisture content of

TABLE 3

Tableting Properties of Two Samples of Spray Dried Amorphous Aluminum Hydroxycarbonate

	Barcroft	Kyowa
Bulk Density, g/ml	0.192	0.337
Tap Density, g/ml	0.242	0.453
Volume of Water Required to Granulate 500 Tablets, ml	344	210
Water Content of Granulation During Drying in Forced Air Oven at 50°C, %		
After 1 hour	23.9	20.8
3 hours	17.5	12.9
24 hours	1.7	1.6
Tablet Thickness, mm	5.79	5.13

the granulation containing the Barcroft sample during drying was also higher although both granulations reached the same approximate water content after 24 hours of drying. The tablets containing the Barcroft sample were thicker than tablets produced using the Kyowa sample when the compression force was adjusted to produce a hardness of 8 kg. This size difference is also believed to be due to the smaller primary particle size and the greater porosity of the secondary particles of the Barcroft spray dried amorphous aluminum hydroxycarbonate.

Thus, although the particle morphology of amorphous aluminum hydroxycarbonate is complex, realization that the basic unit (primary particle) is of angstrom dimensions resolves a number of reports of apparently anomalous behavior and allows the different tableting properties of two samples of spray dried amorphous aluminum hydroxycarbonates to be understood.

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