



CHAPTER IV

DISCUSSION AND CONCLUSION

Physicochemical Properties

Physical Properties

The direct methods which employed to detect the typically forms of gels were transmission electron microscope, x-ray diffraction and IR spectroscopy. The results from these methods indicated that initial aluminum hydroxide gel from various sources were amorphous form. Transmission electron micrographs provided more information on the morphology of aluminum hydroxide gel (Figures 11-17). Examination of the samples (gels 1-7) at high magnification (270,000) clearly showed that the particles of aluminum hydroxide gel were composed of primary particles which vary widely in size (Table 2). Thus, the hypothesis that amorphous aluminum hydroxide was composed of small primary particles could be supported (Scholtz *et al.*, 1983).

Size of the primary particle of aluminum hydroxide gels at initial condition as given in Figures 11A-17A were larger than the previous studied (Liu *et al.*, 1987). However, Wou and Mulley (1984) reported that size of primary particle of aluminum hydroxide gel were ranging from 25 to 3,700 angstrom. It was interesting to noted

that the nature of the primary particle could be clearly seen when the aluminum hydroxide gel was examined by transmission electron microscope. However, the equipment employed to investigate the particle morphology of amorphous aluminum hydroxide gel should be much more realized effective and that the basic unit of primary particle was in angstrom dimension.

A full understanding of the particle morphology of various aluminum hydroxide gels were also successful by using x-ray diffraction and IR spectroscopy. The IR spectra (Figures 18A-24A) showed that all gels at initial condition except for gel 2 were amorphous aluminum hydroxide containing carbonate species. The broad hydroxyl stretching band at $3,460\text{ cm}^{-1}$ indicated that the hydroxyl groups were disordered, while the carbonate bands at $1,520$ and $1,410\text{ cm}^{-1}$ showed the directly coordinated of carbonate to aluminum in the gel structure. The previously mentioned gel structure namely aluminum hydroxycarbonate. In the case of gel 2, a sharp peak at $1,090\text{ cm}^{-1}$ possibly exhibited a symmetry of carbonate ion which associated with aluminum was destroyed. In addition, this was confirmed by the wider splitting of carbonate bands at $1,540$ and $1,400\text{ cm}^{-1}$. These results of carbonate band pattern in gel 2 showed the present of sodium aluminum hydroxycarbonate which was known as crystalline dawsonite (Serna et al., 1978a, 1983; Scholtz et al., 1984a, 1984b). Thus, gel 2 might be the physical mixture of

dawsonite and aluminum hydroxycarbonate. Corresponding to x-ray diffractogram (Figure 26 A), the peak at $15^{\circ} 2\theta$ indicated the dawsonite form (Scholtz et al., 1984a, 1984b). The broad background reflection between 35 and $22^{\circ} 2\theta$ was occurred because the presented of the adsorbed water(Serna et al., 1983).

Chemical Properties

The chemical informations of all gels in this study obtained from the used of indirect methods. The FDA's OTC Panel on antacid recommend two antacid test which are now official in USP XXII. These tests are general in nature, and while it is obligatory that OTC antacid products comply with these requirements for safety and efficacy.

The preliminary antacid test basically is a screening test for antacid products to assure minimal neutralization capacity. The USP requires that the products must be raise the pH of an acid solution (0.5 N HCl) to at least 3.5 in 10 minutes. All gels in this study produced the pH more than 3.5 (Table 5) therefore, its passed the preliminary antacid test. The second test was the acid neutralizing capacity test. This test appeared to function as an indirect assay rather than direct test of antacid properties. The percentage of theoretical acid neutralizing capacity indicated whether

all of the aluminum hydroxide in suspension was reacted completely with acid under the conditions as specified for the test. The acid neutralizing capacity for USP requirement is not less than 65% of the expected milliequivalent value of HCl was neutralized. The results for acid neutralizing capacity indicated that all gels presented a good properties (Table 7).

The results from other methods such as reaction velocity test and hydroxide to aluminum ratio could be utilized to predicted the structure of aluminum hydroxide. Base on the hydroxide to aluminum ratio, the particle size of aluminum hydroxide gel could be estimated. A higher ratio indicated the polymerized of all gels structure which is larger in size. The values of hydroxide to aluminum ratio from this study were in the range of acceptable limit which indicated that a polymer size containing less aluminum atoms. The reaction velocity, however was used to show the rate of acid neutralization and predicted the change in structure of aluminum hydroxide. Serna et al. (1983) reported that dawsonite form of aluminum hydroxide gel usually exhibited a rapid rate of acid neutralization. As was mentioned previously, gel 2 appeared to contain dawsonite form and the result of the reaction velocity study in agreement with the above investigation.

The PZC of aluminum hydroxide is an important property, because of the pH-PZC relationship has been found to affect many important physical properties of aluminum hydroxide gel. For example, when the pH was at PZC, the viscosity of aluminum hydroxide gel increased sharply to a maximum according to the Van der Waals force (Feldkamp et al., 1981). In this study, the PZC of various aluminum hydroxide gels were determined by a continuous titration procedure. In the case of the effect of ionic strength on the pH of aluminum hydroxide gel indicated that the pH tended toward the PZC as the ionic strength increased which similar to recently reported by Feldkamp et al. (1981). Conversely, the pH move away from the PZC as the amount of ionic strength was decreased (Figures 38-44, Appendix). Effect of carbonate which adhered to aluminum hydroxide for the propose of preventing the polymerization reaction tended to lower the PZC of all gels to more acid values (Table 15). Previous studies (Feldkamp et al., 1981; Scholtz et al., 1985), reported that the pH values of various carbonate containing amorphous aluminum hydroxide gels were in the range of 6.3 to 7.3.

Effect of Aging at Ambient Temperature and at 45°C

Physical Properties

The aging effect of aluminum hydroxide gel from various sources at ambient temperature and at 45°C were

compared. The gels aging at ambient temperature for six months still appeared to be amorphous form as the same as at initial condition, however, the size of the primary particles were larged (Figures 11B-17B). This result showed that the small polymers possibly coalesce to form more highly ordered structure during aging. The previous explanation was in consistent with the IR spectra of the gels studied. Their spectra showed decrease in intensity of carbonate bands which indicated that the carbonate ions which coordinated with aluminum atom were released. Even if the lost of some carbonate ions from the gels, but the x-ray diffractograms showed that all gels in this study still retained an amorphous pattern except for gel 2. In the case of gel 2 dawsonite form presented as the same as at initial condition. In addition, the broad background reflection between 35 and $22^\circ 2\theta$ from x-ray diffractograms of initial gels 1-6 were absented. It showed that the adsorbed water were not presented.

The results of the gels aging at 45°C for six months cleary indicated that the rearrangement of aluminum hydroxide structure occurred to form more stable system. The morphology of the gels changed from amorphous to crystalline forms, which were not spherule in shape (Figures 11C-17C). Previous studies, showed that gibbsite ($\text{Al}(\text{OH})_3$) was the crystalline phase that developed on aging (Nail et al., 1975, 1976a, 1976c; Serna et al., 1978a, 1978b, 1983). In addition, the others crystalline

polymorphs such as bayerite ($\text{Al}(\text{OH})_3$), boehmite ($\text{AlO}(\text{OH})$) and nordstrandite ($\text{Al}(\text{OH})_3$) were also presented (Rinse and Donje, 1962; Nail *et al.*, 1976b). The different in IR spectra pattern clearly seen at 45°C storage condition were the band at 850 cm^{-1} was subsequently replaced by the peaks at 970 cm^{-1} and a sharp peak at $1,020\text{ cm}^{-1}$, respectively. The $1,020$ and 970 cm^{-1} peaks could be associated with the gibbsite structure. The IR spectra changed as previously mentioned were observed for all gels, however for gel 4 and gel 6 peak at 970 cm^{-1} were not seen. In addition, gel 6 also showed the intense peak at $1,070\text{ cm}^{-1}$ and small peak at $1,150\text{ cm}^{-1}$ which appeared to be O-H deformations. Moreover, two bands at about 610 and 470 cm^{-1} were in the same frequency as the Al-O vibrations as observed in boehmite (Nail *et al.*, 1975; Serna *et al.*, 1983). The Al-O bands were reported to become ordered more rapidly during aging than hydroxyl bands. Thus, the IR spectra in the regions of $1,200$ - 400 cm^{-1} are more useful for detecting the earliest stages of crystallization. However, the low IR regions were not be able to detect the mixture of bayerite and disorder of boehmite (pseudoboehmite), since the Al-O vibrations were similar in both compounds (Serna *et al.*, 1983). Because the bands at $1,055,600$ and 480 cm^{-1} were observed in gel 7 after aging at 45°C for six months, indicated that pseudoboehmite ($\text{AlOOH} \cdot \text{H}_2\text{O}$) was forming.

The IR spectra of crystalline aluminum hydroxide, which were reported in the previous study (Nail *et al.*, 1975) are given in Table 28. The O-H stretching regions for gibbsite were defined bands at 3,612, 3,520, 3440 and 3,395 cm^{-1} , respectively. An intense peak occurred at approximately 1,030 cm^{-1} with a small peak at 970 cm^{-1} , which were O-H deformations. The general features of bayerite spectrum were similar to gibbsite with peak positions shifted to 3,650, 3,540 and 3,460 cm^{-1} . The O-H deformation regions for bayerite occurred as doublet at 1,010 and 970 cm^{-1} . The O-H stretching frequency regions for boehmite was characterized by two broad peaks at 3,300 and 3,095 cm^{-1} and the O-H deformation frequencies were at 1,150 and 1,070 cm^{-1} .

The removal of proton of aluminum hydroxide gels appeared to be the first of polymerization called deprotonation-dehydration process which facilitated to the decreasing in pH values. More decreasing pH values of gels occurred after aging at 45°C. It suggested that the more deprotonation - dehydration took place. So that the polymerization of the gels storage at accelerated temperature were increased faster than storage at ambient temperature. These results were clarified by using transmission electron microscope and IR spectra.

Table 28

O-H Vibration in Stretching and Bending regions for
crystalline aluminum hydroxide

Phase	Frequency (cm^{-1})	
	O-H stretching regions	O-H bending regions
Gibbsite	3612	1030
	3520	970
	3440	
	3395	
Bayerite	3650	1010
	3540	970 doublet
	3460	
Boehmite	3300	1150
	3095	1070

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

Chemical Properties

The changed in chemical properties of various gels during aging at ambient temperature and at 45°C were observed. At ambient temperature the preliminary antacid test of all gels were more than 3.5 (Table 5), while gels 2, 3, 4, 5 and gel 7 did not pass the USP requirement after aging at 45°C (Table 6). The decrease of the pH values from preliminary antacid test of the gels aging at 45°C were faster than the gels aging at ambient temperature. The lost of acid neutralizing capacity appear to be first order kinetics as in agreement with the recently investigations (Hem *et al.*, 1970; Nail *et al.*, 1975, 1976a, 1976e) for both aging at ambient temperature and at 45°C. The rate constant for the decreasing in acid neutralizing capacity increased with the temperature increased. For example, the rate constant of gel 6 was increased from $2.50 \times 10^{-2} \text{ month}^{-1}$ to $23.68 \times 10^{-2} \text{ month}^{-1}$ for the gel aging at ambient temperature and at 45°C, respectively.

The preliminary antacid test, acid neutralizing capacity and reaction velocity were inversely related to the degree of polymerization. These were contrary to the hydroxide to aluminum ratio which increased with increasing degree of polymerization. For example, gel 1 during aging at ambient temperature, the decreased were occurred from 4.10 to 3.87, 95.51 to 85.67 and 32 to 120 seconds for the preliminary antacid test, percent of acid

neutralizing capacity and reaction velocity, respectively. While the hydroxide to aluminum ratio was increased from 2.48 to 2.60.

Research on the structure and properties of aluminum hydroxide revealed that aluminum hydroxide had a polymer like structure with a basic unit composed of a ring of six octahedral aluminum atoms joined by double hydroxide bridges (Nail et al., 1976b). Particle growth by formation of double hydroxide bridges between the edges of adjacent particles would decrease the number of edges hydroxyls, thus explaining the observed decrease in reaction velocity of the gels during aging. In addition, polymerization would result in a system in which the particles of aluminum hydroxide gel were larger and more highly ordered, therefore they should be less susceptible attack by acid.

The decrease in acid neutralizing capacity was due to a decreased in the reaction velocity. Because of the acid neutralizing capacity test is based on the amount of acid neutralized by the gel within 15 minutes. Previous investigation (Nail et al., 1976 e) showed that the acid reactivity measured by the USP test decreased during aging, although the equilibrium reactivity of the gels was unchanged. Using this parameter, it is difficult to compare gels of different equivalent aluminum oxide content.

Increasing of hydroxide to aluminum ratio, caused by the increase in degree of polymerization. Therefore, the data in this study showed the increase in size of the structure as ratio of OH^-/Al increased. However, it was possible that some hydroxide was not bound to the polymer by double hydroxide bridges. The single bonds to aluminum edge might presented (Nail *et al.*, 1976 b). The presented of nonstructural hydroxide groups possibly caused larger values of hydroxide to aluminum ratio than those predicted from Figure 4. So that various possible methods were employed to attest the change of aluminum hydroxide to obtain the correct ratio of OH^-/Al as possible.

For the same reasons the gels aging at ambient temperature were compared with the results obtained from the gels aging at 45°C for better explanation of the storage assay values. These parameters at different storage conditions suggested a structure change. It was hypothesized that the gels, at initial condition were composed of hydroxyaluminum polymers. Free hydroxyls on the surface of the polymers were readily accessible, react immediately with acid. Durig aging, the small coalesce to form more highly ordered structures and the surface hydroxyls were incorporated into the gel structure as the polymer growth. The proportion of structure hydroxyls increased and the amount of the edge hydroxyls decreased.

Data listed in Table 15 were arranged in order of increasing PZC during aging. For example, the PZC of gel 7

increased from 7.809 to 8.030 after storage at ambient temperature for six months. The first hypothesized mechanism for the increase in the PZC might be the desorption of specifically adsorbed carbonate ions (Morefield *et al.*, 1986). This hypothesized was supported by the IR spectra which showed that intensity of carbonate bands was decreased during aging. The second hypothesis might caused by polymorphic transformation corresponding to highly crystalline forms of aluminum hydroxide, which would be expected to be largely free of specifically adsorbed carbonate ; i.e., the PZC of gibbsite and boehmite were 9.2 and 9.1, respectively (Sepelyak *et al.*, 1984 a).

Comparison of Aluminum Hydroxide Gel from Various Sources and Processes

The physiochemical properties of all aluminum hydroxide gels (gels 1,5-7) in this study showed exceptable antacid properties according to USP XXII (1990), these are preliminary antacid test and acid neutralizing capacity test. In addition, all gels (gels 1, 5-7) appeared to be amorphous form of aluminum hydroxycarbonate as indicated by photomicrographs, IR spectra and x-ray diffractograms. For comparison of the stability at ambient temperature, the rate constants for the loss of acid neutralizing capacity of gels were 1.88×10^{-2} , 2.50×10^{-2} , 3.21×10^{-2}

and $3.33 \times 10^{-2} \text{ month}^{-1}$ for gel 1, gel 6, gel 5 and gel 7, respectively. At 45°C the order of stability were the same as at ambient temperature.

In this study aluminum hydroxide gels from three processes (gels 2-4) were prepared and also compare with other commercial available gels (gels 1, 5-7). Gel 2 appeared to be dawsonite form (sodium aluminum hydroxycarbonate) which showed rapid reaction velocity. However, it usually contain high sodium content and may not suitable for the patient who has deficient cardiovascular function (McEvoy, 1988). It will be more advantage if dawsonite form of gel 2 should be minimized. The dawsonite form may probably due to the prolong contact between alum solution and sodium carbonate at the initial state of production before the final pH adjustment. Gel 3 and Gel 4 were prepared to minimize dawsonite form and to approach an amorphous form of aluminum hydroxycarbonate by mutual reaction of alum solution and sodium carbonate solution into the reactor. The addition rate of alum solution was adjusted to be more than sodium carbonate solution for preventing the excess of sodium carbonate bound to the finish product during process of preparation. The results of two processes as was mentioned previously showed that gel 3 and gel 4 were amorphous form of aluminum hydroxycarbonate. However, during aging at ambient temperature, gel 3 and gel 4 showed less stability

as compared with gel 2 and various commercial gels. So that the manufacturing processes should be improved. The improvement probably by decreasing concentration of the reactants or inducing the titrant addition rate to produced homogeneous precipitation and the precipitate should be washed when the pH equal to PZC to minimize the impurity (Serna et al., 1978c). Moreover, sorbitol may be added after washing process.

Effect of Sorbitol on the Stability of Aluminum Hydroxide Gel

Comparison of the changes in pH, preliminary antacid test, acid neutralizing capacity, reaction velocity and hydroxide to aluminum ratio of aluminum hydroxide gels with represent by gel 1 and gel 2, identical gels containing 2% and 5% w/w of sorbitol are given in Tables 4, 6, 8, 12 and 14, respectively. It showed that the instability responsible for aging was strongly inhibited by sorbitol. The effect of sorbitol concentration used to stabilize aluminum hydroxide gel was seen as a reduction in the reaction velocity. This effect was clearly seen in Table 12 where the reaction velocity decreased in direct relationship to the concentration of sorbitol. In contrast, after aging the change in reaction velocity of aluminum hydroxide gel with sorbitol were smaller than the gels without sorbitol.

The results of preliminary antacid test, acid neutralizing capacity test and pH values were similar to reaction velocity test with the change after aging decreased. Figure 45 illustrated the pH of gel 1 and gel 2 as a function of time. Compared to gel 1 and gel 2 containing sorbitol. The ln of percent of theoretical acid neutralizing capacity of gels 1, 2 and gels 1, 2 with sorbitol are illustrated in Figure 46. It was found that the rate constant of aluminum hydroxide gels with sorbitol were decreased. Sorbitol appeared to interfere with polymerization reaction that occurred on aging by forming hydrogen bonding between the hydroxyl groups of sorbitol and the edge of the hydroxyaluminum particles. However, the negative effect of sorbitol also occurred since sorbitol reducing the reaction velocity of the gel as seen in Table 12 and also increasing the precipitation rate of the suspended aluminum hydroxide particles. Therefore, the concentration of sorbitol to used could be optimum. The reduction of reaction velocity was related to the concentration of sorbitol. For example, the reaction velocity of gel 1 decreased from 32 seconds to 75 and 115 seconds for the gel containing 2% and 5% w/w of sorbitol, respectively. Nevertheless, after storage at 45°C for two months, the reaction velocity of the gels with sorbitol were faster than the gels without sorbitol for both gel 1 and gel 2. Thus, sorbitol was found to be effective in minimizing polymerization and, consequently, the structural changes that ultimately lead to the inactive

crystalline forms of aluminum hydroxide were also minimized. Because of the reduction of reaction velocity of gels by sorbitol, therefore, the concentration of sorbitol must be carefully selected to maximize the desired effect of stabilizing the gel structure.

The stabilize effects of sorbitol were also appeared for the change of the pH values and preliminary antacid test (Tables 4, 6). The stability of the pH values of the gels containing sorbitol comparative to the gels without sorbitol was strong evidence for the inhibition of deprotonation-dehydration reaction.

The Surface Adsorption of Preservatives by Aluminum Hydroxide

Meeting the USP requirement for bacterial limit in the manufacture of antacid suspensions has been a difficult problem largely because most preservatives are either inactive or unstable at relative high pH of antacid suspension (Hem et al., 1982). The factors caused preservatives inactivation were pH, phase distribution, incompatibility and adsorption (McCarthy, 1984). The adsorption of preservative in antacid suspensions were a well documented source of preservative failure (Armstrong and Clake, 1976; Morefiled et al., 1985).

This study was intended to compare the adsorption and consequent loss of activity of various preservatives

in aluminum hydroxide suspension for better utilization and selection of the preservative system to preserve the suspension. The extent of adsorption would depend upon the nature of the suspended solid, the surface area, surface charge, the polarity of the preservative and also pH of the system (McCarthy, 1984).

As was mentioned previously, the nature of the surface and ionic form of aluminum hydroxide was negative at pH values below the PZC. In contrast, the positive charge of aluminum hydroxide was occurred if the pH conditions above the PZC (Feldkamp *et al.*, 1981). Schmidt and Benke (1988a) showed that sorbic acid and benzoic acid were strongly adsorbed by aluminum hydroxide according to ionic mechanism.

This present study compared the adsorption of esters of parabens and chlorhexidine gluconate onto aluminum hydroxide particles. In the case of esters of parabens, adsorption to aluminum hydroxide decreased as pH rose (Tables 16-21, 24-26). Since the PZC of gel 1 and gel 2 were 6.55 and 6.93, respectively. Thus, the surface charge was negative when the pH value of the suspension more than 6.55 and 6.93 for gel 1 and gel 2, respectively. In contrast, the positive charged occurred when the pH of the suspension less than those PZC. In this study, at low pH values of suspension, the pH values still below the pKa of parabens esters (pKa of paraben is 8.4) thus, the unionized form of these parabens were presented (Martin,

1983). Adsorption may be associated with non-ionic forces. The pH values close to the pKa of these parabens the negative hydrophilic region of parabens could experience electrostatic repulsion with the negative surface charge of aluminum hydroxide and decreasing of non-ionized form of parabens, therefore the adsorption was highly decreased according to the increase in pH. However, the more adsorption of butyl paraben than propyl paraben and methyl paraben can not be described by the non-ionic effect so that the mechanism of this adsorption is still not clear.

The adsorption of chlorhexidine gluconate onto the aluminum hydroxide particles also depended upon the pH values of the suspension. However, chlorhexidine gluconate is only a salt compound when dissolved in solution positive charge of chlorhexidine always appeared and had little effect by the pH. Increasing the pH values from 6 to 8 resulting in an increase in negative charge of aluminum hydroxide and also increasing the adsorption of chlorhexidine could be observed. The higher the pH values the greater the adsorption occurred. In this case, the mechanism of adsorption appeared to be the attractive force between the opposite charge of chlorhexidine and aluminum hydroxide. The adsorption depends only on the net charge of aluminum hydroxide concentration. At pH below the PZC adsorption decreased as the hydroxyl charge decreased. As pH increased the edge charge of aluminum hydroxide became more negative owing to the amphoteric

effect of the aluminum ions so that adsorption increased. As the hydronium ion concentration decreased so that competition site of aluminum hydroxide was less. Therefore, the more adsorption of chlorhexidine gluconate at high pH values could be attributed to the high negative charge and less competition of the hydronium ion on the surface of aluminum hydroxide gel.

Conclusions

Comparative evaluation aluminum hydroxide gel from various sources and processes were studied. The results from transmission electron microscope indicated that the morphology of all samples were amorphous form with vary in size of primary particles at initial condition. The result was in agreement to IR spectra and x-ray diffractograms. In addition, IR spectra also indicated that gels 1,3-7 were aluminum hydroxycarbonate while gel 2 appeared to be dawsonite form. After aging at ambient temperature and at 45°C for six months the desorption of carbonate occurred. While, the morphology of the particles was changed to form a more crystalline form. X-ray diffractograms showed that no structural change occurred due to the aging at ambient temperature for six months.

The chemical properties were studies by preliminary antacid test, acid neutralizing capacity test, reaction velocity test, hydroxide to aluminum ratio and

PZC. The results from these methods were confirmed that further polymerization occurred during aging. The decrease in pH values of all gels after aging were in consistent with deprotonation-dehydration condensation polymerization reaction between hydroxyaluminum particles. Polymerization would result in a system in which the hydroxyaluminum particles are larger and more highly order. Therefore, they should be less susceptible to attack by acid. The PZC of all gels increased during aging as was expected by the desorption of carbonate ion. The comparison of aluminum hydroxide gel from various sources and processes was evaluated. The order of stability was Gel 1 > Gel 6 > Gel 5 > Gel 7 > Gel 2 > Gel 3 > Gel 4 and Gel 1 > Gel 2 > Gel 6 > Gel 4 > Gel 3 > Gel 5 > Gel 7 for the gels aging at ambient temperature and at 45°C, respectively.

Sorbitol was effective in minimizing polymerization of aluminum hydroxide gel. However, sorbitol had reverse effect in reducing the reaction velocity and decreasing the acid neutralizing capacity of the gels. These behaviors could be explained by hydrogen bonding between the hydroxyl groups of sorbitol and the edge of hydroxyaluminum particles, thus inhibition further polymerization after aging. The sorbitol concentration used to stabilize aluminum hydroxide gel must be carefully selected because the adsorbed sorbitol may also slow down the rate of acid neutralization.

The surface adsorption of preservatives by aluminum hydroxide in this study was based on the pH values of the suspension. In the case of esters of parabens, the adsorption increased when the pH of the aluminum hydroxide suspension was decreased. The mechanism was described by the adsorption of non-ionized form of parabens, however this mechanism still unclear. In the case of chlorhexidine gluconate, the increase in adsorption occurred at the higher pH values. This could be described by the ionic mechanism. When the pH of the aluminum hydroxide suspension greater than the PZC, the attractive force from negative surface charge of aluminum hydroxide and positive charge of chlorhexidine occur. The results of this study suggest that the pH-PZC relationship will provide a useful guideline for predicting adsorption reactions in the formulation of aluminum hydroxide suspension.

The suggestion in the manufacturing of aluminum hydroxide compressed gel to approach good stability should contain carbonate and appropriate amount of sorbitol. In addition, care should be taken in the manufacturing and packaging to minimize the desorption of specifically adsorbed carbonate.