(22) L. Tan, *ibid.*, **45**, 68 (1969).

(23) E. Watson, P. Tramell, and S. M. Kalman, *ibid.*, **69**, 157 (1972).

(24) W. E. Wilson, S. A. Johnson, W. H. Perkins, and J. E. Ripley, *Anal. Chem.*, **39**, 40 (1967).

(25) A. H. Kibbe and O. E. Araujo, *J. Pharm. Sci.*, **62**, 1703 (1973).

(26) M. C. Castle, *J. Chromatogr.*, **115**, 437 (1975).

(27) W. Lindner and R. W. Frei, *ibid.*, **117**, 81 (1976).

(28) F. Nachtmann, H. Spitzy, and R. W. Frei, *ibid.*, **122**, 293 (1976).

(29) F. Erni and R. W. Frei, *ibid.*, **130**, 169 (1977).

(30) L. A. Sternson and R. D. Shaffer, *J. Pharm. Sci.*, **67**, 327 (1978).

(31) T. Sonobe, S. Hasumi, T. Yoshino, Y. Kobayashi, H. Kawata, and T. Nagai, *ibid.*, **69**, 410 (1980).

(32) Y. Fujii, H. Fukuda, Y. Saito, and M. Yamazaki, *J. Chromatogr.*, **202**, 139 (1980).

(33) B. Desta and K. M. McErlane, *J. Chromatogr.*, in press.

# Formation of Hydrotalcite in Mixtures of Aluminum Hydroxycarbonate and Magnesium Hydroxide Gels

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**Abstract** ☐ IR and X-ray analysis demonstrate that hydrotalcite forms during the aging of aluminum hydroxycarbonate gel and magnesium hydroxide gel mixtures. The formation of hydrotalcite produces a change in the pH-stat titrigram and a sharp increase in the pH of the mixture. Hydrotalcite was noted earlier in mixtures having a high molar ratio of magnesium to aluminum, a high total gel concentration, a high initial pH, or in mixtures stored at elevated temperatures. The addition of sorbitol to the mixtures substantially delayed the appearance of hydrotalcite. Nonacid-reactive hydrotalcite formed when mixtures of chloride-containing aluminum hydroxide gel and magnesium hydroxide gel were aged.

**Keyphrases** ☐ Hydrotalcite—formation, mixtures of aluminum hydroxycarbonate and magnesium hydroxide gels, IR and X-ray analysis ☐ Mixtures—formation of hydrotalcite in mixtures of aluminum hydroxycarbonate and magnesium hydroxide gels ☐ Gels—aluminum hydroxycarbonate and magnesium hydroxide gels, mixtures, formation of hydrotalcite

It has been reported recently that amorphous aluminum hydroxycarbonate gel forms a coating on magnesium hydroxide particles due to electrostatic attraction (1). This interaction was detected because the rate of acid neutralization of mixtures of aluminum hydroxycarbonate gel and magnesium hydroxide gel was slower than expected, based on individual rates of acid neutralization. The interaction occurred immediately and an additive rate of acid neutralization only occurred when the gels were separately added to the reaction vessel. As the mixtures aged, the rate of acid neutralization decreased further, suggesting that the amorphous aluminum hydroxycarbonate coating was becoming more ordered as the amorphous to crystalline phase transition occurred.

It was noticed, however, that the rate of acid neutralization in some aged mixtures was greater than the initial rate of acid neutralization. Thus, a further reaction appeared to be occurring during the aging of mixtures of aluminum hydroxycarbonate and magnesium hydroxide gels. This interaction is the focus of this study.

## EXPERIMENTAL

Magnesium hydroxide gel[1] was obtained commercially as a paste containing the equivalent of 21% (w/w) MgO. Aluminum hydroxycarbonate gel was prepared as described previously (2) by the addition of 0.47 $M$ $AlCl_3 \cdot 6H_2O$ to 0.53 $M$ $NaHCO_3$ and 0.23 $M$ $Na_2CO_3$ to a final pH of 6.5. Chloride-containing aluminum hydroxide gel was prepared as described previously (2) by the addition of 13% (v/v) strong ammonia solution to 0.29 $M$ $AlCl_3 \cdot 6H_2O$ to a final pH of 7.0.

Aluminum and magnesium content were determined by chelatometric titration (3).

Mixtures of aluminum hydroxycarbonate gel or chloride-containing aluminum hydroxide gel and magnesium hydroxide gel were prepared on a weight basis. For example, a 200-g mixture containing a total of 0.6 mmole of metal/g in a magnesium–aluminum molar ratio of 5:1 was prepared by weighing magnesium hydroxide gel and aluminum hydroxycarbonate gel or chloride-containing aluminum hydroxide gel containing 100 mmoles of magnesium and 20 mmoles of aluminum, respectively. A solution containing an excipient was added when necessary. The final weight was adjusted to 200 g with double-distilled water and the mixture was stirred mechanically until uniform. The mixtures were aged in widemouth polyethylene bottles.

The acid neutralization reaction was monitored by an automated[2] pH-stat titrator at pH 3.0, 25° using a sample size which would theoretically neutralize 2.25 mEq (4).

X-ray diffractograms were obtained using air-dried samples in McCreery mounts (5). Diffractograms were recorded from 6 to 40° (2 $\theta$) under the following conditions[3]: $CuK_\alpha$ radiation, 30 kV, 28 mamp, 2°/min.

IR[4] spectra were recorded using potassium bromide disks containing 0.8–2.0 mg of air-dried sample and 300 mg of KBr.
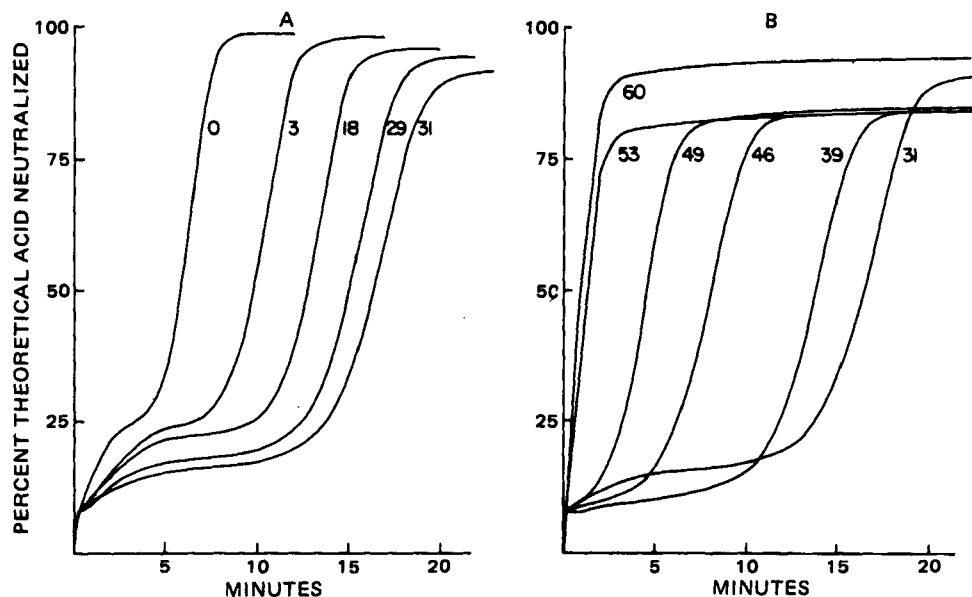
## RESULTS AND DISCUSSION

The rate of acid neutralization of a mixture of aluminum hydroxycarbonate gel and magnesium hydroxide containing 0.6 mmole of metal/g in a magnesium–aluminum molar ratio of 5:1 decreased during the first 31 days of aging at 25° (Fig. 1A). A slight decrease in the total acid reac-

**Figure 1**—*pH-stat titrigram of a magnesium–aluminum molar ratio (5:1) of an aluminum hydroxycarbonate gel–magnesium hydroxide gel mixture containing 0.6 mmole of metal/g during aging at 25°. Each titrigram is labeled with the age of the mixture in days.*

tivity was also noted. After 31 days, a major reversal occurred in the rate of acid neutralization, i.e., the rate of acid neutralization progressively increased until the mixture reacted in a rapid, single-phase reaction (Fig. 1B). With the establishment of a single, highly reactive phase, the total acid reactivity increased to the theoretical value. The acid reactivity of the mixture was monitored for 375 days at 25° but no further significant changes in the pH-stat titrigrams were observed.

Corresponding to the period of a decreasing rate of acid neutralization observed in Fig. 1A, the pH of the mixture (Fig. 2) decreased slightly during the initial aging period, which is consistent with the polymerization of aluminum hydroxide by the formation of double hydroxide bridges (6). After 37 days, the mixture exhibited a drastic change in pH, rising to pH 11.3 after 80 days at 25°. The pH remained at 11.3 until the study was terminated at 500 days.
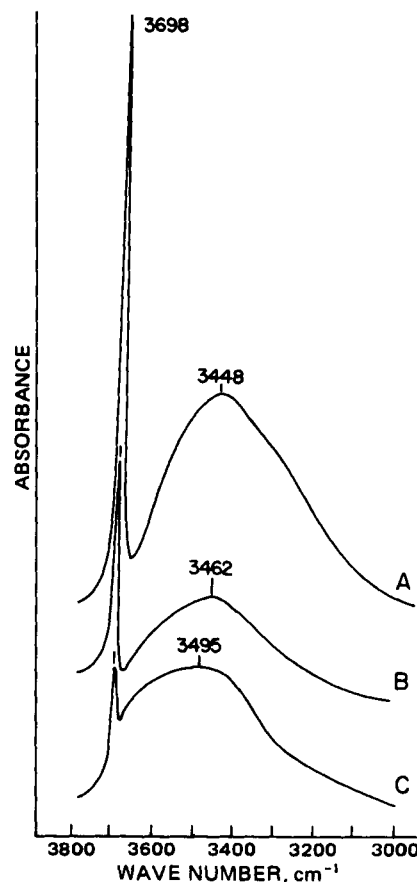
The hydroxyl-stretching region of the IR spectrum of the freshly prepared mixture is shown in Fig. 3, Curve A. The broad absorption band between 3000 and 3700 cm$^{-1}$ is characteristic of amorphous aluminum hydroxycarbonate gel with hydroxide groups in a continuum of environments, indicative of a highly disordered state (7). The sharp peak at 3698 cm$^{-1}$ is indicative of the rigid environment of the brucite structure of magnesium hydroxide gel (8). After 48 days (Fig. 3, Curve B), the absorption band at 3698 cm$^{-1}$ showed a dramatic decrease, signaling a reduction in the amount of magnesium present as brucite in the mixture. The decrease in the peak at 3698 cm$^{-1}$ continued as the mixture aged, but the position of the brucite peak remained constant (Fig. 3, Curve C). The maximum absorption of the diffuse hydroxyl-stretching band shifted toward higher energy absorption.

Figure 4 shows the region of carbonate absorption in the IR spectrum of the mixture. The large initial split (Fig. 4, Curve A) in the carbonate peaks at 1406 and 1540 cm$^{-1}$ is a result of coordination of carbonate to
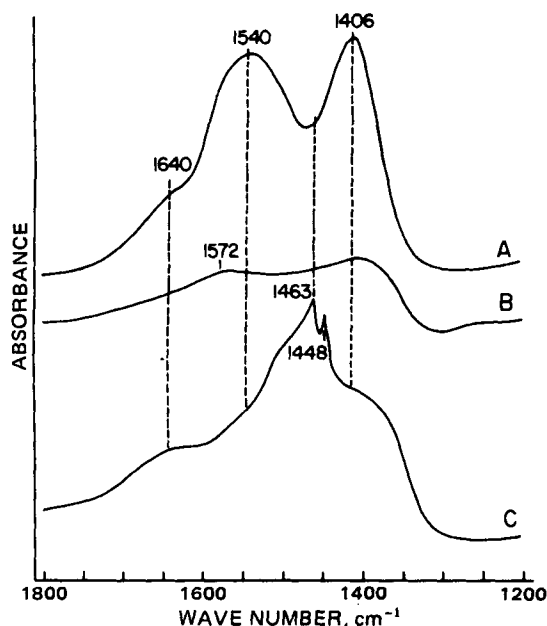
aluminum in the aluminum hydroxycarbonate gel (9). The shoulder at 1640 cm$^{-1}$ is due in large part to free water adsorbed by the aluminum hydroxycarbonate. The region of carbonate absorption became less well defined after 48 days (Fig. 4, Curve B) while the splitting of the carbonate peaks increased slightly. A major structural change occurred by Day 61 as the peak at 1406 cm$^{-1}$ was reduced to a shoulder and the peak at 1540 cm$^{-1}$ was almost completely replaced by a single strong absorbance at 1463 cm$^{-1}$ with a well-defined shoulder at 1448 cm$^{-1}$. This shift indicates
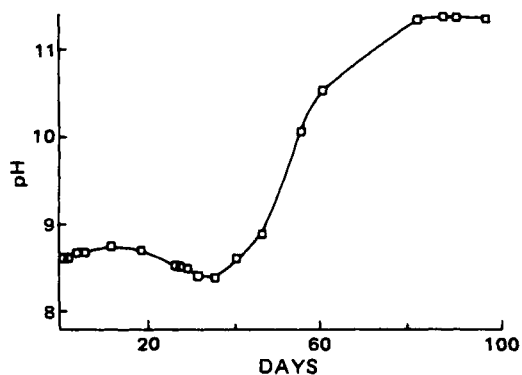


**Figure 2**—*pH of a magnesium–aluminum molar ratio (5:1) of an aluminum hydroxycarbonate gel–magnesium hydroxide gel mixture containing 0.6 mmole of metal/g during aging at 25°.*



**Figure 3**—*Hydroxyl-stretching region of the IR spectrum of a magnesium–aluminum molar ratio (5:1) of an aluminum hydroxycarbonate gel–magnesium hydroxide gel mixture containing 0.6 mmole of metal/g during aging at 25°. Key: (A) initial; (B) 48 days; (C) 61 days.*
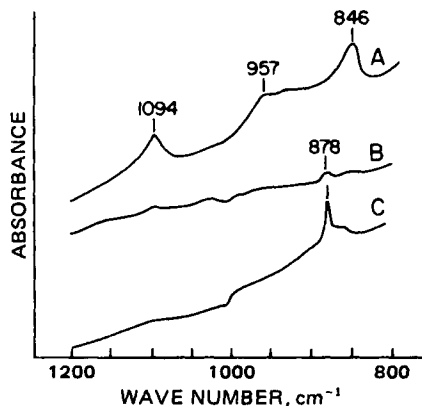
**Figure 4**—*Carbonate absorption region of the IR spectrum of a magnesium–aluminum molar ratio (5:1) of an aluminum hydroxycarbonate gel–magnesium hydroxide gel mixture containing 0.6 mmole of metal/g during aging at 25°. Key: (A) initial; (B) 48 days; (C) 61 days.*

that the carbonate ion is no longer strongly associated with aluminum but is in a less perturbed state. The peak of 1448 cm$^{-1}$ is characteristic of a symmetrical carbonate anion as in sodium carbonate (10). The strong peak at 1463 cm$^{-1}$ may result from the carbonate anion regaining its symmetrical character but being in a slightly different environment compared to sodium carbonate.

Figure 5 shows the 800–1200 cm$^{-1}$ region of the IR spectrum during aging of the mixture at 25°. In the fresh mixture, the broad shoulder at 957 cm$^{-1}$ indicates the disordered hydroxyl environment in the aluminum hydroxycarbonate gel. The peaks at 846 and 1094 cm$^{-1}$ are present only when there is distortion of the carbonate ion, while the peak which appears at 878 cm$^{-1}$ after 48 days is characteristic of unperturbed carbonate ion as found in sodium carbonate (11). The disappearance of the peak at 1094 cm$^{-1}$ and the appearance of the free carbonate band at 878 cm$^{-1}$ suggest that structural changes occurred in the mixture which resulted in a drastic change in environment for the carbonate ion.

X-ray diffractograms of the mixture during aging also suggest that structural changes occurred (Fig. 6). The initial X-ray diffractogram (Table I) had peaks at interplanar spacings of 4.74, 2.369, 1.794, 1.569, and 1.491 Å which corresponded to the peaks for brucite. In addition, there was a diffuse band between 15 and 35° (2 θ) which was attributed to disordered, amorphous aluminum hydroxycarbonate. After 48 days (Fig. 6, Curve B), the brucite peaks had diminished in intensity but remained sharp. In the case of both X-ray and IR observations, the peaks



**Figure 5**—*Hydroxyl-bending region of the IR spectrum of a magnesium–aluminum molar ratio (5:1) of an aluminum hydroxycarbonate gel–magnesium hydroxide gel mixture containing 0.6 mmole of metal/g during aging at 25°. Key: (A) initial; (B) 48 days; (C) 61 days.*

**Table I—X-ray Spacings of a Magnesium–Aluminum Molar Ratio (5:1) of Aluminum Hydroxycarbonate Gel–Magnesium Hydroxide Gel Mixture** [a]

| Age | Mixture, $d$Å | Brucite[b], $d$Å$(I/I_0)$ | Hydrotalcite[c], $d$Å $(I/I_0)$ |
|---|---|---|---|
| Initial | 4.74 | 4.77 ( 90) | 7.84 (100) |
| | 2.369 | 2.365 (100) | 3.90 ( 60) |
| | 1.794 | 1.794 ( 55) | 2.60 ( 40) |
| | 1.569 | 1.573 ( 35) | 2.33 ( 25) |
| | 1.491 | 1.494 ( 18) | |
| 61 days | 7.82 | | 7.84 |
| | 4.72 | 4.77 | |
| | 3.91 | | 3.90 |
| | 2.576 | | 2.60 |
| | 2.354 | 2.365 | |
| | 2.33–2.30 | | 2.33 |
| | | 1.794 | |
| | | 1.573 | |
| | | 1.494 | |

[a] During aging at 25°, compared to reference brucite and hydrotalcite. [b] "Selected Powder Diffraction Data for Minerals," Joint Committee on Powder Diffraction Standards, Swarthmore, Pa., 1974, File 7-239. [c] *Ibid*, File 22-700.

corresponding to brucite decreased in intensity while maintaining a high degree of sharpness. This indicated a decrease in the total amount of brucite in the mixture but a high degree of crystallinity in the remaining brucite. The brucite peaks did not shift in location, even after 510 days, suggesting that the structure of the remaining brucite was not altered.

After 61 days, the peaks corresponding to brucite had decreased substantially and a new set of moderately sharp peaks appeared (Fig. 6, Curve C). After checking the mineralogical literature, the new peaks were indexed to be virtually identical to those of hydrotalcite, a magnesium aluminum hydroxycarbonate (Table I). The structure of hydrotalcite (Fig. 7) is unique, as it is composed of two layers of brucite in which aluminum replaces some magnesium. The positive charge on the brucite layer which results from the substitution is balanced by carbonate, hydroxyl, and other anions which are sandwiched between the substituted brucite layers (12–19).

The changes in the rate of acid neutralization, pH, IR spectrum, and X-ray diffraction of the magnesium–aluminum (5:1) mixture are consistent with the formation of hydrotalcite. The pH-stat titrigram after
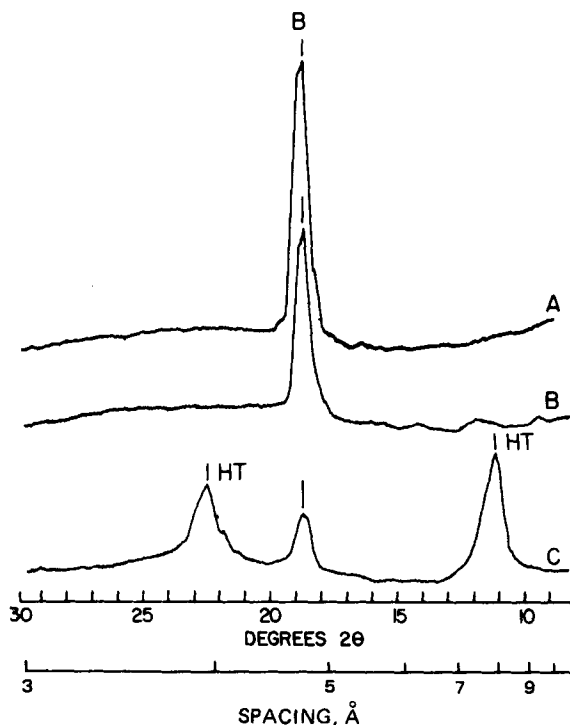


**Figure 6**—*X-ray diffractogram in the 3–9 Å region of a magnesium–aluminum molar ratio (5:1) of an aluminum hydroxycarbonate gel–magnesium hydroxide gel mixture containing 0.6 mmole of metal/g during aging at 25°. B and HT indicates the peaks corresponding to brucite and hydrotalcite, respectively. Key: (A) initial; (B) 48 days; (C) 61 days.*
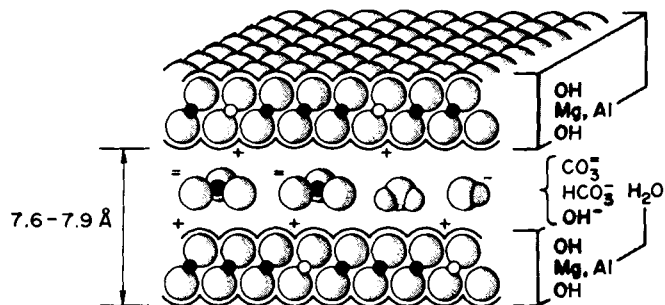
**Figure 7**—*Schematic representation of hydrotalcite (from ref. 8).*

60 days at 25° showed the same rapid, one-phase reaction as is characteristic of magneisum hydroxide. The reaction rate of hydrotalcite would be expected to be similar to magnesium hydroxide as both minerals are based upon the brucite crystal lattice.

The initial pH of the mixture, 8.7, was intermediate between pH 10.35 for the magnesium hydroxide gel, and pH 6.5 for the aluminum hydroxycarbonate gel. The rise in pH associated with the formation of hydrotalcite may be attributed to the presence of carbonate in the interlayer space of hydrotalcite. Carbonate ion neutralizes the positive charge of the substituted brucite layer more efficiently than hydroxyls and will, therefore, displace hydroxyls which cause the bulk pH to rise.

The formation of hydrotalcite in the mixtures was first noted in the IR spectrum by the decrease in the intensity of the brucite peak. The change in the carbonate band from a highly perturbed state, due to coordination to aluminum in aluminum hydroxycarbonate to a virtually unperturbed state (as would occur if carbonate functioned as a counterion between the substituted brucite layers), is consistent with the formation of hydrotalcite during aging of the mixtures. The X-ray diffractograms showed evidence of hydrotalcite at 61 days. Prior to this time, some decrease in the intensity of the brucite peaks was noted, but a sharp decrease in the intensity of the brucite peak occurred with the formation of hydrotalcite. Since the appearance of hydrotalcite in the mixture is sudden rather than gradual, and since no further significant changes were noted, it appears that some threshold condition must be reached after which the rapid formation of hydrotalcite can occur.

The magnesium to aluminum ratio in mixtures of aluminum hydroxycarbonate gel and magnesium hydroxide gel substantially affects the length of time before hydrotalcite is formed in the mixtures. A series of mixtures was prepared where each contained 0.6 mmole of metal/g but the magnesium–aluminum molar ratio was 5:1, 2:1, 1:1, 1:2, and 1:5. X-ray diffraction showed that hydrotalcite formed in the magnesium–aluminum mixture (5:1) after ~30–40 days of aging at 25°. Hydrotalcite was detected in the magnesium–aluminum mixture (2:1) after 200 days. The magnesium–aluminum mixtures (1:1 and 1:2) showed the presence of hydrotalcite before 516 days, while the magnesium–aluminum mixture (1:5) remained free of hydrotalcite through 516 days. Thus, the higher the molar ratio of magnesium to aluminum, the sooner hydrotalcite was formed. This may be due to the higher pH of the mixtures which contain a higher magnesium–aluminum ratio. The solubility of aluminum hydroxycarbonate increases in alkaline medium, thus facilitating the conversion to hydrotalcite.
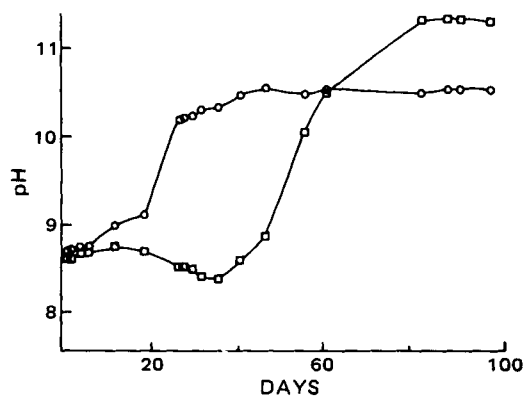


**Figure 8**—*pH of a magnesium–aluminum molar ratio (5:1) of an aluminum hydroxycarbonate gel–magnesium hydroxide gel mixture during aging at 25°. Key: (□) 0.6 mmole of metal/g; (○) 1.2 mmole of metal/g.*
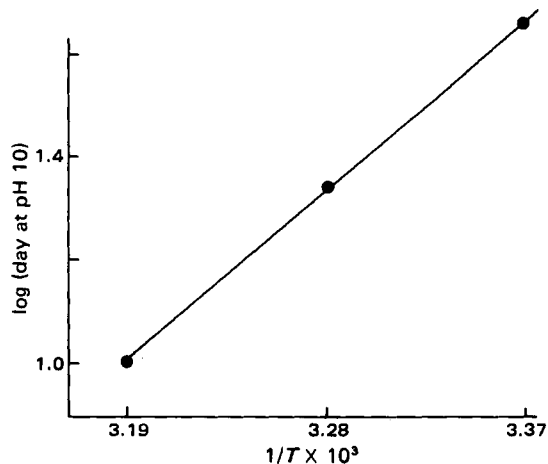


**Figure 9**—*Relationship of aging temperature to time for pH to increase to 10 for a magnesium–aluminum molar ratio (5:1) of an aluminum hydroxycarbonate gel–magnesium hydroxide gel mixture containing 0.6 mmole of metal/g.*

Hydrotalcite also appeared more rapidly as the concentration of the mixture was increased. As seen in Fig. 8, the pH of a magnesium–aluminum mixture (5:1) at 1.2 mmoles of metal/g rose sharply after ~20 days at 25°, while the pH of a magnesium–aluminum mixture (5:1) containing 0.6 mmole of metal/g increased after ~40 days at 25°. X-ray diffractograms and changes in the pH-stat titrigrams confirmed that hydrotalcite had formed in these mixtures. The formation of hydrotalcite would be expected to occur sooner in concentrated mixtures if, as suggested earlier, some threshold condition must be reached to initiate its formation.

Higher aging temperatures promoted more rapid formation of hydrotalcite, probably due to increased solubility at higher temperatures. Figure 9 is an Arrhenius-type plot of the log of the time for magnesium–aluminum mixture (5:1) containing 0.6 mmole of metal/g to reach pH 10 *versus* the reciprocal of the aging temperature ($T$). A linear relationship exists with a heat of activation of ~8.6 kcal/mole.

To observe the effect of initial suspension pH, a magnesium–aluminum mixture (5:1) containing 0.6 mmole of metal/g was divided into six portions. One portion served as the control, while three portions were brought to either pH 9.5, 10.0, or 10.5 with sodium hydroxide. One portion was brought to pH 10 with sodium carbonate to determine if the carbonate anion played a role in initiating the formation of hydrotalcite. The pH of the final portion was not altered, but a small amount of a similar mixture in which hydrotalcite had formed was added to serve as a seed. As seen in Table II, the time required for the pH to rise, indicating hydrotalcite formation, is inversely related to the initial pH of the mixture. The pH of the samples, which had been adjusted to pH 10.5 and 10.0, increased within 1 day, while the sample at pH 9.5 showed evidence of the formation of hydrotalcite within 10 days. The main factor appears to be pH rather than the reagent used to adjust the pH as similar results were obtained when either sodium hydroxide or sodium carbonate was used to adjust the pH. The increased solubility of aluminum hydroxycarbonate at higher pH conditions is believed to be responsible for the pH effect. Seeding the mixture with hydrotalcite had no effect as the pH profile of the seeded sample was similar to the control.

**Table II—pH of Magnesium–Aluminum [a] at Different Initial pH**

| Day | Control | Initial pH Adjusted with NaOH | | | Initial pH Adjusted with Na$_2$CO$_3$ | Seeded |
| | | 9.5 | 10.0 | 10.5 | 10.0 | |
|---|---|---|---|---|---|---|
| 0 | 8.75 | 9.50 | 10.00 | 10.50 | 10.00 | 8.75 |
| 1 | 8.47 | 9.53 | 10.48 | 11.36 | 10.37 | 8.44 |
| 10 | 8.34 | 11.09 | 10.50 | 11.63 | 11.02 | 8.32 |
| 18 | 8.34 | — | — | — | — | 8.45 |
| 21 | 8.34 | — | — | — | — | 8.74 |
| 24 | 8.71 | — | — | — | — | 8.74 |
| 28 | 8.81 | — | — | — | — | 9.66 |
| 30 | 9.58 | — | — | — | — | 9.97 |
| 34 | 10.11 | — | — | — | — | 10.20 |
| 41 | 10.41 | — | — | — | — | — |
| 167 | 11.27 | 11.81 | 12.03 | 12.34 | 11.51 | 11.51 |

[a] Magnesium–aluminum mixtures (5:1) containing 0.6 mmole of metal/g.
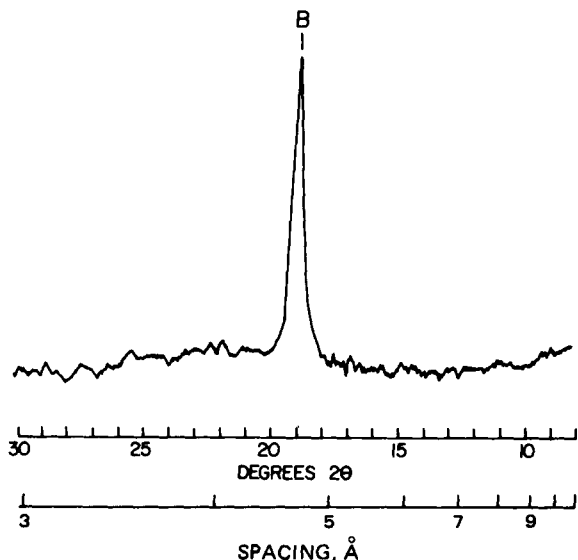
**Figure 10**—*X-ray diffractogram in the 3–9 Å region of a magnesium-aluminum molar ratio (2:1) of an aluminum hydroxycarbonate gel-magnesium hydroxide gel mixture containing 0.6 mmole of metal/g and 2% sorbitol after aging for 616 days at 25°. B indicates the peak corresponding to brucite.*

Two experiments were performed to determine if any excipients would act to stabilize the mixture by controlling the formation of hydrotalcite. A magnesium-aluminum mixture (2:1) containing 0.6 mmole of metal/g was divided into four portions. One portion served as the control, while the other three portions contained either 2% sorbitol, 0.5% simethicone, or 1% polysorbate 80. Hydrotalcite was found in the control and the mixtures containing simethicone or polysorbate 80 at approximately the same time, *i.e.*, after 200 days at 25°. As seen in Fig. 10, the X-ray diffractograms of the sample containing 2% sorbitol showed a very sharp brucite peak and no evidence of hydrotalcite after aging for 616 days at 25°.

Various other excipients were compounded with magnesium-aluminum mixtures (5:1) containing 0.9 mmole of metal/g. The mixtures were aged at 32° and the time required to reach pH 10 was recorded. As seen in Table III, all but two of the mixtures reached a pH of at least 10 within 18 days. Five control samples were included in the experiment to give an indication of the variability in the time required for hydrotalcite to form. The average time for the pH of the control to reach 10 was 12.6 days with 1.5 *SD*. Only the higher concentration of sodium citrate (0.5%) and 2% sorbitol were able to prevent the formation of hydrotalcite during the 52 days of the experiment. Sorbitol is known to hydrogen bond with aluminum hydroxycarbonate gel, while citrate anion is a chelating agent for aluminum. Figure 11 compares the pH-stat titrigrams of selected samples. Initial titrigrams of all samples except the sodium citrate-containing samples were identical. Mixtures containing sodium citrate exhibited

**Table III—Effect of Selected Excipients on the Formation of Hydrotalcite in Magnesium-Aluminum Mixtures** [a]

| Excipient | Concentration, % | Time to Reach pH 10, days |
|---|---|---|
| Control | — | 11 |
| Control | — | 12 |
| Control | — | 12 |
| Control | — | 13 |
| Control | — | 15 |
| Amaranth | 0.1 | 13 |
| Bentonite | 0.1 | 12 |
| Disodium Edetate | 0.1 | 16 |
| Aminoacetic Acid | 0.1 | 18 |
| Methylparaben} | 0.18 | 11 |
| Propylparaben} | 0.02 | |
| Napthol Yellow S | 0.1 | 16 |
| Sodium Citrate | 0.1 | 15 |
| Sodium Citrate | 0.5 | [b] |
| Sodium Saccharin | 0.01 | 13 |
| Sorbitol | 2.0 | [b] |

[a] Magnesium-aluminum mixtures (5:1) containing 0.9 mmole of metal at 32°. [b] pH did not rise above 10 for at least 52 days.
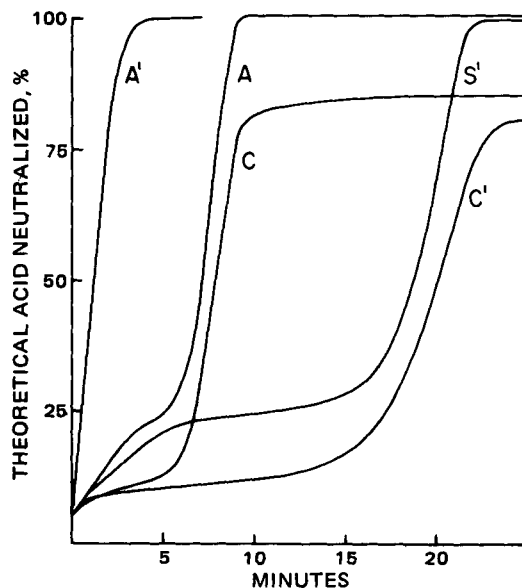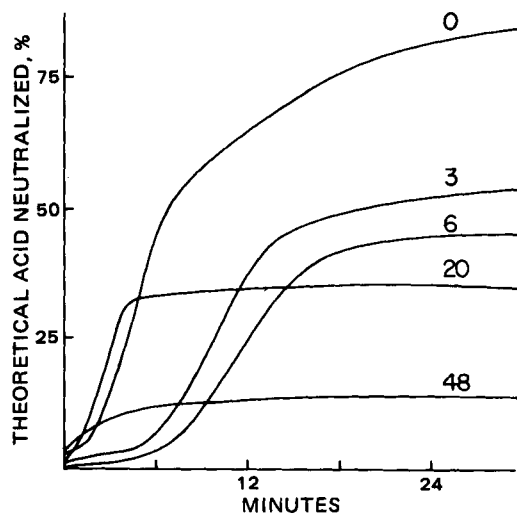


**Figure 11**—*pH-stat titrigram of magnesium-aluminum molar ratio (5:1) of an aluminum hydroxycarbonate gel-magnesium hydroxide gel mixture containing 0.9 mmole of metal/g containing various excipients. Key: (A) initial for all mixtures except sodium citrate-containing mixtures; (C) initial for 0.5% sodium citrate-containing mixture; (S¹) 2% sorbitol-containing mixture aged at 32° for 52 days; (C¹) 0.5% sodium citrate-containing mixture aged at 32° for 52 days; (A¹) all mixtures except sorbitol- and sodium citrate-containing mixtures aged at 32° for 52 days.*

a decrease in both rate and extent of acid reactivity in the region of aluminum hydroxycarbonate gel neutralization which was directly related to the concentration of sodium citrate, while the magnesium hydroxide portion of the pH stat titrigram was unaffected (1).

After 52 days at 32°, the pH-stat titrigram of the control and all the mixtures, except those containing 2% sorbitol or 0.5% sodium citrate, consisted of a single, highly-reactive phase which is characteristic of the formation of hydrotalcite. The rate of acid neutralization of the sorbitol-containing mixture had decreased but the sample was completely reactive. The sodium citrate-containing sample exhibited both a decreased rate and extent of acid neutralization. Both sorbitol and sodium citrate substantially delayed the formation of hydrotalcite, although the use of citrate anion is not recommended due to its deleterious effect on acid neutralization.

The observations of the factors affecting the formation of hydrotalcite in mixtures of aluminum hydroxycarbonate gel and magnesium hydroxide gel support a previous conclusion (20) that the formation of hy-



**Figure 12**—*pH-stat titrigram of magnesium-aluminum molar ratio (1:1) of a chloride-containing aluminum hydroxide gel-magnesium hydroxide gel mixture containing 0.6 mmole of metal/g during aging at 25°. Each titrigram is labeled with the age of the mixture in days.*
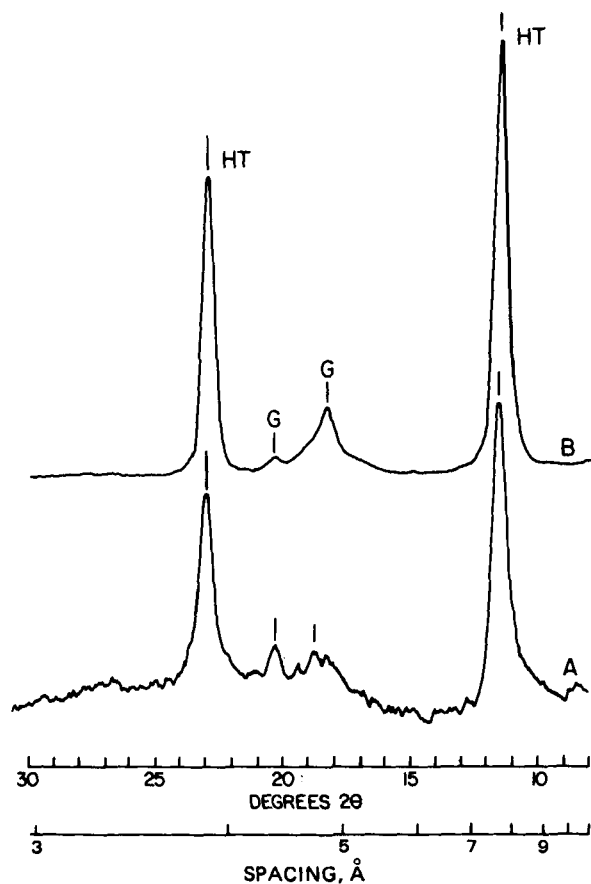
**Figure 13**—*X-ray diffractogram in the 3–9 Å region of a magnesium–aluminum molar ratio (1:1) of a chloride-containing aluminum hydroxide gel–magnesium hydroxide gel mixture containing 0.6 mmole of metal/g during aging at 25°. HT and G indicate the peaks corresponding to hydrotalcite and gibbsite, respectively. Key: (A) 69 days; (B) 173 days.*

drotalcite is a solution phenomena of the following type:

$$Na^+Al(OH)_4^- + 2[(MgOH)^+Cl^-] \rightarrow [AlMg_2(OH)_6]^+Cl^- + NaCl$$

(Eq. 1)
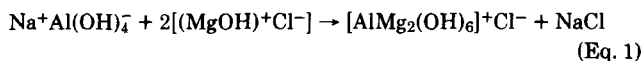
This conclusion was based on the observation that hydrotalcite formed when separate dialysis sacks containing aluminum hydroxide and magnesium carbonate were suspended in water at 60° for 3–6 months (21). Hydrotalcite (~90%) was found in the sack which initially contained aluminum hydroxide, ~10% was found in the dialysis medium, and virtually none was present in the sack which initially contained magnesium carbonate. Hydrotalcite had been precipitated previously (22) from a solution equimolar in aluminum chloride and magnesium chloride at pH 10 in the presence of $4\ N$ $Na_2CO_3$.

The following sequence of reactions are hypothesized to occur when hydrotalcite forms during the aging of mixtures of aluminum hydroxy-carbonate gel and magnesium hydroxide gel. At pH 8–9 magnesium hydroxide will have a relatively high tendency to donate hydroxyls:

$$Mg(OH)_2 \rightarrow MgOH^+ + OH^-$$

(Eq. 2)
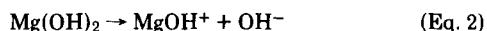
Under these conditions aluminum hydroxide will tend to gain hydroxyls to form aluminate:

$$Al(OH)_3 + OH^- \rightarrow Al(OH)_4^-$$

(Eq. 3)

At first the pH of the mixture remains relatively constant due to the balance of Eqs. 2 and 3. After a period of time, the aluminum hydroxide is no longer able to readily assimilate hydroxyls and the suspension pH begins to rise due to the continued dissolution of magnesium hydroxide. The formation of hydrotalcite occurs by the same mechanism as proposed previously (20), *i.e.*, the coalesence of the products of Eqs. 2 and 3 as shown by Eq. 1. This mechanism is consistent with the sudden appearance of hydrotalcite in mixtures and also with the effect of magnesium–aluminum ratio, concentration, pH, and temperature observed in this study.
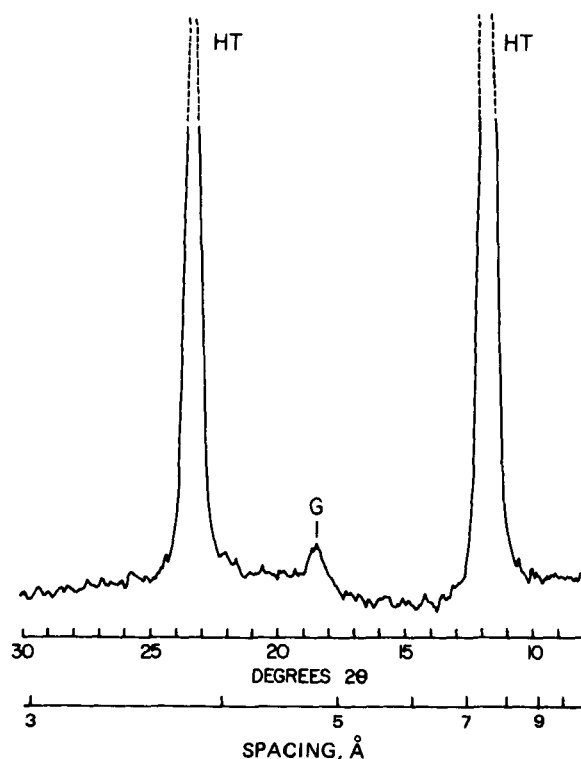


**Figure 14**—*X-ray diffractogram in the 3–9 Å region of the nonacid-reactive component of a magnesium–aluminum molar ratio (1:1) of a chloride-containing aluminum hydroxide gel and magnesium hydroxide gel containing 0.6 mmole of metal/g after aging for 173 days at 25°. HT and G indicate the peaks corresponding to hydrotalcite and gibbsite, respectively.*

A nonacid-reactive form of hydrotalcite is produced when a mixture of a chloride-containing aluminum hydroxide gel and magnesium hydroxide is aged at 25°. Compared to an aluminum hydroxycarbonate gel, a chloride-containing aluminum hydroxide gel shows a more rapid decrease in the rate of acid neutralization, and the total amount of acid neutralized at pH 3 also decreases (4). The pH of a mixture containing 0.6 mmole of metal/g in a magnesium–aluminum molar ratio of 1:1 increased from 6.6 to 8.5 after 8 days at 25°. The pH-stat titrigram also showed a change in shape at this same time (Fig. 12). However, in contrast to mixtures containing aluminum hydroxycarbonate gel, (Fig. 1) the total amount of acid neutralized decreased to ~15% of the theoretical yield after aging for 48 days. Well-crystallized hydrotalcite peaks were evident in the X-ray diffractograms after 69 days at 25° (Fig. 13, Curve A). No magnesium hydroxide peaks were present in the X-ray diffractogram, but peaks at 4.82 and 4.34 Å indicated the presence of gibbsite, a crystalline polymorph of aluminum hydroxide. An X-ray diffractogram of the mixture after 173 days at 25° (Fig. 13, Curve B) showed a further increase in the crystallinity of hydrotalcite.

The sharp peaks suggested a larger crystallite size for the hydrotalcite formed in the chloride-containing aluminum hydroxide gel and magnesium hydroxide gel mixtures than formed in the aluminum hydroxycarbonate gel and magnesium hydroxide gel mixtures. After 118 days at 25°, the unreactive fraction from the pH-stat test was collected and washed. An X-ray diffractogram (Fig. 14) shows that the nonacid reactive component is chiefly highly crystalline hydrotalcite. Thus, a nonacid-reactive aluminum hydroxide gel quickly gave rise to a nonacid-reactive form of hydrotalcite.

The formation of hydrotalcite during the aging of mixtures of aluminum hydroxide gel and magnesium hydroxide gel is important because the *United States Pharmacopeia* recognizes two mixtures of aluminum hydroxide gel and magnesium hydroxide gel, as well as magaldrate (23) which is a form of hydrotalcite having sulfate as the principal interlayer anion. Alumina and magnesia oral suspension (3) may contain a magnesium–aluminum molar ratio of between 0.4 and 0.8 and a total metal content of between 0.8 and 1.2 mmoles of metal/g. Magnesia and alumina oral suspension (24) may contain a magnesium–aluminum molar ratio of between 1.4 and 2.4 and a total metal content of between 0.9 and 1.2 mmoles of metal/g. These mixtures are within the range of magnesium–

aluminum and total metal concentration of the mixtures in which hydrotalcite was found to form on aging.

The present monographs for these mixtures do not contain any tests which would detect the presence of hydrotalcite, nor do they require the inclusion of sorbitol in the mixtures. Thus, there is the possibility of the formation of hydrotalcite during the aging of official aluminum hydroxide gel and magnesium hydroxide gel mixtures.

## REFERENCES

(1) R. K. Vanderlaan, J. L. White, and S. L. Hem, *J. Pharm. Sci.*, **68**, 1498 (1979).
(2) S. L. Hem, E. J. Russo, S. M. Bahal, and R. S. Levi, *ibid.*, **59**, 317 (1970).
(3) "The United States Pharmacopeia," 20th rev., United States Pharmacopeial Convention, Inc., Rockville, Md., 1980, p. 23.
(4) N. J. Kerkhof, R. K. Vanderlaan, J. L. White, and S. L. Hem, *J. Pharm. Sci.*, **66**, 1528 (1977).
(5) H. P. Klug and L. E. Alexander, "X-Ray Diffraction Procedures for Polycrystalline and Amorphous Materials," Wiley, New York, N.Y., 1954, p. 300.
(6) S. L. Nail, J. L. White, and S. L. Hem, *J. Pharm. Sci.*, **65**, 1188 (1976).
(7) *Ibid.*, **65**, 231 (1976).
(8) C. J. Serna, J. L. White, and S. L. Hem, *ibid.*, **67**, 324 (1978).
(9) J. L. White and S. L. Hem, *ibid.*, **64**, 468 (1975).
(10) C. J. Serna, J. L. White, and S. L. Hem, *Soil Sci. Soc. Am. J.*, **41**, 1009 (1977).
(11) K. Nakamoto, "Infrared Spectra of Inorganic and Coordination Compounds," Wiley, New York, N.Y., 1963, p. 159.
(12) L. Ingram and H. F. W. Taylor, *Mineral. Mag.*, **36**, 465 (1967).
(13) R. Allmann, *Acta Crystallogr.*, *Sect. B*, **24**, 972 (1968).
(14) R. Allmann and H. H. Lohse, *N. Jb. Miner. Mh.*, 161 (1966); through *Chem. Abst.*, **66**, 23112 g (1967).
(15) R. Allmann and H. P. Jepson, *N. Jb. Miner. Mh.*, 544 (1966); through *Chem. Abst.*, **72**, 60153 y (1970).
(16) R. Allmann, *N. Jb. Miner. Mh.*, 552 (1966); through *Chem. Abst.*, **72**, 60156 b (1970).
(17) R. Allmann, *Chimia*, **24**, 99 (1979); through *Chem. Abst.*, **73**, 8203 w (1970).
(18) R. Allmann, *Fortschr. Mineral.*, **48**, 24 (1971); through *Chem. Abst.*, **75**, 144866 h (1971).
(19) F. A. Mumpton, H. W. Jaffe, and C. S. Thompson, *Am. Mineral.*, **50**, 1893 (1965).
(20) H. Besson, S. Caillere, and S. Henin, *Clay Miner.*, **12**, 239 (1977).
(21) H. Besson, S. Caillere, and S. Henin, *C.R. Acad. Sci.*, **277**, 1273 (1973).
(22) M. M. Mortland and M. C. Gastuche, *ibid.*, **255**, 2131 (1962).
(23) "The United States Pharmacopeia," 20th rev. United States Pharmacopeial Convention, Inc., Rockville, Md., 1980, p. 457.
(24) *Ibid.*, p. 458.

## ACKNOWLEDGMENTS

# Toxicity of Polyalkylcyanoacrylate Nanoparticles I: Free Nanoparticles

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**Abstract** □ The present report describes preliminary results concerning the acute toxicity of placebo polyalkylcyanoacrylate nanoparticles used as drug carrier. It was demonstrated that nanoparticles induced cellular damage only at relatively high concentrations in the cell culture medium. The absence of mutagenicity was shown for both nanoparticles and their degradation products, and the $LD_{50}$ for polybutyl- and polyisobutylcyanoacrylate nanoparticles was also determined.

**Keyphrases** □ Polyalkylcyanoacrylate—toxicity of nanoparticles □ Nanoparticles—polyalkylcyanoacrylate toxicity □ Toxicity—polyalkylcyanoacrylate nanoparticles □ Drug carrier systems—nanoparticles, toxicity of polyalkylcyanoacrylate

Previous studies have demonstrated the interest of polyalkylcyanoacrylate nanoparticles as a drug carrier (1, 2). The main advantage of these particles is their degradability at a rate depending on the length of the alkyl chain (3). These ultrafine particles (diameter of ~0.2 μm) are able to efficiently adsorb a variety of drugs in a stable and reproducible way (4). It has been shown previously that the binding of cytostatic drugs to nanoparticles modifies their distribution pattern in rat tissues and generally increases the tissue capture of these drugs (5, 6).

Recently, preliminary results of experimental chemotherapy were published (7) using actinomycin D-loaded polymethylcyanoacrylate nanoparticles against the growth of a transplantable soft sarcoma tissue of the rat. The results indicated that the use of polymethylcyanoacrylate nanoparticles as a drug carrier increased the anticancer activity of actinomycin towards subcutaneous sarcoma. Furthermore, these particles could be of interest in the field of long-acting insulin therapy (8).

However, it was important to have information about the toxicity of the carrier to determine if these results did not prohibit the use of nanoparticles in human medicine. The present report describes preliminary results concerning the acute toxicity of nondrug-bound nanoparticles towards cells in culture and the determination of the $LD_{50}$ of the carrier.

## EXPERIMENTAL

**Polyalkylcyanoacrylate Nanoparticles Preparation**—Polymethyl-, polybutyl-, and polyisobutylcyanoacrylate nanoparticles were prepared following previous methods (1, 6), slightly modified. To an