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Effect of Water on Degradation of Propantheline Bromide mixed with Dried Aluminum Hydroxide Gel[1)]

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Effect of humidity and water content on the degradation of propantheline bromide mixed with dried aluminum hydroxide gel was examined. Degradation of propantheline bromide in this system is accelerated with increasingly higher humidity until under 75% RH and decreased under more high humidity, and was the most marked when 0.2 ml of water was added per 5 g of the mixture. Degradation became slower as the amount of water added became greater or smaller than that. Addition of 0.2 ml/5 g of water means that water molecule forms a monolayer on the surface of dried aluminum hydroxide gel. Since the gel used orginally contained 4% of water, addition of 0.2 ml/5 g means that two layers of water molecule were formed on the surface of the gel. Degradation of propantheline bromide is most marked when water molecule forms a monolayer to several layers on the surface of the gel. This degradation was assumed to be initiated through the layer on the surface of dried aluminum hydroxide gel.

Keywords——propantheline bromide; dried aluminum hydroxide gel; antacids; antimuscarinic drugs; Jander's equation; Wicke's adsorption equation; stability of solid and solid; degradation-water relationship

We have previously reported that propantheline bromide mixed with dried aluminum hydroxide gel underwent rapid degradation and lost its pharmaceutical effect.[3,4)] In the present series of work, we examined the relation between the water content and degradation of propantheline bromide in a mixture with dried aluminum hydroxide gel.

Experimental

Materials——Propantheline bromide and dried aluminum hydroxide gel used were the same as those reported previously.[3)]

Preparation of Samples——Samples at Various Relative Humidity: Dried aluminum hydroxide gel was dried at a reduced pressure, stored at 37° in the atmosphere of various relative humidities, and samples considered to have reached equilibrium adsorption were used. For producing varied relative humidity (RH), saturated aqueous salt solutions were used; $Mg(NO_3)_2 \cdot 6H_2O$ for 50% RH, $NaNO_2$ for 62% RH, NaCl for 75% RH, and KNO_3 for 88% RH.

Accurately weighed 75 mg of propantheline bromide and 4.925 g of dried aluminum hydroxide gel maintained at one of the above relative humidity were mixed in a high speed vibration mill (Heikosha, Fukushima) for 2 min, this homogenous mixture was maintained in a desiccator of various relative humidity, and change in the content of propantheline bromide was measured at various time intervals.

Moistured Sample: To a mixture of 75 mg of propantheline bromide and 4.925 g of dried aluminum hydroxide gel, 0.1, 0.2, 0.5, 0.7, 1.0, 1.5 or 2.0 ml of distilled water was added per 5 g of the mixture, this was mixed homogeneously in a high-speed vibration mill for 2 min, and the mixture was placed in a glass-stoppered weighing bottles (4 cm diameter, 1.5 cm height). These bottles were maintained in a thermostat of 37° and content of propantheline bromide was measured at intervals. In order to avoid temperature variation, the chemicals, bottles, and vessels of the vibration mill were preliminarily kept in a thermostat of 37°. A high-vacuum grease was used to seal the stopper of weighing bottles to prevent vaporization of water.

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1) This constitutes Part IV of a series entitled "Studies on the Compatibility of Antacids with Other Drugs." Part III: M Horioka, T. Aoyama, T. Maeda, Y. Murayama, and K. Takada, *Yakuzaigaku*, 34, 27 (1974).
2) Location: *Maidashi 3-1-1, Higashi-ku, Fukuoka 812, Japan.*
3) M. Horioka, T. Aoyama, T. Maeda, and K. Shirahama, *Yakuzaigaku*, **34**, 16 (1974).
4) M. Horioka, T. Aoyama, and H. Karasawa, *Chem. Pharm. Bull.* (Tokyo), **25**, 175 (1977).

Determination of Propantheline Bromide——The analytical method utilizing bromocresol green reported previously[5] was used. To an accurately weighed 400 mg of the mixed sample, 50 ml of 0.4 N HCl solution was added, this was mixed at 37° for 30 min to effect dissolution, and 3 g of sodium tartrate was added to the cooled mixture. This solution was adjusted accurately to pH 5.6 with 2 N NaOH and 0.1 N NaOH, and the whole volume was brought exactly to 100 ml with H_2O. In a glass-stoppered test tube, 4 ml of this solution was placed, 2 ml of bromocresol green–sodium hydroxide test solution, and 10 ml of potassium hydrogen phthalate buffer solution (pH 5.6), and 20 ml of $CHCl_3$ were added, the whole mixture was shaken vigorously for 5 min, and the mixture was cooled to *ca.* 10°. The $CHCl_3$ layer was collected by centrifugation and absorbancy of the organic solution was measured at 416 nm.

Results and Discussion

Effect of Humidity

Fig. 1 shows the periodical changes in the content of propantheline bromide mixed with dried aluminum hydroxide gel maintained at relative humidity of 50, 62, 75, and 88%. It will be seen that degradation of propantheline bromide is markedly accelerated with increasing humidity until 75% RH and decreased under 88% RH.

Maulding and others[6] examined degradation of aspirin, 25 mg of microcrystalline cellulose, 24 mg of corn starch, 11 mg of stearic acid, and 10 mg of lactose, added with dried aluminum hydroxide gel or magnesium trisilicate to 10% concentration, and reported that degradation is accelerated by increasing humidity. However, our present experiments with propantheline bromide differs from the degradation experiments on aspirin by Maulding and others, because propantheline bromide is highly soluble in water and the ratio of aluminum hydroxide gel to propantheline bromide was *ca.* 65: 1, making it necessary to consider the degradation mechanism by a different kinetics.

In a previous report,[3] we showed that degradation of propantheline bromide mixed with dried aluminum hydroxide gel followed Jander's degradation rate equation, which takes dispersion as the rate-limiting step. We have, therefore, examined the present results with Jander's equation(Fig. 2) and found that the equation applies also for the present case.

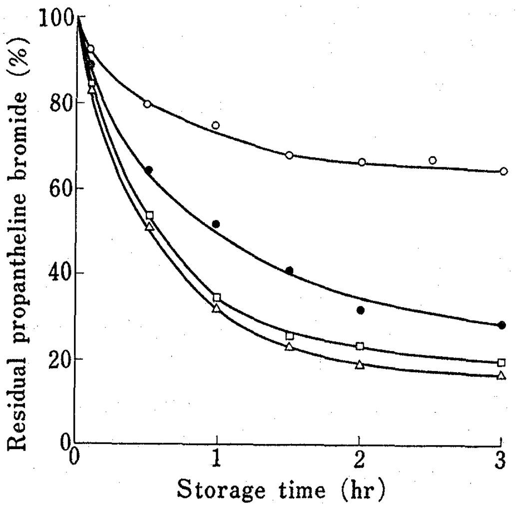

Fig. 1. Degradation of Propantheline Bromide mixed with Dried Aluminum Hydroxide Gel, at 37° and Various Relative Humidity

□ 88% RH, △ 75% RH, ● 62% RH, ○ 50% RH.

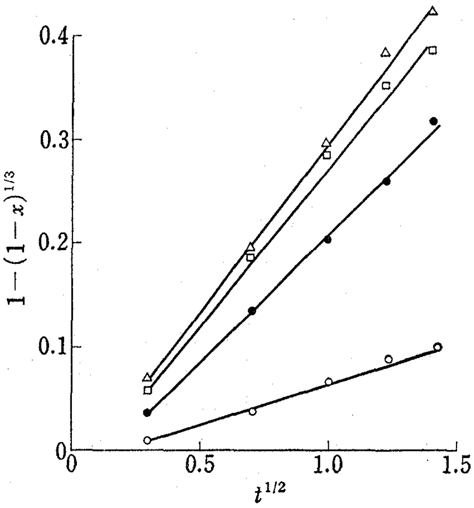

Fig. 2. Jander's Plot for Degradation of Propantheline Bromide mixed with Dried Aluminum Hydroxide Gel, at 37° and Various Relative Humidity

□ 88% RH, △ 75% RH, ● 62% RH, ○ 50% RH.

5) M. Horioka, T. Aoyama, T. Maeda, and K. Takata, *Yakuzaigaku*, 34, 27 (1974).
6) H.V. Maulding, M.A. Zoglio, F. Epigrosis, and M. Wagner, *J. Pharm. Sci.*, **58**, 1359 (1969).

Quantity of Adsorbed Water

Periodical changes in the amount of water adsorbed on dried aluminum hydroxide gel, placed under reduced pressure, at a relative humidity of 50, 62, 75 and 88% were measured, and saturated adsorption was calculated from Wicke's adsorption equation[7,8] which corrected Langmuir's adsorption isotherm had shown that a plot of ln $\theta e/\theta e\text{-}\theta$ against t was obtained a straight line through zero point, where θe is the saturated adsorption percent of water, θ is the adsorption percent of water at the time (Fig. 3). The results thereby obtained were plotted on the adsorption isotherm of Nogami, *et al.*[9], and this result is illustrated in Fig. 4. The amount of water adsorbed by the dried aluminum hydroxide gel used in the present experiments (surface area, 129 m^2/g, as measured by the BET method) was 3.8, 4.2, 8.9 and 15.0% at a relative humidity of 50, 62, 75 and 88%, respectively. The dried aluminum hydroxide gel used by Nogami and others had a surface area of 90 m^2/g and, due to the difference in the method of manufacture and aging of the chemical, it is not possible to obtain a strict coincidence but the present values were very close to their's.

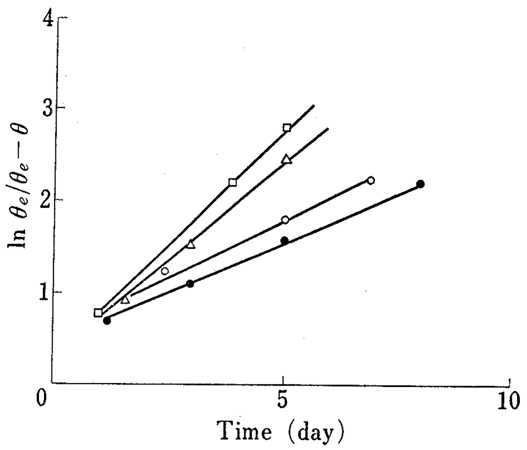

Fig. 3. Wicke's Adsorption Equation for Dried Aluminum Hydroxide Gel

□ 50% RH θe=0.0377, △ 62% RH θe=0.0420,
○ 75% RH θe=0.0891, ● 88% RH θe=0.1497.

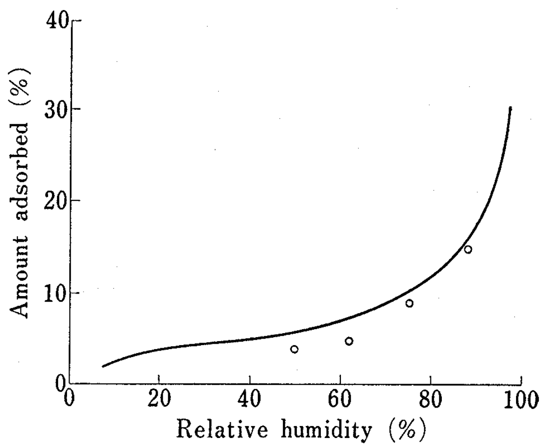

Fig. 4. Adsorption Isotherm of Water on Dried Aluminum Hydroxide Gel

Curve taken from H. Nogami, *et al.*[9]
○ Dried aluminum hydroxide gel used in the present experiment.

Effect of Addition of Water

Periodical changes in the degradation of propantheline bromide when a definite quantity of water was added to dried aluminum hydroxide gel are shown in Fig. 5. It will be seen from this graph that addition of up to 0.2 ml of water, or to 4%, in 5 g of the mixture markedly accelerates the degradation, while addition of a larger amount of water inversely slows the degradation. This result is expressed by Jander's equation in Fig. 6, showing that a good linearity is obtained in $1\text{-}(1\text{-}x)^{1/3}$ *vs* $t^{1/2}$. When the slope of the degradation rate under various condition in Jander's equation is taken as K, the plot of the relation between log K_{app} and H_2O appeares as shown Fig. 7. With the addition of 0.2 ml of water per 5 g of dried aluminum hydroxide gel (*i.e.* water content is *ca.* 0.4 ml per 5 g of dried aluminum hydroxide gel placed in a reduced pressure and it is same water content adsorbed under 75% RH) as the peak, log K_{app} decreases with either a greater or smaller amount of water content.

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7) E. Wick, *Kolloi Z.*, **86**, 167 (1939).
8) T. Kagitani, "Kagaku-hanno no Sokudoron teki Kenkyu-hō," 1st ed., Kagaku Dojin, Kyoto, 1970, p. 402.
9) H. Nogami, T. Nagai, T. Kasai, and T. Kajima, *Chem. Pharm. Bull.* (Tokyo), **14**, 159 (1966).

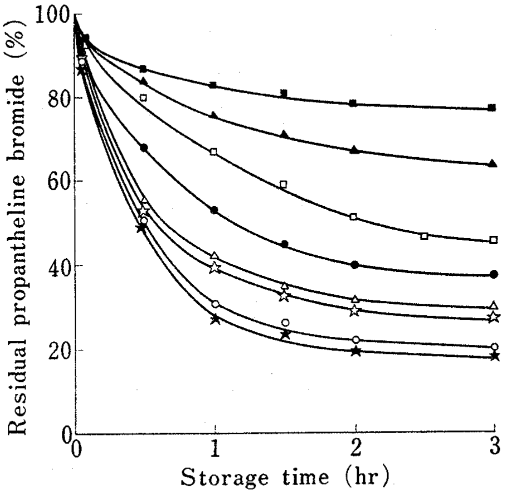

Fig. 5. Effect of Water on Degradation of Propantheline Bromide mixed with Dried Aluminum Hydroxide Gel at 37°

☆ 0 ml/5 g, ○ 0.1 ml/5 g, ★ 0.2 ml/5 g, △ 0.5 ml/5 g, ● 0.7 ml/5 g, □ 1.0 ml/5 g, ▲ 15 ml/5 g, ■ 2.0 ml/5 g.

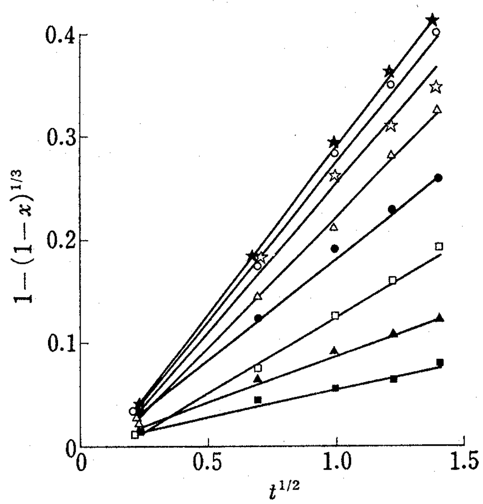

Fig. 6. Effect of Water on Degradation of Propantheline Bromide mixed with Dried Aluminum Hydroxide Gel at 37°, according to Jander's Equation

Figures in parentheses are the value of x.
☆ 0 ml/5 g, ○ 0.1 ml/5 g, ★ 0.2 ml/5 g, △ 0.5 ml/5 g, ● 0.7 ml/5 g, □ 1.0 ml/5 g ▲ 1.5 ml/5 g, ■ 2.0 ml/5 g.

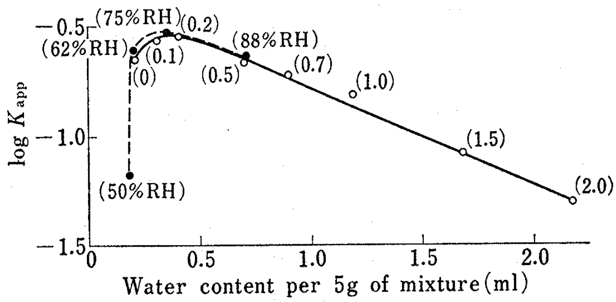

Fig. 7. Relation between Logarithm of Slope on Jander's Equation and Water Content adsorbed or added in Mixed Sample

● under various relative humidity.
○ water added in mixture, figures in parentheses are the volume of water added in 5 g of mixture.

The dried aluminum hydroxide gel used for the present study was dried over a silica gel in a desiccator, at a reduced pressure, in room temperature for 2 months and its decrease in weight was 4.05%. When this additionally dried gel was allowed to stand at 37°, under 50% RH, 62% RH, 75% RH and 88% RH for 2 weeks, increase in its weight was 3.7%, 4.6%, 8.08% and 14.4%, respectively. This result agrees with the amount of saturated adsorption described above. The dried aluminum hydroxide gel used in the present experiments showed an increase of 4.09% in weight when allowed to stand at 37° under 75% RH for 2 weeks.

From these facts, it is known that the dried aluminum hydroxide gel used in the present study contained *ca.* 4% of water and adsorbed further 4% of water in an atmosphere of 75% RH. If the surface of dried aluminum hydroxide gel is simply covered with water molecules, water content of 8% means that about 2 layers of water molecule formed on the surface of dried aluminum hydroxide gel.

When dried aluminum hydroxide gel was dried in a reduced pressure, degradation of propantheline bromide hardly occurred. Consequently, degradation of propantheline bromide depends largely on the formation of water layer on the surface of the gel. Degradation of propantheline bromide occurs rapidly when the water molecule on the surface of the gel forms a monolayer (no addition of water, *i.e.* water content of *ca.* 4% which is water content contained in commercial dried aluminum hydroxide gel) to several layers (0.5 ml/5 g of water), and the degradation is most rapid when there are two layers (addition of 0.2 ml/5 g of water or adsorption under 75% RH, *i.e.* water content of *ca.* 8%).

Carstensen and others[10] measured the degradation rate of thiamine in thiamine hydrochloride tablets containing magnesium stearate and microcrystalline cellulose, and they examined the relation between the water content and degradation rate from the equation $\log (A-A_{\infty})=-Kt$, where A_{∞} is the equilibrium thiamine content (mg/tablet) when thiamine reaches an equilibrium with its degradation product. They found that the degradation was most rapid when water content was 5% and the rate became slower at a lower or higer content of water. They also reported that thiamine was hardly degraded in the state of suspension, and also that degradation of thiamine in the state of powder occurred when water molecule formed a monolayer on the surface of microcrystalline cellulose, the degradation becoming slower as the surface had more than a monolayer of water. This similar to the present results.

Details of the degradation mechanism of propantheline bromide mixed with dried aluminum hydroxide gel are still unknown but, from the foregoing results, it may be suggested that the reaction of propantheline bromide takes place through the water layer present on the surface of the gel. As stated earlier, propantheline bromide is easily soluble in water. The amount of water required to bring this reaction to the maximum depends on the solubility of drugs in water and the dissolution rate, and further may be affected by the kind of antacids present. Present series of experiments has shown that degradation rate in the propantheline bromide-dried aluminum hydroxide gel system is quite rapid.

Conclusion

1) Degradation of propantheline bromide mixed with dried aluminum hydroxide gel is accelerated with higher humidity until under 75% RH and decreased under more high humidity.

2) This degradation becomes the maximum with addition of 4% of water (water content 8%), and the degradation becomes slower with larger or smaller amount of water added.

3) The dried aluminum hydroxide gel used in the present series of work contained *ca.* 4% water originally and addition of 0.2 ml of water per 5 g of the mixture content 8% or adsorption of water under 75% RH) corresponds to the amount of water producing two layers of water molecule on the surface of the gel. Degradation of propantheline bromide in its mixture with dried aluminum hydroxide gel becomes especially marked when the water molecule forms a monolayer to several layers on the surface of the gel.

10) J.H. Carstensen, M. Osadca, and S.H. Rubin, *J. Phar. Sci.*, **58**, 549 (1969).