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Effect of Interaction of Aluminum Hydroxycarbonate Gel and Magnesium Hydroxide Gel on Acid Neutralization

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Abstract □ Acid neutralization by mixtures of aluminum hydroxycarbonate gel and magnesium hydroxide gel differs from the sum of the acid neutralization of each gel. Acid neutralization by magnesium hydroxide gel in the mixture is not observed until after a substantial portion of the aluminum hydroxycarbonate gel has reacted with acid, even though magnesium hydroxide gel is the faster reacting of the two gels. It is hypothesized that amorphous aluminum hydroxycarbonate forms a coating on the crystalline magnesium hydroxide particles due to electrostatic attraction. This coating prevents protons from reaching the highly reactive magnesium hydroxide until the coating is dissolved by the acid neutralization of aluminum hydroxycarbonate.

Keyphrases □ Aluminum hydroxycarbonate gel—acid neutralization, effect of interaction with magnesium hydroxide gel □ Magnesium hydroxide gel—acid neutralization, effect of interaction with aluminum hydroxycarbonate gel □ Antacids—aluminum hydroxycarbonate, magnesium hydroxide, effect of interaction on acid neutralization

Aluminum hydroxycarbonate gel (1) and magnesium hydroxide gel are formulated in combination in many antacid products. Aluminum hydroxycarbonate gel exhibits antacid activity only when amorphous. With aging, order develops in the amorphous structure, which reduces the acid reactivity and ultimately leads to the formation of an inactive crystalline state (2, 3).

A chemical property of aluminum hydroxycarbonate gel that makes it useful as an antacid is its ability to maintain pH 3.5–4.0 while reacting with acid (4). Aluminum hydroxycarbonate is not systemically absorbed and, aside from causing constipation, is free of side effects (5).

BACKGROUND

The solid phase of magnesium hydroxide gel has a crystalline structure known mineralogically as brucite. However, in contrast to the behavior of crystalline aluminum hydroxide, the crystalline magnesium hydroxide gel rapidly reacts with acid (6). Due to its well-ordered crystal structure, it exhibits excellent stability.

Magnesium hydroxide gel reacts with acid at a constant pH of 8.0–8.5. This pH is not as desirable as the one maintained during acid neutralization by aluminum hydroxycarbonate gel and, therefore, magnesium hydroxide gel is not frequently used as an antacid. In addition, magnesium ion produced during acid neutralization may be systemically absorbed, so a warning to patients with kidney disease is required (5). Magnesium ion also causes a cathartic effect, which balances the action of aluminum hydroxide gel on the intestine and provides the rationale for combining aluminum hydroxycarbonate gel and magnesium hydroxide gel in antacid products.

The addition of less than stoichiometric amounts of acid does not lower the pH of magnesium hydroxide gel below 8. However, a mixture of aluminum hydroxycarbonate gel–magnesium hydroxide gel drops to ~pH 4 after the addition of a relatively small amount of acid. Furthermore, it remains at ~pH 4 even when more acid is added (7). This behavior suggests an interaction between the amorphous aluminum hydroxycarbonate and the crystalline magnesium hydroxide gels. The investigation was undertaken to study this interaction, with emphasis on its effect on acid neutralization.

EXPERIMENTAL

Materials—Aluminum hydroxycarbonate gel containing the equivalent of 4% Al_2O_3 was prepared by the reaction of aluminum chloride, sodium bicarbonate, and sodium carbonate to a final pH of 6.5 (8).

Magnesium hydroxide gel[1] was obtained commercially, and a gel containing the equivalent of 7% MgO was prepared by dilution.

All chemicals were either official or reagent grade.

Preparation of Gel Mixtures—Mixtures of aluminum hydroxycarbonate gel and magnesium hydroxide gel containing 0.6 mmole of metal ion/g were prepared on a weight basis. For example, a 200-g mixture with a 5:1 molar ratio of magnesium to aluminum was prepared by weighing magnesium hydroxide gel and aluminum hydroxycarbonate gel containing 100 mmoles of magnesium and 20 mmoles of aluminum, respectively. The final weight of the mixture was adjusted to 200 g with double-distilled water, and the mixture was stirred mechanically until uniform.

Analytical Procedures—The aluminum and magnesium contents of the mixtures were determined by chelatometric titration (9).

The acid-neutralization reaction was monitored by an automated[2] pH-stat titration (10). For a typical pH-stat titration, 20 ml of double-distilled water was added to the reaction flask and brought to pH 3.0. An accurately weighed gel mixture sample, which would theoretically neutralize 2.25 meq of acid, was added; the recorder was started simultaneously. The cumulative amount of acid needed to maintain pH 3.0 was recorded as a function of time.

Atomic absorption spectrophotometry was employed to determine the concentrations of aluminum and magnesium ions in solution during acid neutralization. The pH-stat titration was halted at various times, the reaction medium was filtered quickly through a 0.22-μm filter, and the filtrate was analyzed for aluminum and magnesium.

RESULTS

Characteristic pH-stat titrigrams of aluminum hydroxycarbonate gel and magnesium hydroxide gel are shown in Fig. 1.

Kerkhof *et al.* (10) characterized the pH-stat titrigram of an aluminum

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[1] HydroMagma, Merck & Co., Rahway, N.J.
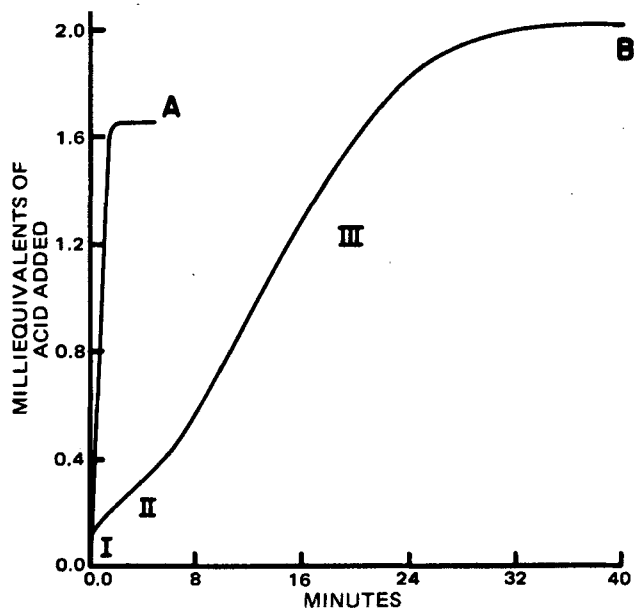[2] PHM 26, TTT II, ABU 12 (2.5 ml), TTA 3, SBR 2, Radiometer, Copenhagen, Denmark.

Figure 1—*The pH-stat titrigrams at pH 3.0 of magnesium hydroxide gel (A) and aluminum hydroxycarbonate gel with the three phases of the neutralization reaction indicated as described by Kerkhof et al. (10) (B).*

Figure 2—*The pH-stat titrigram at pH 3.0 of a 5:1 magnesium–aluminum molar ratio mixture of aluminum hydroxycarbonate gel and magnesium hydroxide gel with the four phases of the neutralization reaction indicated.*

hydroxycarbonate gel as consisting of three phases. The first phase represents a rapid reaction, which exceeds the maximum rate of acid addition and is attributed to the neutralization of free hydroxyl and carbonate as well as to small aluminum hydroxycarbonate polymers. Additional carbonate reacts in the second phase, which disrupts the polymeric structure and permits the rapid neutralization observed in the third phase.

The pH-stat titrigram of magnesium hydroxide gel exhibits a single high reactivity phase.

The pH-stat titrigram of a mixture of aluminum hydroxycarbonate gel and magnesium hydroxide gel shows four phases (Fig. 2). The first phase is a period of relatively rapid acid neutralization. Close examination of Phase I reveals three phases similar to those observed for aluminum hydroxycarbonate gel. Phase II, a lag phase, is a period of minimal acid reactivity. Phase III is characterized by a very rapid rate of acid neutralization, as is seen in the magnesium hydroxide gel titrigram. Phase IV represents the termination of the reaction and may be characterized either by an immediate cessation in acid neutralization or by a prolonged period of slow neutralization.

The pH-stat titrigram obtained when an aluminum hydroxycarbonate gel and a magnesium hydroxide gel were injected simultaneously into the pH-stat reaction vessel so that the gels were not mixed prior to the neutralization reaction is shown in Fig. 3A. The titrigram shows a phase of very rapid acid reactivity followed by slower neutralization during the termination phase. The aluminum hydroxycarbonate gel and the magnesium hydroxide gel appear to react simultaneously, with the neutralization reactions being additive.

A quite different neutralization reaction occurred if the aluminum hydroxycarbonate gel and magnesium hydroxide gel were mixed prior to being introduced into the pH-stat reaction vessel. A contact time of only 15 min prior to testing resulted in a four-phase titrigram (Fig. 3B) similar to the titrigram seen for mixtures of aluminum hydroxycarbonate gel and magnesium hydroxide gel (Fig. 2).

Clearly, an immediate interaction takes place between the aluminum hydroxycarbonate gel and the magnesium hydroxide gel, which yields a pH-stat titrigram that cannot be interpreted in terms of the simple sum of the acid reactivities of the two gels.

The acid reactivity of a 5:1 magnesium–aluminum molar ratio mixture of magnesium hydroxide gel and aluminum hydroxycarbonate gel was examined at different pH values along with the acid reactivity of each gel. Figure 4 compares the effect of pH on the acid-neutralization reactions of aluminum hydroxycarbonate and magnesium hydroxide gels.

Magnesium hydroxide gel reacts very rapidly at pH 3.0 and 4.5. Since magnesium hydroxide is not precipitated by base below pH 9.5 (11), the difference in the driving force for dissolution between neutralization reactions at pH 3.0 and 4.5 would be expected to be relatively small.

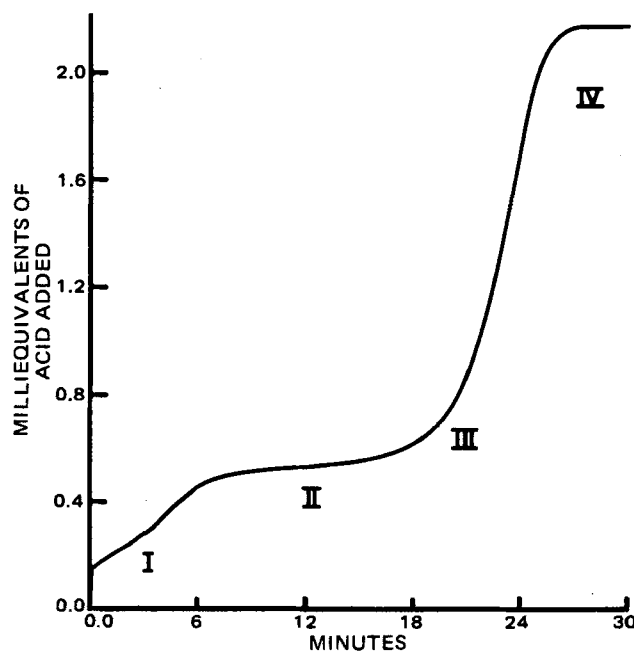The pH-stat titrigram for aluminum hydroxycarbonate gel at pH 3.0

shows that the theoretical amount of acid is neutralized. However, negligible acid is neutralized by aluminum hydroxycarbonate gel at pH 4.5. Since aluminum hydroxycarbonate gel may be precipitated at a pH as low as 4 (12), the relative difference in the forces causing the aluminum hydroxycarbonate gel dissolution are great between pH 3.0 and 4.5. Rapid aluminum hydroxycarbonate dissolution would not be expected at a pH where precipitation of aluminum hydroxycarbonate may occur.

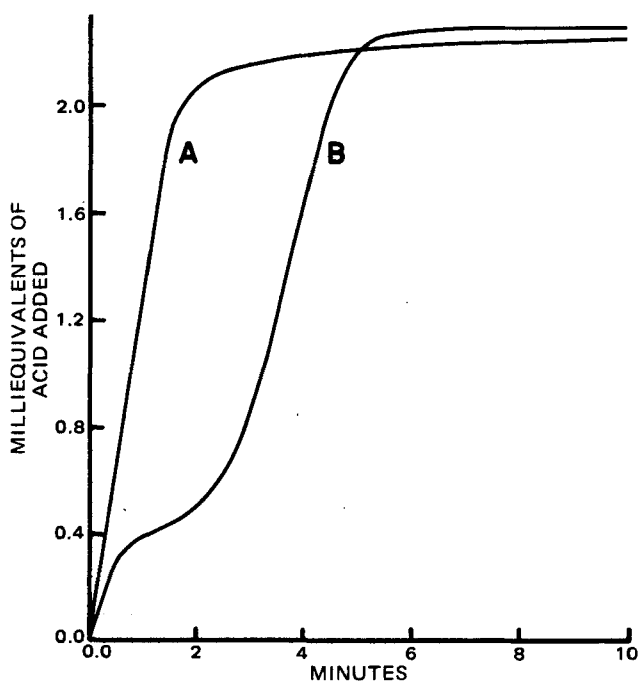Titrigrams of the aluminum hydroxycarbonate gel–magnesium hy-

Figure 3—*The pH-stat titrigrams at pH 3.0 of a 5:1 molar ratio magnesium hydroxide gel and aluminum hydroxycarbonate gel mixture. Key: A, gels injected simultaneously into the reaction vessel without premixing; and B, gels mixed for 15 min before injection of the mixture into the reaction vessel.*
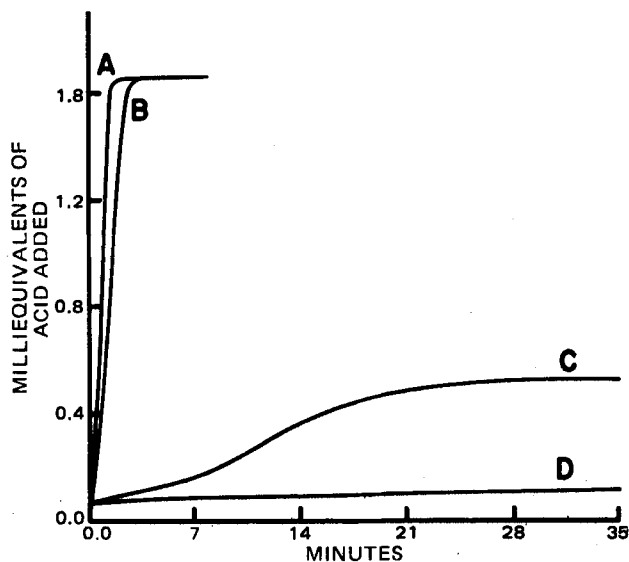
Figure 4—*The pH-stat titrigrams of magnesium hydroxide gel at pH 3.0 (A) and 4.5 (B) and of aluminum hydroxycarbonate gel at pH 3.0 (C) and 4.5 (D).*

droxide gel mixture were obtained at pH 1.5–4.5. Figure 5 shows that the titrigram retains its four-phase profile between pH 1.5 and 4.25 and that the time required for neutralization increases substantially as the pH approaches 4.5.

However, the neutralization reaction of the mixture at pH 4.5 showed no increase in acid neutralization, even after 6 hr. Although aluminum hydroxycarbonate gel was expected to be unreactive at pH 4.5, the magnesium hydroxide gel exhibited rapid reactivity at pH 3.0 and 4.5 (Fig. 4).

The total amount of acid neutralized by the mixtures was the sum of the acid neutralized by each component for pH 1.5–4.0. The aluminum hydroxycarbonate became unreactive at pH 4.5, as did the mixture of aluminum hydroxycarbonate gel and magnesium hydroxide gel, even though individually the magnesium hydroxide reacted completely with acid at this pH (Fig. 4).
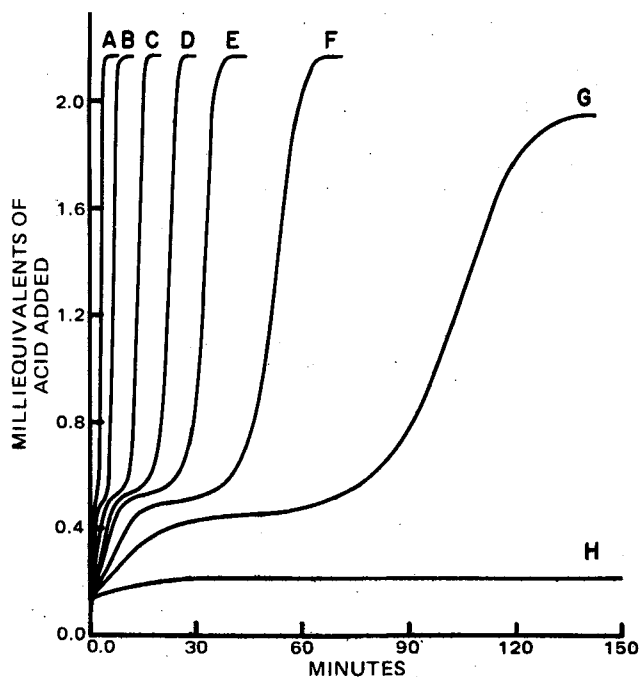

Figure 5—*The pH-stat titrigrams of 5:1 molar ratio mixtures of magnesium hydroxide gel and aluminum hydroxycarbonate gel at pH 1.5 (A), 2.0 (B), 2.5 (C), 3.0 (D), 3.5 (E), 4.0 (F), 4.25 (G), and 4.5 (H).*
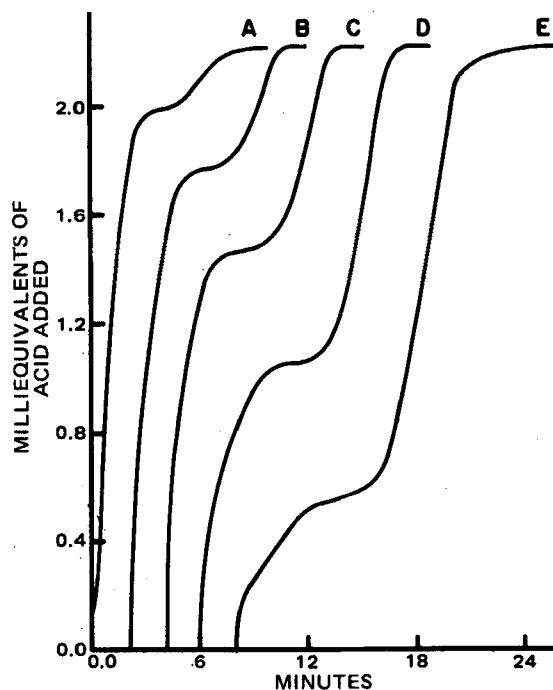

Figure 6—*The pH-stat titrigrams at pH 3.0 of mixtures of aluminum hydroxycarbonate gel and magnesium hydroxide gel of various molar ratios of magnesium to aluminum. Key: A, 1:5; B, 1:2; C, 1:1; D, 2:1; and E, 5:1.*

The pH-stat titrigrams of five aluminum hydroxycarbonate gel and magnesium hydroxide gel mixtures containing 0.6 mmole of metal/g at various magnesium to aluminum molar ratios are compared in Fig. 6. A direct relationship is seen between the magnesium to aluminum ratio of the gel mixture and the ratio of the amounts of acid neutralized during Phases III and I. In each case, the aluminum hydroxycarbonate gel appears to react with acid before the magnesium hydroxide gel reacts.

The liberation of aluminum and magnesium ions during the pH-stat neutralization at pH 3.0 of an aluminum hydroxycarbonate gel–magnesium hydroxide gel mixture was monitored by atomic absorption spectrophotometry. The milliequivalents of each metal ion in solution were compared to the milliequivalents of acid neutralized (Fig. 7). The magnesium-ion concentration did not begin to increase until virtually all of the aluminum was in solution. The total milliequivalents of metal ion in solution showed the expected 1:1 relationship to the milliequivalents of acid neutralized.

DISCUSSION

The pH of the aluminum hydroxycarbonate gel and magnesium hydroxide gel mixtures ranged from 8.0 for the 1:5 magnesium–aluminum molar ratio mixture to 8.6 for the 5:1 magnesium–aluminum molar ratio mixture. The magnesium hydroxide gel pH was 10.3, while the aluminum hydroxycarbonate gel was precipitated to pH 6.5.

The apparent surface charge of a particle in suspension is determined by the isoelectric point or zero point charge. The apparent surface charge is negative when the pH is above the zero point charge and positive if the pH is below the zero point charge (13).

The isoelectric point of magnesium hydroxide gel was reported as pH 12 (14). At the pH of the gel mixtures, the magnesium hydroxide surface would be expected to have a net positive charge.

Isoelectric points from pH 6.3 to 9.1 were reported for aluminum hydroxide (15–18) as a result of the diverse nature of the substance commonly termed aluminum hydroxide. Schott (17) recently reported an isoelectric point of 8.5 for aluminum hydroxide but was very careful to exclude coordinating anions from the aluminum hydroxide. According to Parks (13), anions such as those found in aluminum hydroxide gels with desirable acid reactivity for use as antacids substantially lower the isoelectric point. Thus, at the pH of the gel mixtures, the aluminum hydroxycarbonate surface would be expected to be negative.

It is hypothesized that the electrostatic attraction between the aluminum hydrocarbonate gel and the magnesium hydroxide gel causes
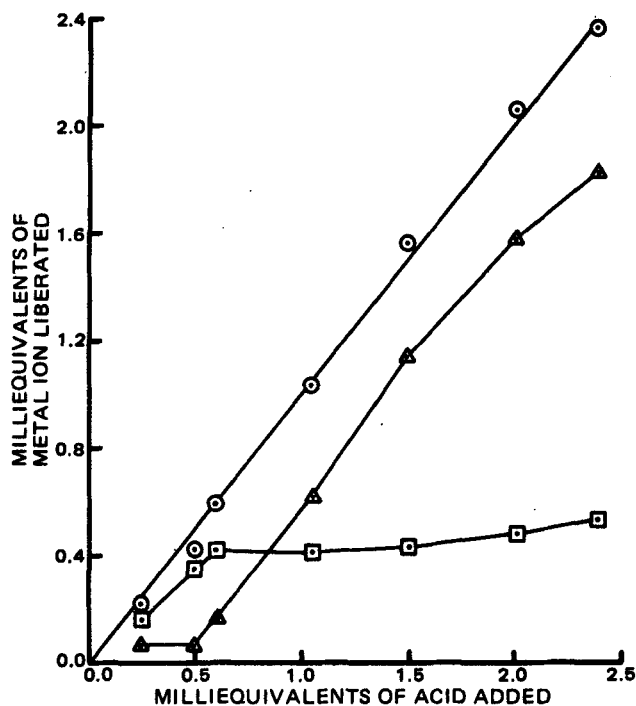
Figure 7—*Milliequivalents of metal ion liberated during pH-stat titration at pH 3.0 of a 5:1 magnesium–aluminum molar ratio mixture of aluminum hydroxycarbonate gel and magnesium hydroxide gel. Key: △, milliequivalents of magnesium ion in solution; □, milliequivalents of aluminum ion in solution; and ○, total milliequivalents of magnesium and aluminum ions in solution.*

agglomeration in the gel mixtures. Treadwell and Bernasconi (19) proposed an adsorption bonding of this type. Thus, the amorphous aluminum hydroxycarbonate would form a coating on the crystalline brucite magnesium hydroxide gel. The aluminum hydroxycarbonate coating would prevent protons from reaching the highly reactive brucite until

the coating dissolves due to acid neutralization of the aluminum hydroxycarbonate. As was observed in the pH-stat titrigrams of mixed aluminum hydroxycarbonate-magnesium hydroxide gels, the acid neutralization will occur more slowly than expected due to the coating of the faster reacting magnesium hydroxide gel by the slower reacting aluminum hydroxycarbonate gel.

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Simple Epoxide Analogs of Trichothecans

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Abstract □ To define clearly the epoxide grouping role in trichothecan biological activity, a series of hindered epoxides was prepared. They possessed α,α'-substitution reminiscent of the epoxide environment of the natural products. None of these analogs demonstrated biological activities similar to the natural toxins.

Keyphrases □ Trichothecans—epoxide analogs, structure–activity relationships, toxicity □ Fungistatic agents—trichothecans, epoxide analogs, structure–activity relationships, toxicity

In 1946, as part of a program to discover new antibiotics, a highly fungistatic principle was isolated from a culture filtrate of *Metarrhizium glutinosum* S. Pope (1). This principle was highly irritating to human skin. Similar agents were produced by various microorganisms, including *Trichothecium roseum* and species of *Fusaria* and

Trichoderma (2). Continued work with these materials led to the isolation in pure form of one of these principles; it was named trichothecin (3). Since that time, many related compounds have been isolated and characterized and are collectively known as the trichothecans (I), a name coined for the ring system possessed by all of these materials (4).

BACKGROUND

All trichothecans contain a 12,13-epoxy group, a 9,10-double bond, and the 4-β-hydroxyl. The simplest of the group, trichodermin (II), contains an acetate ester and only functionalities characteristic of all trichothecans. The most complex materials contain a fifth, macrocyclic ring, which is formed *via* esterification of hydroxyls at positions 4 and 15 by a long chain diacid.