



CHAPTER I

INTRODUCTION

RATIONALE

Aluminum hydroxide gel is an effective antacid largely due to its rapid rate of acid neutralization and the neutralizing pH is between 3.5-4.0. Although many aspects of its structure and acid reactivity are not fully understood. The initial precipitate resulting from the reaction of a soluble aluminum salt with a base during process of manufacture is probably a highly random structure. During aging, it is found that structural rearrangement occurs to form a more thermodynamically stable system. For example, a polymerization-like process may produce a highly ordered system which is resistant to attack by acid. The rate of this process has been related to many factors including pH of solution during precipitation (Hem, Russo, Bahal et al., 1970), type and concentration of ions present, temperature (Hem, Russo, Harwood et al., 1970) and order of addition of the reactants.

The end-product after the aging process is usually changed to crystalline form of aluminum hydroxide. However, a number of reports have suggested that the aluminum hydroxide which containing specifically adsorbed

anions such as Cl^- , SO_4^{2-} and CO_3^{2-} should better stability and facilitate the acid neutralization reaction for a long period of time (White and Hem, 1975; Nail, White, and Hem, 1976c; Kerkhof, White, and Hem, 1977; Serna, White, and Hem, 1978a; Serna *et al.*, 1983). Polyols were employed to stabilize the aluminum hydroxide gel for the purpose of inhibition of polymerization reaction (Nail, White, and Hem, 1976d).

Aluminum hydroxide suspension belongs to the so-called non-sterile drugs. It is not dispensed as sterile products by nevertheless bacterial contamination has to be avoided. This could indeed lead to deterioration of the product and form a potential danger for the patients' health (Nakamori *et al.*, 1975; Renolds, 1989).

Good microbiological quality of the product could be achieved by respecting the GMP-assurance. In addition, the incorporation of a preservative should prevent excessive proliferation of bacterial or fungal contamination, introduced during manipulation of the product by the patients.

The choice of the preservative depends on several factors, such as compatibility with other ingredients and pH, the latter possibly being of substantial importance in aluminum hydroxide suspension. It is also being described that certain substances such as aluminum hydroxide and suspending agents present in aluminum hydroxide suspension

are counteracting the activity of some certain preservatives. Therefore, the adsorption of preservatives in aluminum hydroxide suspension is a well documented source of preservative failure.

In this present study intend to evaluate aluminum hydroxide gel from various processes of manufacture by comparing with various products in the market. The comparisons were in term of physicochemical properties, the adsorption isotherms of some preservatives and the stability after aging. These information however, are not much readily available to manufacturing and will be of advantage in production of antacid.



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PURPOSES OF THE STUDY

As it was mentioned previously, aluminum hydroxide gel is most widely used as antacid and could present stability problem and adsorption of preservative upon aging. The objectives of this research were to:

1. Evaluate physicochemical properties and stability of aluminum hydroxide gel from various sources and various processes of manufacture.
2. Study the effect of pH on the surface adsorption of some preservatives by aluminum hydroxide gel.
3. Study the effect of sorbitol on the stability of aluminum hydroxide gel.

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LITERATURE REVIEW

General Properties of Aluminum Hydroxide Gel

Aluminum hydroxide gel is a white, odorless, appeared in the form of amorphous in which there is a partial substitution of carbonate for hydroxide.

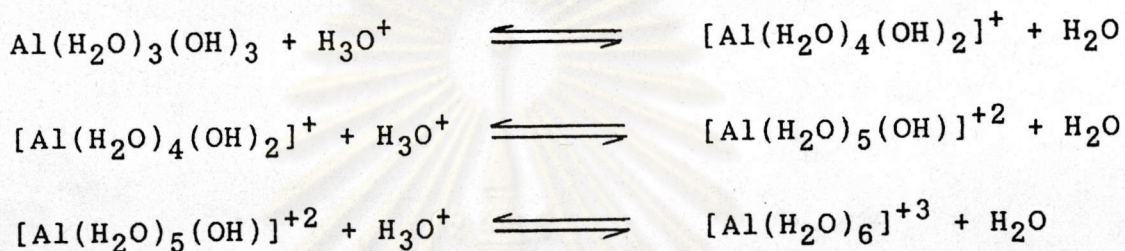
Practically insoluble in water and alcohol, but soluble in alkali and acid solution in the present of some water. This product should store in airtight containers, and avoid freezing (Reynold, 1989; USP XXII., 1990).

Pharmacology of Aluminum Hydroxide Gel

The clinical use of antacids is based on their ability to increase the pH of gastric secretions by reduce the concentration of acid in gastric juice. The ultimate goal of therapy is to bring the gastric content to a pH values of between 3.5 and 4. The reason may be due to the optimum pH for pepsin activity is between 1.5-2.5 and progressive inhibition occurs as gastric pH increase, at above pH 4, the proteolytic activity of pepsin is minimal. With usual doses, antacid products generally should not increase and maintain gastric pH above 4-5. Although antacids do not neutralized all gastric acid, increasing pH from 1.3 to 2.3 and to 3.3 mean neutralized 90% and 99% of gastric acid, respectively. Consequently, the gastric acid can back diffuse through the gastric mucosa and the

amount of reaching the duodenum is decreased (McEvoy, 1988).

Aluminum hydroxide is slowly solubilized in the stomach and reacts with hydrochloric acid as shown in the following equations : (Nairn, 1990)



It shown that aluminum hydroxide is a nonsystemic antacid because of it forms compound that are not appreciably absorbed and thus do not exert any systemic effect.

Stability of Aluminum Hydroxide Gel

The formation of polynuclear hydroxyaluminum complexes in dilute solution was described by Hem and Roberson (Hem and Roberson, quoted in Nail, White, and Hem, 1976b) as a stepwise process involving a deprotonation-dehydration mechanism. In aqueous aluminum salt solution below pH 4, aluminum exists primary as the trivalent cation with six water molecules in octahedral coordination, $\text{Al}(\text{H}_2\text{O})_6^{3+}$ (Figure 1).

The first step in the conversion of hydrated

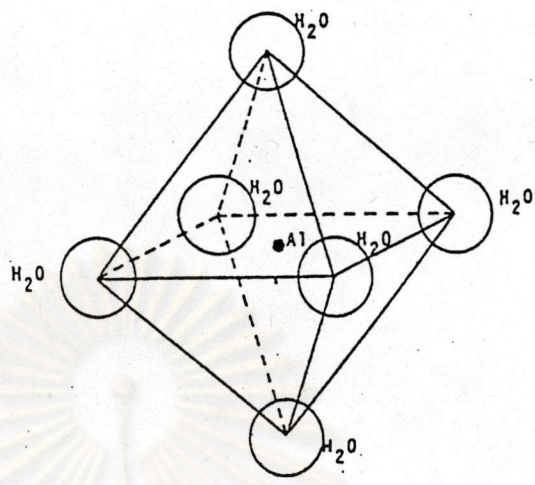


Figure 1 Hydrolyzed aluminum ion $Al(OH_2)_6^{+3}$

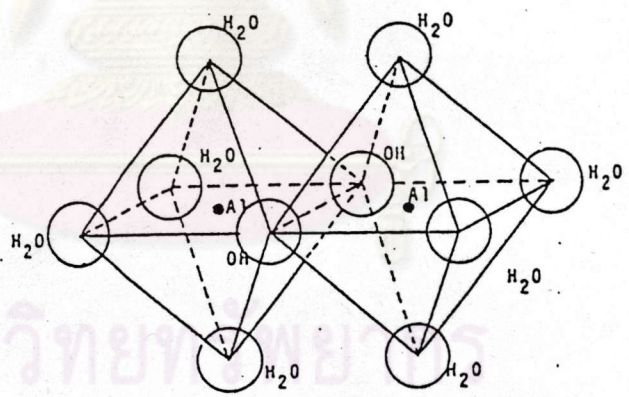
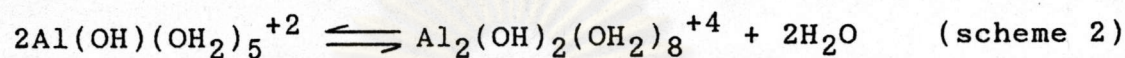
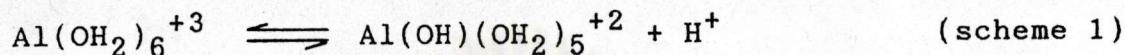


Figure 2 Dimeric cation $Al_2(OH)_2(OH_2)_8^{+4}$

aluminum ions to polymerized species involves deprotonation of one of the coordinated water molecules of the aluminum cation (Scheme 1). Two deprotonated octahedra can then join to form a dimer (Scheme 2).



This unit contains the characteristic of double hydroxide bridge between aluminum ions (Figure 2). Dimers then can join to form either a chain structure or a ring structure by the same deprotonation-dehydration mechanism (Figure 3). The general formula for a chain structure would be : $\text{Al}_m(\text{OH})_{2m-2}(\text{OH}_2)^{+(m+2)}$. The six-membered rings may then coalesce further by continued polymerization, resulting in a higher ratio of structural hydroxyl to aluminum. The hydroxide to aluminum ratio will approaches 3 as the structure increase in size. The growth of a hydroxyaluminum particle by formation of six-membered rings and multiples thereof is shown in Figure 4 (Nail et al., 1976b). The developement of a highly ordered structure of aluminum hydroxide gel which growth by a deprotonation-dehydration mechanism also causes a decrease in acid neutralization (Nail et al., 1976c). This mechanism is inhibited by anions such as Cl^- , SO_4^{2-} and CO_3^{2-} (Hem, Russo, Bahal, et al., 1970; Serna et al., 1983). Recent reports showed that carbonate plays an

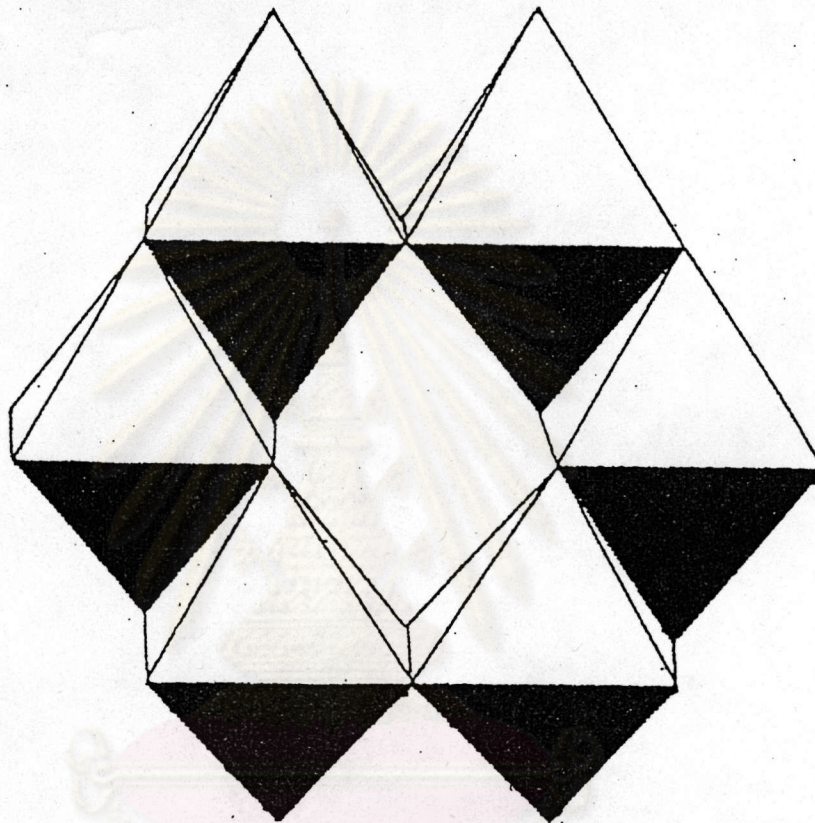


Figure 3 Ring structure formed by six aluminum hydroxide octahedra

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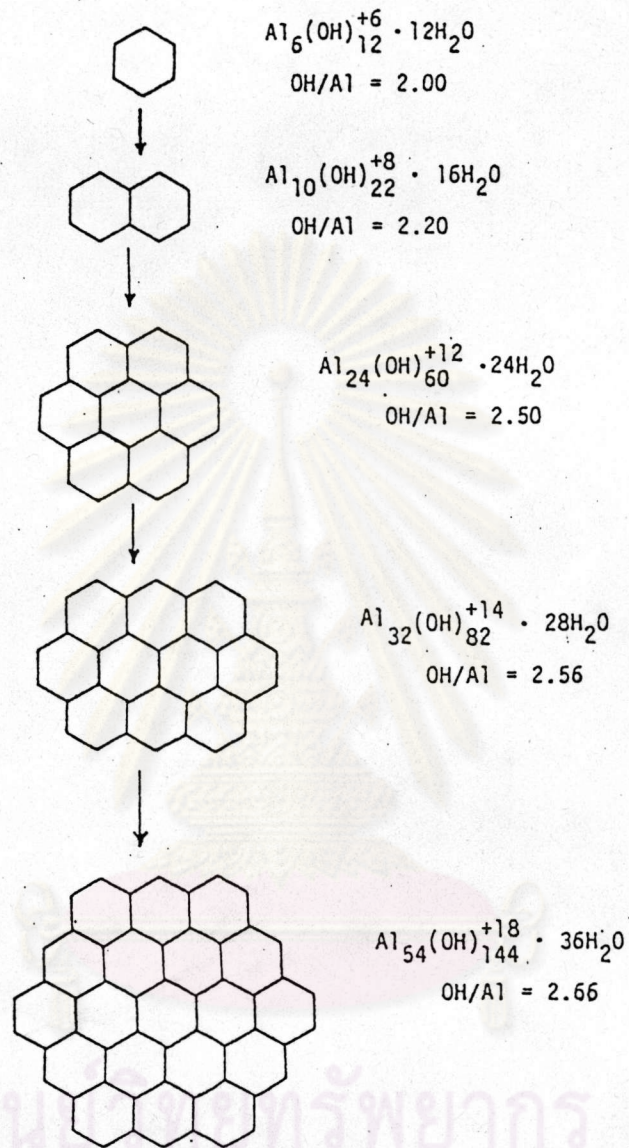


Figure 4 Proposed development of crystalline aluminum hydroxide

important role in stabilization of gel (Kerkhof, White et al., 1977) as well as in acid neutralization (Hem, Russo, Bahal et al., 1970). Carbonate appears to replace a hydroxyl in the double hydroxide bridges. The carbonate is reacted with the initial acid then, the gel structure is disrupted and causes an increased porosity and surface area (Kerkhof, White et al., 1977).

The particle morphology of amorphous aluminum hydroxycarbonate is of interest because of some apparently anomalous behaviors. For example, numerous studies have concluded that specifically adsorbed carbonate only substituted for hydroxyl at surface sites and is not contained within the interior of the particle (Scholtz et al., 1985). Furthermore, the carbonate to aluminum ratio of samples which exhibiting good antacid properties is usually between 0.2 and 0.5 (Scholtz et al., 1984a). These two facts can only be reconciled if the particle size is very small. In addition, the kinetics of acid neutralization by amorphous aluminum hydroxycarbonate are different from other antacid compounds. In the case of sodium bicarbonate and calcium carbonate these exhibit a linear rate of acid neutralization under pH-stat condition (Vanderlaan, White, and Hem, 1979, 1982). In contrast, the pH-stat titrgram of amorphous aluminum hydroxycarbonate contains three phases rather than the linear rate of acid neutralization as expected for and acid-base titration.

The pH-stat titrigrum has been recently interpreted based on the hypothesis that three types of particles exist : primary particles, secondary particles and aggregates. 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 as described by the Derjaguin, London, Verveij, Overbeek (DLVO) theory (Scholtz et al., 1983).

Previously, the term carbonate-containing aluminum hydroxide gel was used to describe the highly reactive gels used as antacid (Kerkhof et al., 1977; Serna et al., 1978a). However, this gel is now well enough understood to justify its description as amorphous aluminum hydroxycarbonate. Serna et al. (1978b) studied the effect of washing on the precipitate of amorphous aluminum hydroxycarbonate containing the greatest carbonate to aluminum ratio (pH 6.4) to test the model structure proposed in Figure 5. Carbonate is shown coordinated to aluminum by unidentate interaction and present in the stern layer and the diffuse layer. Sodium is present mainly in the diffuse layer. A dramatic change occurred in the carbonate content of the precipitate during the first wash. Further washing did not substantially lower

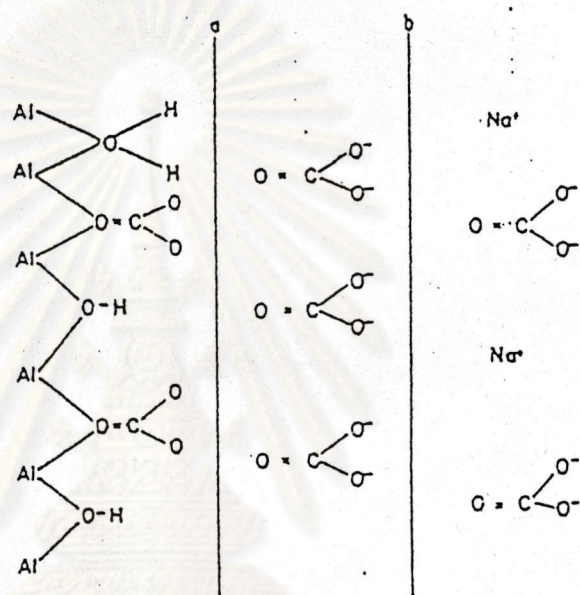


Figure 5 Proposed structure of amorphous aluminum hydroxy-carbonate surface/liquid interface
 Key; a: inner Helmholtz plane
 b: outer Helmholtz plane
 Water, hydroxide, and protons have not been included

the carbonate content of the gel and did not alter the carbonate interaction. This result is in contrast to the behavior of sodium, which was almost completely removed after three washes. The gel particles are positively charged at pH of approximately 6.4, but the charge is reversed in concentrated salt solution because of preferential adsorption of anions compressing the double layer. As the anions are removed by washing, the gel's positive charge is observed. Therefore the washing process is important because it could determine the physical stability of the colloidal particles and, consequently, the rheological properties of the gel.

Many processes for the preparation of aluminum hydroxide gel have been reported. Aluminum hydroxide gel for pharmaceutical use is often prepared by the neutralization of an aluminum salt solution with base. Three methods have been utilized. The first method involves the addition of the aluminum salt to the base (Serna, White, and Hem, 1978b) and is limited to batch processing. The second method is adding the base to the aluminum salt solution (Hem, Russo, Bahal *et al.*, 1970; Nail, White, and Hem, 1976e; Serna, White, and Hem, 1978c). The second method is also a batch process. In the third, an aluminum salt solution and a base are simultaneously mixed (Scholtz *et al.*, 1984b). This method can be either a batch or a continuous process.

Although far less common than other methods, the method of simultaneous mixing of reactants permits the precise control of pH. Since the solubility of aluminum hydroxide is very sensitive to pH, fixing this variable during the precipitation reaction should have a strong influence on the properties of the precipitate. The IR spectra of the precipitates found is shown in Figure 6. At a pH of precipitation (pHp) of 6.0, 6.5 and 7.0 are typical for amorphous aluminum hydroxide containing specifically adsorbed carbonate (Serna et al., 1978a, 1978b) and indicate the presence of only an amorphous component. The precipitates formed between pHp 7.5 and 9.5 exhibit a number of absorption bands in addition to the carbonate-containing aluminum hydroxide bands. The new absorption bands corresponding to the mineral dawsonite, a crystalline sodium aluminum hydroxycarbonate $[\text{NaAl}(\text{OH})_2\text{CO}_3]$. The IR analysis indicates that the precipitate formed at pHp 8.5 contained the largest fraction of dawsonite.

Mechanism of Interaction between Polyols and Aluminum Hydroxide Gel.

The polyols such as sorbitol were used to improve the stability of aluminum hydroxide gel. (Alford, 1959; Greene et al 1969; Nail et al, 1976d.).

Shah et al. (1981) investigated the mechanism of interaction between polyols and aluminum hydroxide gel and

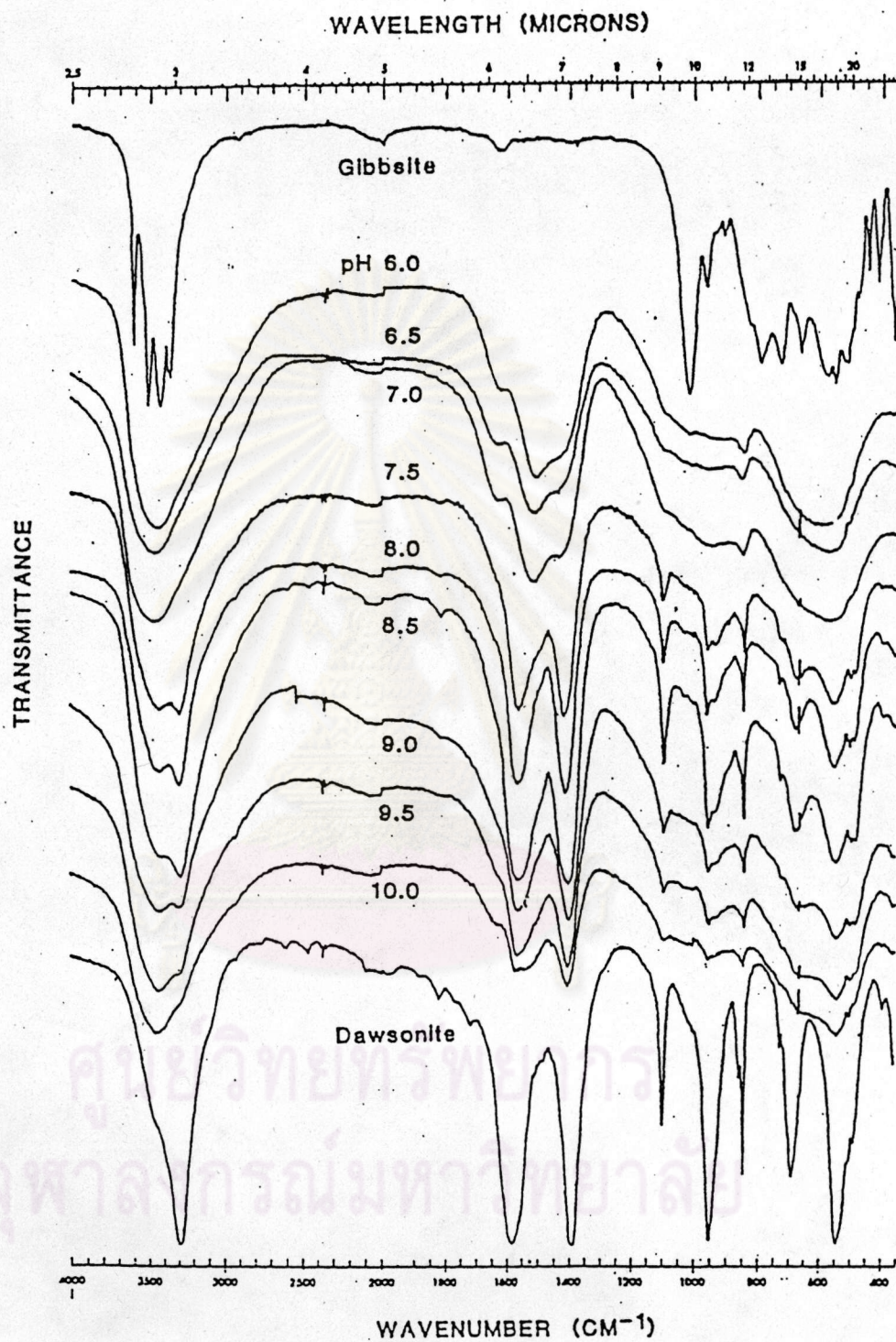


Figure 6 IR spectra of precipitates formed at various pH values

reported that hydrogen bonding is responsible for this interaction. Mannitol and sorbitol, both linear polyols, interacted with aluminum hydroxide, while inositol, a cyclic polyol, did not interact. The adsorbed polyol has the favorable effect of inhibiting the polymerization reaction that occurs on aging, but the rate of acid neutralization was reduced. Thus, the specific polyol and concentration must be carefully selected to maximize the desired effect of stabilizing the gel structure. The presence of mannitol in the reaction medium during precipitation did not significantly enhance gel structure, because the mannitol was desorbed during the washing process as a consequence of the weak adsorption forces.

The methods were employed to study the physicochemical properties of aluminum hydroxide gel which reported in the past are:

1. pH stat Titration (Scholtz et al., 1983)

The pH-stat titration has provided some insights into :

- 1.1 The structure of aluminum hydroxycarbonate (Kerkhof et al., 1977; Serna et al., 1978a).

- 1.2 The adsorption of polybasic acids (Wang, White, and Hem, 1980), and polyols (Shah, White, and Hem, 1981) by aluminum hydroxycarbonate.

- 1.3 The interaction of aluminum hydroxycarbonate and magnesium hydroxide (Vanderlaan et al., 1979, 1982)

2. Infrared Spectroscopic Analysis (Nail, White, and Hem, 1975, 1976a)

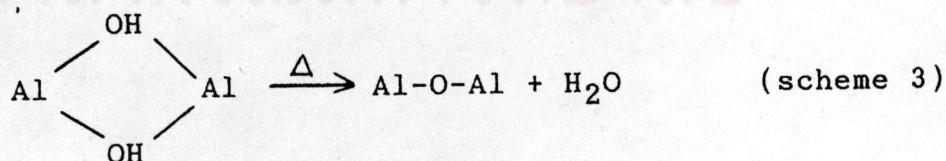
IR spectral analysis of aluminum hydroxide gel detects well-defined absorption bands in the O-H bending and O-H deformation regions of the spectrum as the gel ages.

3. X-Ray Diffraction Analysis

Nail et al. (1975) showed that x-ray diffraction could reflect to structural changes occurring in aluminum hydroxide gel during aging.

4. Differential Thermal Analysis (Nail, White, and Hem, 1976f)

The physical changes detectable by differential thermal analysis when aluminum hydroxide gel is heated are the loss of water of hydration in the range of 100-120°C and the loss of structural hydroxyl as water (Scheme 3).



The temperature at which the dehydroxylation of the double hydroxide bridges occurs is a characteristic that allows the identification of crystalline aluminum

hydroxide.

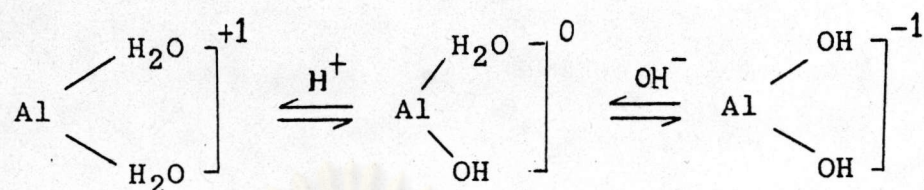
5. Electron Microscope (Wou and Mulley, 1984; Sepelyak et al., 1984b; Liu et al., 1987)

Transmission electron micrographs provide more information on the morphology of aluminum hydroxide than scanning electron micrographs. For example, gibbsite ($\text{Al}(\text{OH})_3$) particles appear to have a well-defined structure with distinct edges, while boehmite ($\text{AlO}(\text{OH})$) particles did not have well-defined.

Point of Zero Charge (PZC)

The PZC is an important property of the aluminum hydroxide gel. It is the pH at which the net surface charge is zero; at this pH the densities of the positive and negative charges are equal. There is no electrostatic repulsion to oppose the interparticle attraction due to London-Van der Waals forces. Hence, the most extensive aggregation occurs at the PZC. At the surface, the terminal aluminum atoms are coordinated with hydroxyl and aquo groups. Aluminum hydroxycarbonate has the same basic structure as aluminum hydroxide, except that carbonate groups are present at the surface in addition to hydroxyl and aquo groups (Scholtz et al., 1984b). The apparent surface can be controlled by adjusting the pH to be either below or above the PZC to produce a positive or negative

surface charge respectively as shown in the following scheme:



It is well established that the specific adsorption of anions by metal oxides displaces the PZC to lower values. The previous study by Serna *et al.* (1978b) concluded that carbonate and bicarbonate ions chemisorb to aluminum hydroxide but that the carbonate is the prevalent form on the surface. Scholtz *et al.* (1985) showed that the PZC of 36 carbonate-containing aluminum hydroxide gels decreased with increasing carbonate to aluminum ratio. This was found to be the case as the PZC ranged from 6.3 to 7.3 for various commercial carbonate-containing amorphous aluminum hydroxides (Feldkamp *et al.*, 1981). It will be a substantial change, as the PZC of anion-free aluminum hydroxide is more than 9 (Schott, 1977).

Shah *et al.* (1982) showed that magnesium cation is completely adsorbed under pH conditions where the gel has a negative surface charge. Docusate anion is more strongly adsorbed when the gel has a positive charge. However, adsorption also occurred when the pH was above the PZC suggesting that adsorption of the hydrophobic portion of docusate anion by Van der Waals forces also

contributes to the overall mechanism. Mannitol is adsorbed under all pH conditions. However, greater adsorption occurs when the pH is above the PZC. The adsorption of polyols occurring by hydrogen bonding rather than electrostatic attraction (Nail et al., 1976b; Shah et al., 1981).

The pH - PZC relationship will provide a useful guideline for predicting adsorption reactions in the formulation of antacid dosage forms and may also be useful in predicting drug interactions arising from the coadministration of drugs and aluminum-containing antacid. (Morefield et al., 1987)

Analytical Procedures for PZC

The methods were used to determine the PZC of aluminum hydroxide gel are :

1. Potentiometric Titration Procedure (Feldkamp et al., 1981)

The titration technique used to measure the PZC was based on the principle that changes in the ionic strength will have no effect on proton adsorption or release by the aluminum hydroxide gel when the aluminum hydroxide gel surface charge is zero.

2. Viscosity Measurements Procedure (Felkamp et al., 1981)

It is based on the principle that the viscosity of the aluminum hydroxide gel is maximum when the pH is equal to the PZC. The coulombic repulsive force and the Van der Waals attractive force are of prime importance. In fact, when the charge on the particle surfaces is sufficiently reduced, the Van der Waals forces are responsible for aggregation and associated phenomena. Feldkamp et al. (1981) and Morefield et al. (1987) found that the apparent viscosity increased sharply as the pH was increased to approach PZC. The viscosity, however, decreased as the pH was raised above the PZC but the apparent viscosity did not decrease as rapidly when the pH was above the PZC as when the pH was below the PZC.

3. Electrophoresis Determination Procedure

The electrophoresis determination used to measure the PZC was based on the principle that the net surface charge of aluminum hydroxide gel is zero when the pH is at the PZC. Then the electrophoretic mobility of aluminum hydroxide (at constant ionic strength) at the PZC is zero (Schott., 1977).