Surface Chemistry of Colloidal Silica and a Possible Application to Stabilize Aspirin in Solid Matrixes

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Abstract □ The surface chemistry of colloidal silica was investigated in relation to its application as a stabilizer for a hydrolabile drug, aspirin, in tablets. Water vapor adsorption properties of the selected silicas were studied as a function of vapor pressure at 40°. Silica I, a precipitated colloidal form, exhibited a type IV adsorption isotherm, characteristic of multilayer adsorption with limited pore volume. Therefore, the Brunauer, Emmett, and Teller (BET) theory of multilayer adsorption was employed to quantify the monolayer capacity (X_m) and the specific surface area available for water vapor adsorption (S_w). The surface area and average particle diameter of I, determined by BET nitrogen adsorption, were 714.4 m^2/g and 3.8 nm, respectively. Silica I, which had the greatest moisture adsorption capacity, was then evaluated for its stabilizing effects on aspirin in tablet form. Since silica increased the tablet void space in proportion to its concentration, control (aspirin) and sample (aspirin–silica) tablets with controlled void space (held constant at 20%) were subjected to accelerated stability evaluation. In general, silica enhanced aspirin stability; a concentration of 3% offered maximum stabilization. Tablets with higher silica concentrations (up to 15%) showed poorer stability and approached the control tablets in aspirin content at the end of 120 days.

Keyphrases □ Silica, colloidal—surface chemistry, evaluated for stabilizing effect on aspirin in tablets □ Aspirin—stability in tablets, effect of colloidal silica □ Stability—aspirin in tablets, effect of colloidal silica □ Tablets—aspirin, effect of colloidal silica on stability □ Dosage forms—tablets, effect of colloidal silica on aspirin stability □ Analgesics—aspirin, effect of colloidal silica on stability in tablets

The hydrolytic decomposition of aspirin has been widely studied, especially in the last two decades. While some work concerned the kinetics of the hydrolytic degradation of aspirin in aqueous systems, much of the published work dealt with the stability of aspirin in tablets as influenced by various common excipients.

Aspirin hydrolysis in solid dosage forms can be considered to proceed in the microfilm of moisture at the surface of the aspirin particles. The hydrolysis rate is a function of the available water content, pH, and temperature. The higher the available moisture content, the more rapidly the hydrolysis proceeds. An increase in temperature greatly increases the rate of hydrolysis due to the increased rate constant governing the reaction and the increased amount of aspirin in solution. Furthermore, according to Martin (1), an increase in the surface area of aspirin apparently has no discernible effect on hydrolysis. In the absence of any substance in the tablet that affects the pH of the microenvironment, the aspirin dissolved in the moisture will have the pH at which aspirin exhibits maximum stability. The presence in the tablet of any substance that increases aspirin solubility or modifies the pH will increase the decomposition rate (1).

Byrn (2) suggested a possible mechanism for solid-state aspirin hydrolysis. At elevated temperatures in the presence of moisture, he theorized that the reaction takes place through solution of aspirin from the water vapor adsorbed and in contact with the aspirin surface. The sublimation of salicylic acid observed on the surface of aspirin tablets under stress conditions (3) suggests that other factors than those operating in a pure solution theory must be operable, since it seems unlikely that salicylic acid would sublime out of an aqueous solution. It also was suggested that the degradation reaction may be affected by the dissolution of aspirin in acetic acid as it forms, depending on the rates at which acetic acid volatilizes and is formed by hydrolysis (2).

Colloidal silicas are well known for their large surface area and highly polar silanol surface favorable for water vapor adsorption. Such materials possess a high moisture adsorption capacity and, therefore, are commonly used as desiccants to protect hygroscopic chemicals and pharmaceuticals from atmospheric moisture. Their structural and physicochemical characteristics suggested a possible application for these agents as stabilizers for hydrolabile drugs in solid dosage systems by their acting as local moisture scavengers and by their adsorbing the free moisture within the tablet micropores, rendering it unavailable for interaction with the drug molecules.

The primary objective of this research was to study the moisture adsorption properties and mechanisms of selected silicas, followed by an evaluation of their stabilizing effect for a model hydrolabile drug, aspirin, in solid dosage forms under selected experimental conditions.

EXPERIMENTAL

Surface Chemistry of Colloidal Silicas—An experimental colloidal silica, I[1], and two other commercially available silicas, II[2] (a precipitated silica) and III[3] (a pyrogenically fumed silica), were investigated for their water vapor adsorption properties at selected vapor pressure conditions at 40°.

An adsorption isotherm was established for each material by subjecting a known weight of a preconditioned sample to an atmosphere equilibrated at a selected vapor pressure corresponding to a relative humidity (RH) between 0 and 100%. The amount of moisture adsorbed per gram of silica was thus determined from the total gain in sample weight at the time of equilibrium. This process was then repeated for another preconditioned sample of the same material by subjecting it to the next higher vapor pressure. In this manner, the moisture adsorption data were generated for the entire vapor pressure range at the selected temperature condition, and an adsorption isotherm was constructed by plotting the values of the equilibrium moisture adsorption against the corresponding vapor pressure conditions (Fig. 1).

Apparatus—An electrobalance[4] in conjunction with a recorder[5] was employed to monitor continuously the weight gain of the sample exposed to the selected vapor pressure and temperature conditions. The balance chamber containing the weighing assembly was placed inside an incubator oven[6] maintained at 40 ± 1.0°. The chamber was made air tight, and the selected vapor pressure condition was maintained by inclusion of a suitable saturated salt solution.

[1] Lubrisilk, supplied by Robertshaw Chemical Corp., Phoenix, Ariz.
[2] "Quso" F-2, Philadelphia Quartz Co., Philadelphia, Pa.
[3] "Cabosil" M-5, Cabot Corp., Boston, Mass.
[4] RG, Cahn Instruments Co., Paramount, Calif.
[5] SR, E. H. Sargent and Co., Chicago, Ill.
[6] Thelco, Precision Scientific Co., Evanston, Ill.

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Table I—Control and Sample [a] Tablet Formulations Used in the Stability Study

Tablet Formulation	Aspirin–I Ratio	Weight, mg/tablet		
		Aspirin	I	Starch
Control A (no starch)	100:0	460.0	0.0	0.0
Control B (5% starch)	100:0	460.0	0.0	23.0
Sample 1	99:1	455.4	4.6	23.0
Sample 2	97:3	446.2	13.8	23.0
Sample 3	95:5	437.0	23.0	23.0
Sample 4	90:10	414.0	46.0	23.0
Sample 5	85:15	391.0	69.0	23.0

[a] The sample tablets contained 5% starch equilibrated at 40°. The equilibrated starch contained 5.5% moisture by weight.

The control unit of the electrobalance and the recorder were located outside the oven. The mechanical operation of the electrobalance was not affected by the selected humidity and temperature conditions, as verified during preliminary tests. The change in sample weight, due to adsorption of water vapor, was recorded until an equilibrium was reached under each environmental condition.

Colloidal silicas (such as I) with an active silanol surface desorb any physically bound moisture substantially completely on exposure to temperatures above 110° over 1–2 hr (4, 5). In these experiments, exposure of I to 150° for 2 hr was adequate to ensure complete desorption of the physically bound moisture without alteration of the surface characteristics. Therefore, silica samples used in the adsorption study and later in the preparation of tablets were preconditioned by drying under these conditions to desorb any moisture bound physically under ambient storage.

A known weight of the sample, at room temperature, was transferred to the weighing chamber, which was preequilibrated at the selected vapor pressure condition overnight. The electrobalance was precalibrated for the estimated change in sample weight, and the gain in sample weight was continuously recorded over 3–4 hr or until the sample reached equilibrium. An average of three replicates thus represented the equilibrium weight gain for each material at each vapor pressure level.

Saturated solutions of various salts in contact with an excess of their solid phase (6, 7) were employed to achieve the vapor pressure conditions corresponding to 20–100% RH. For humidity conditions below 20%, appropriate concentrations of sodium hydroxide solutions were used (8). Moisture adsorption properties of aspirin powder USP also were investigated under identical experimental conditions, and equilibrium weights were recorded over the entire vapor pressure range at 40°.

Preparation and Porosity Determination of Aspirin–Silica Tablets—Control (aspirin) and sample (aspirin–I) tablets were prepared according to the formulations listed in Table I. Based on the results of the moisture adsorption study, I, having superior moisture adsorption properties, was chosen for the stability study of aspirin tablets. The ingredients for a batch of about 50 tablets of each formulation were thoroughly mixed in a small laboratory mixer and stored in a vacuum desiccator until ready for compression. The tablets were compressed on a hydraulic press[7] with an 11-mm flat-faced punch and die set.

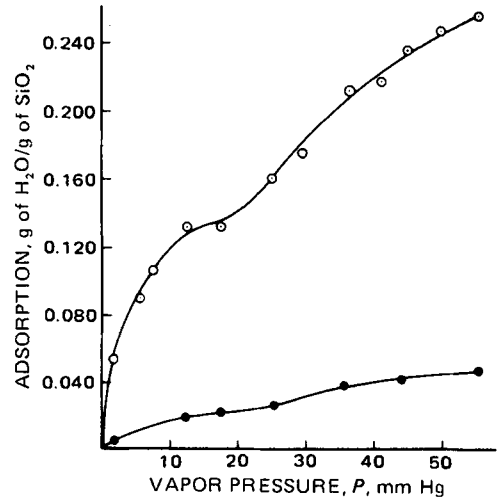

Figure 1—*Adsorption isotherms of I (○) and II (●) at 40°.*

Table II—Compression Conditions, Tablet Thickness, Tablet Hardness, and Percent Void Volume for Various Tablet Formulations

Tablet Formulation[a], Aspirin–I Ratio	Compression Conditions		Tablet Hardness[b], kg	Tablet Thickness[c], mm	Percent Void Volume
	Force, kg	Seconds			
Control A, 100:0	227	1	1.8	3.89	19.66
Control B, 100:0	272	1	1.6	4.10	19.84
Sample 1, 99:1	272	1	4.5	4.06	19.60
Sample 2, 97:3	318	2	6.0	4.04	19.66
Sample 3, 95:5	364	4–5	8.4	4.01	19.52
Sample 4, 90:10	864	3–4	10.6	3.94	19.27
Sample 5, 85:15	1136	12–13	14.9	3.89	19.60

[a] All tablet formulations except Control A contained preequilibrated starch at 5% of the total aspirin–silica content. [b] Average value for five tablets. Measurements were made using the Pfizer hardness tester. [c] Thickness variability was within ± 0.025 mm of the reported mean values.

Initially, tablets of each formulation (Table I) were compressed to a constant hardness using appropriate loading force and time combinations. Porosity (percent void space) determinations were made on each set of tablets by using a method reported earlier (9, 10). This method involved a determination of apparent tablet volume from tablet dimensions measured with a micrometer. The volume occupied by each ingredient in the tablet was estimated from the known values of its weight and true density. The latter values for the three tablet components were obtained by the pycnometer method with petroleum ether as a nonsolvent medium.

Since the porosity determinations on aspirin–I tablets compressed to constant hardness indicated porosity increasing with silica content, it was considered necessary to hold the porosity constant at a selected level to eliminate its effect on the evaluation of aspirin stability. Therefore, the tablets used in the stability study were compressed to a constant porosity by controlling the tablet thickness (and, thus, the tablet volume), using the predetermined values of compression force and loading time for a particular composition. The selected compression conditions and the resultant tablet properties are listed in Table II.

The tablet void space as influenced by the I content also was investigated under constant compression conditions. The sample tablets containing aspirin and I in differing ratios of 3–15% silica content were compressed on the hydraulic press, using a compression force of 454 kg and a compression time of 5 sec. Tablet thickness was determined by means of a thickness gauge[8], and the percent void space was determined by the method described earlier.

The tablets containing 100% aspirin and various combinations of aspirin and I showed poor disintegration properties. Therefore, all test formulations for the stability study were modified to contain 5% corn starch USP to achieve a disintegration time within USP limits. A formulation containing aspirin alone also was included as a primary control in the stability program to determine if the hygroscopic nature of starch interfered with the adsorption properties of silica and, consequently, aspirin stability. The starch powder used was preconditioned to limit its moisture content to an equilibrium level of 5.5%.

Stability Evaluation of Aspirin–Silica Tablets—The stability study was conducted under the conditions of a continuous moisture supply at an elevated temperature (82% RH at 40°). The test samples were placed in a desiccator preequilibrated at 82% RH with a saturated solution of potassium chloride and stored in an incubator oven set for 40°. During the initial period, the gain in weight of the tablets was monitored every 2 hr through the first 12 hr, followed by weighings every 12 hr for 4 days.

Control and sample tablets then were assayed for residual aspirin content at various time intervals during the test period of 120 days by the method reported earlier (3). This method essentially involves simultaneous spectral determination of aspirin and salicylic acid, the hydrolytic degradation product, in a pH 7.4 buffer solution at 262 and 296.5 nm, respectively. The method was modified to exclude the insoluble silica particles from the final dilution before the spectrophotometric measurements. Appropriate corrections for the increased tablet weight due

[7] Fred S. Carver and Co., Summit, N.J.
[8] B. C. Ames Co., Waltham, Mass.

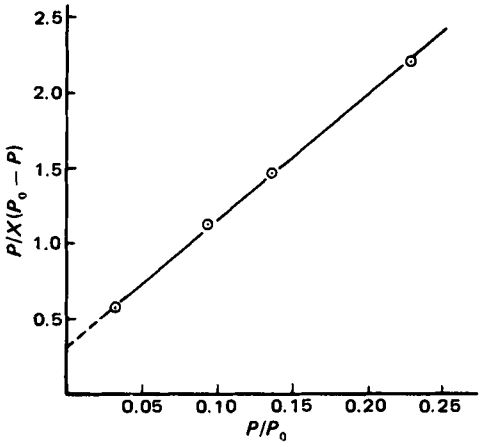

Figure 2—*BET plot for water vapor adsorption isotherm for I at 40°.*

to moisture sorption were made before the residual aspirin content per tablet was determined.

RESULTS

Adsorption Properties of Silicas—Adsorption isotherms, constructed from the data generated in the moisture adsorption study of I and II, are presented in Fig. 1. The isotherm for I showed a close resemblance to the type IV isotherm, typical of adsorbents with limited pore volume and multilayer adsorption. Therefore, the data from the I isotherm were treated according to the Brunauer, Emmett, and Teller (BET) theory of multilayer adsorption to quantify the monomolecular layer capacity (X_m) and the specific surface area (S_w) for I (11–13). This calculation is represented by the equation:

$$\frac{P}{X(P_0 - P)} = \frac{1}{X_m C} + \left(\frac{C-1}{X_m C}\right)\left(\frac{P}{P_0}\right) \qquad \text{(Eq. 1)}$$

where P is the vapor pressure of the adsorbate at the temperature of the experiment, P_0 is the saturation vapor pressure at that temperature, X is the quantity of adsorbate (water) adsorbed per gram of adsorbent, X_m is the quantity of adsorbate required for completion of the monolayer, and C is a constant dependent on the difference between the heat of adsorption for the completion of the monolayer (E_m) and the heat of condensation of successive layers (E_L) and is expressed by the equation:

$$C = e^{(E_m - E_L)/RT} \qquad \text{(Eq. 2)}$$

where R is the gas constant and T is the absolute temperature.

A BET plot of $P/[X(P_0 - P)]$ as a function of P/P_0 yields a straight line, with the slope being equal to $(C-1)/X_mC$ and the y-intercept equal to $1/X_mC$ (Fig. 2). This plot was linear up to a value for P/P_0 (*i.e.*, relative vapor pressure) equal to 0.25, corresponding to the vapor pressure at which the monomolecular layer had been completed. The location of this monolayer depends on the value of C and, therefore, on the heat of adsorption. The slope and y-intercept of the linear portion of this curve were used to calculate the values of X_m and C. From the value of C, the quantity $(E_m - E_L)$, defined earlier, was calculated.

The specific surface area of the adsorbent (S_w) available for adsorption of water vapor as a monolayer can be calculated from a knowledge of X_m and A_m, the area of a single closely packed adsorbate (water) molecule adsorbed in the monolayer, using the following equation (13, 14):

$$S_w = \frac{X_m N A_m}{M/\rho} \qquad \text{(Eq. 3)}$$

where N is Avogadro's number and M/ρ is the molar specific volume of the adsorbate (22,400 ml/mole at standard temperature and pressure).

The value of A_m for water molecules adsorbed on the surface of silica may be calculated from the knowledge of the molecular weight of water (M) and its density in the adsorbed state at the temperature of the experiment (ρ), as given by the relationship (15):

$$A_m = 1.091\left[\frac{M}{N\rho}\right]^{2/3} \qquad \text{(Eq. 4)}$$

The coefficient 1.091 is the appropriate packing factor and involves two assumptions: (*a*) the adsorbate molecules are held in a two-dimensional packing arrangement on the surface, and (*b*) the area occupied by each molecule is the projected cross section of the molecular volume calculated from the density of the condensed adsorbate (12).

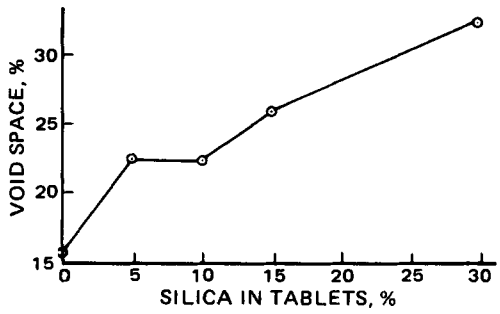

Figure 3—*Percent void space as a function of percent I in tablets of constant hardness (5.5 kg).*

Since the silica surface is covered with silanol groups, the water molecules are adsorbed on the surface through hydrogen bonding. If it is assumed that each water molecule adsorbed on the surface of the silica is held by one hydroxyl group, leading to a closely packed arrangement, and that the adsorbed water is in a liquid state, the value of A_m = 10.6 Å^2 as calculated from Eq. 4 should be accurate.

With this value for A_m, the specific surface area (S_w) for water vapor adsorption was calculated from Eq. 3. The surface area for I calculated from BET nitrogen adsorption data[9] was used to calculate the mean volume surface diameter (d_{vs}) from the relationship (14):

$$d_{vs} = \frac{6}{\rho_s S_w} \qquad \text{(Eq. 5)}$$

where ρ_s is the true density of I. The value of d_{vs} thus calculated was 3.82 nm.

The isotherm for II (Fig. 1) indicates inferior moisture adsorption properties as compared to I at identical vapor pressure conditions. Silica III, a pyrogenic fumed silica, showed little or no moisture adsorption even under saturation vapor pressure conditions and, therefore, is not presented in Fig. 1. The adsorption properties of aspirin, when investigated under identical conditions, also showed no evidence of moisture adsorption at saturation vapor pressure (P/P_0 = 1.0), thus indicating that aspirin has no physical affinity for moisture, although it undergoes hydrolytic degradation at ambient temperature conditions.

On the basis of these results, I was chosen for the study of stabilizing properties for a moisture-sensitive drug (aspirin) in tablet dosage form.

Determination of Tablet Porosity and Effect of Silica on Tablet Voids—Tablets of selected formulations (Table I), compressed to a constant hardness, were evaluated for their total void space by a method described previously (9, 10).

The percent void volume (*i.e.*, porosity), defined as the percent of total volume (V_{tablet}) occupied by the void space (V_v), is given by:

$$\%\ \text{voids} = \left(\frac{V_v}{V_{tablet}}\right) 100 \qquad \text{(Eq. 6)}$$

The volume occupied by the voids is obtained by subtracting the calculated volume occupied by each ingredient within the tablet from the total tablet volume, determined by dimensional measurements.

For the tablet formulations under study, this value of V_v is given by:

$$V_v = V_{tablet} - (V_{aspirin} + V_{silica} + V_{starch}) \qquad \text{(Eq. 7}a\text{)}$$

or:

$$V_v = V_{tablet} - \left[\frac{W_{aspirin}}{\rho_{aspirin}} + \frac{W_{silica}}{\rho_{silica}} + \frac{W_{starch}}{\rho_{starch}}\right] \qquad \text{(Eq. 7}b\text{)}$$

where W and ρ stand for the weight and true density for the components, respectively.

In Fig. 3, the percent void space is plotted against the silica content for tablets having equal hardness. This plot illustrates that I significantly increased the tablet void space. The contributions made by the two tablet components to the tablet void space are illustrated in Fig. 4, which shows

[9] The surface area by BET nitrogen adsorption was determined by the American Instruments Co., Silver Spring, Md., using a model 4-4680 adsorptomat.

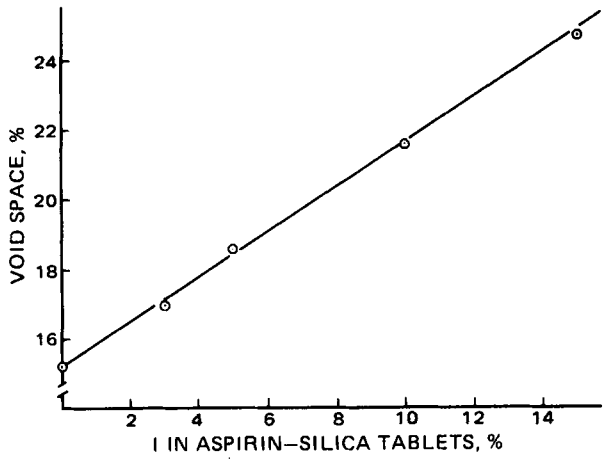

Figure 4—*Percent void space as a function of percent I in aspirin–I tablets under constant compression conditions.*

the relationship between the percent void space and the silica content of tablets compressed under constant compressional forces. A positive linear relationship and a positive y-intercept suggest that the void space contributed by I, on a unit weight basis, remains constant over the range of 0–15% silica content. The relative contributions made by each of the two ingredients to the total void space is estimated from Fig. 5, which represents a plot of the apparent specific volume, *i.e.*, the reciprocal of apparent tablet density, as a function of the weight fraction of silica in the tablets. Equation 8 describes this relationship:

$$\overline{V}_{tablet} = \overline{V}_{aspirin} + m W_{silica} \qquad \text{(Eq. 8)}$$

where $\overline{V}_{tablet}$ and $\overline{V}_{aspirin}$ are the specific volumes of the tablets under test and of tablets containing 100% aspirin, respectively; W_{silica} stands for the weight fraction of silica; and m is the slope of the line (being equal to the difference between the values of $\overline{V}_{silica}$ and $\overline{V}_{aspirin}$). The linearity of this plot suggests that the specific volumes of 100% aspirin and 100% silica tablets remain constant over the range of tablet compositions studied. Since it was not possible to compress tablets containing 100% silica under identical compressional conditions, the value of $\overline{V}_{silica}$ is obtained by extrapolating the line to the right y-intercept or by calculating from the slope.

If reciprocals of true densities of aspirin and silica in their pure crystalline states (*i.e.*, with zero porosity) represent their specific volumes in that state, then the difference between their respective specific volumes of tablet and crystalline states should represent their volume contributions to the void space in a tablet form. The values of $\overline{V}_{void}$ calculated in this manner for aspirin and silica are presented in Table III. These values only represent the data for the set of compressional conditions used in this study and will vary with changes in compressional load.

These data suggest that I increased the tablet void spaces in aspirin–silica tablets to an extent of nearly 600% of that produced by aspirin on an equal weight basis. These results may be explained in terms of the size and geometry of the particles. The needle-shaped aspirin particles, although larger, apparently can pack more tightly than the spherical silica particles. The irregularity of aspirin particles, possibly their deformability

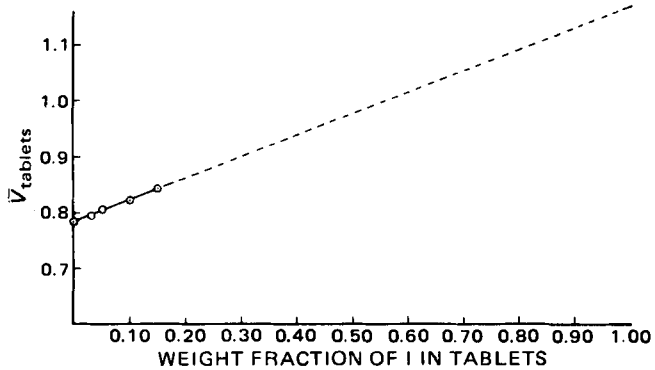

Figure 5—*Specific volume of the tablets as a function of the weight fraction of I in aspirin–I tablets.*

Table III—Specific Volumes of Aspirin and I in Powder and Tablet Form

Component	$\overline{V}_{powder}$, ml/g	$\overline{V}_{tablet}$, ml/g	$\overline{V}_{voids} = \overline{V}_{tablet} - \overline{V}_{powder}$, ml/g
Aspirin powder USP	0.6680	0.7863	0.1183
Silica I	0.4566	1.1700	0.7134

and particle-size distribution, may allow for the interstitial spaces to be filled in a relatively more efficient manner than the nearly spherical and more rigid silica particles with their very narrow size distribution.

Thus, the variable tablet void space as influenced by the silica content could conceivably interfere with an evaluation for any potential stabilizing effect silica may have in aspirin tablets due to variable pore spaces available for water vapor penetration. This possibility necessitated controlling the void space to a constant level of 20% for all aspirin–silica formulations under stability evaluation.

Moisture Sorption by Aspirin–Silica Tablets—The moisture sorption properties of the control and sample tablets subjected to the selected storage conditions (82% RH at 40°) were monitored during the initial test period (Fig. 6). These plots show increasing moisture sorption by the tablets with increased silica content. The tablets containing 0–5% silica adsorbed moisture to their full capacity within the first 8–10 hr, whereas those containing 10 and 15% silica required 24 hr or longer to reach equilibrium. No substantial gain or loss in weight was observed on further exposure up to 72 hr. The control tablets (Formulations A and B) showed no significant weight change over 72 hr. (Formulation B is not presented in Fig. 6.)

Stability of Aspirin–Silica Tablet Systems—The control and sample tablets of the selected formulations (Table I) subjected to the stability study were assayed (3) at selected time intervals for residual aspirin content. The overall variability in the aspirin content for each tablet formulation at a given time was within ±0.5% (Fig. 7). These results clearly demonstrate the stabilizing effect of I, with improved aspirin stability being apparent in tablets containing 1–5% silica as compared to the control tablets. Both controls, with and without starch, showed comparable stability curves.

The decomposition of aspirin in tablets containing 10 and 15% silica, although initially less than that of the control tablets, reached the levels of control tablets by the end of the 120-day test period. The data also indicate that a 3% concentration probably offers maximum aspirin stabilization in these formulations. This conclusion is further demonstrated in Fig. 8, where data are presented as a function of the silica concentration at the end of 30, 60, and 120 days.

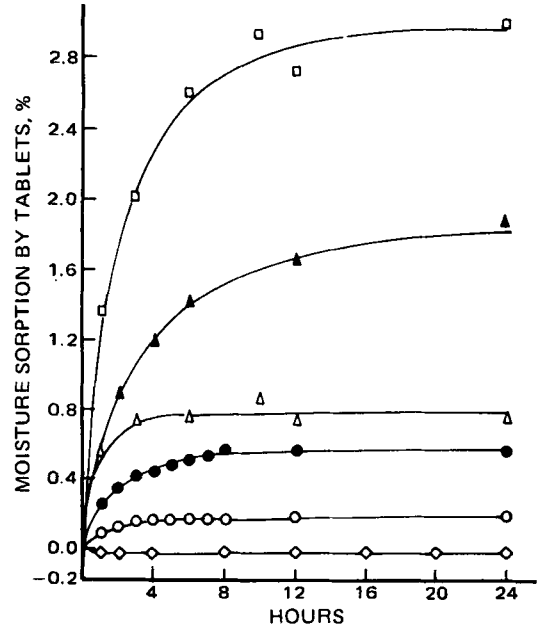

Figure 6—*Percent moisture sorption as a function of time for aspirin and aspirin–I tablets. Key (Formulations in Table I): ◇, A; ○, 1; ●, 2; △, 3; ▲, 4; and □, 5.*

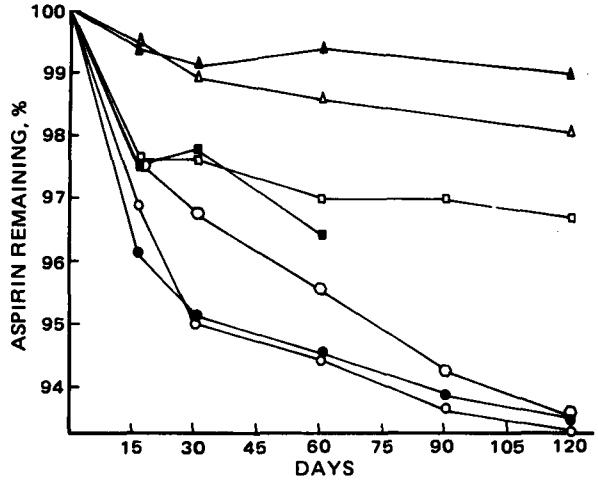

Figure 7—*Stability curves for aspirin in aspirin–I tablets under storage at 81.7% RH and 40°. Key (Formulations in Table I): ○, A; ●, B; △, 1; ▲, 2; □, 3; ■, 4; and ○, 5.*

DISCUSSION

Surface Properties of Silicas—The surface characteristics of I obtained from adsorption isotherm studies are: X_m (monolayer capacity for water vapor adsorption), 0.115 ml of liquid water/g of I; $(E_m - E_L)$, 2.002 kcal/mole of water; S_w (specific surface for water vapor adsorption), 3276 cm^2/g of I; S_w (specific surface from nitrogen adsorption), 714.4 m^2/g of I; and d_{vs} (mean volume surface diameter from nitrogen adsorption), 3.82 nm.

The results for the adsorption of water vapor and nitrogen appear to agree with results reported earlier. Sing and Madeley (16, 17), in a study of the surface properties of certain commercial and laboratory-made silica gels, observed that the value of X_m varied between 0.04 and 0.18 ml/g, depending on the type and method of preparation of the silica gels. The S_w values obtained from nitrogen adsorption isotherms varied within a range of 530–750 m^2/g. Brunauer *et al.* (11), in their original work on the adsorption isotherms of various gases on different adsorbents, reported X_m and S_w values for silica gels to be within 116.2–127.9 ml/g and 534–560 m^2/g, respectively. The specific surface and monolayer capacity of I determined in this study are in agreement with those reported previously.

Based on these results and those of earlier workers, a general hypothesis can be built to suggest a structural configuration of hydrated silica. A finding that the monolayer capacity for water vapor adsorption is significantly lower than that for nitrogen adsorption suggests that the polar water molecules are adsorbed at specific sites on the silica surface. The adsorption of nitrogen gas on the surface of silica gel probably leads to

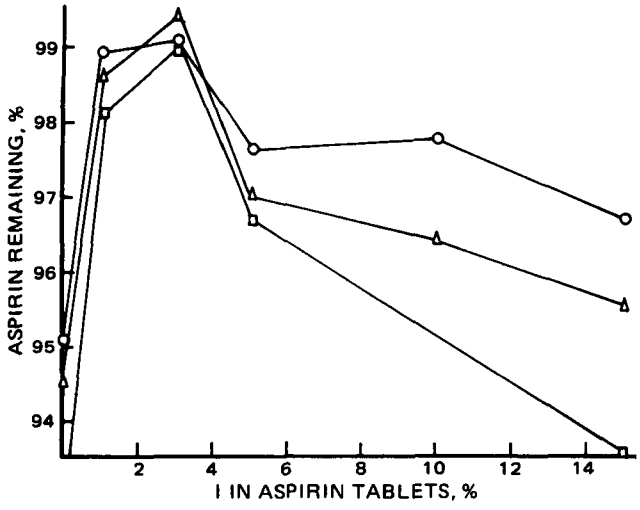

Figure 8—*Percent aspirin remaining as a function of percent I content of tablets at the end of 30 (○), 60 (△), and 120 (□) days of storage at 81.7% RH and 40°.*

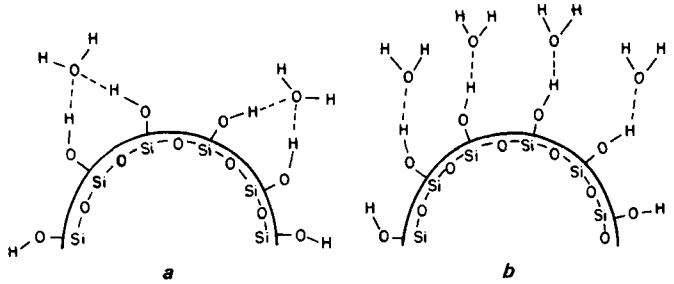

Figure 9—*Two suggested concepts for the adsorption of water on the hydrated surface of I.*

the formation of a continuous monomolecular film and, hence, yields a much higher X_m value. The adsorption of water molecules at the silica surface is thought to be due to hydrogen bonding between the hydrogen of the silanol group and the oxygen of the water molecules, thus leading to adsorption only at silanol sites (4).

Two different theoretical concepts (Fig. 9) were proposed for the adsorption of water vapor on a silica surface. One view (4) implies that adsorption of water and alcohols on the surface of silica may be regarded as a special case since either chemisorption or physisorption may occur, depending on the degree of surface hydration of the silica. This concept (Fig. 9*a*) proposes that a single water molecule is adsorbed by hydrogen bonding to two neighboring silanol groups. If this bonding occurs, a considerably smaller volume of water vapor would suffice for the completion of the monolayer.

According to the second hypothesis (5), the binding of water to the silanol groups on the silica surface in a unimolecular film is in a ratio of 1:1 instead of 1:2, as proposed by Hockey (4) (Fig. 9*b*). Zhdanov (18) quantitatively estimated how surface dehydration affects the adsorption of polar water molecules. Subjecting silica to high temperatures of 600–800° leads to dehydration of silanol groups to siloxane groups. Accordingly, for every silanol group lost from the silica surface, one less water molecule is adsorbed in the monolayer.

However, the data presented in this study are insufficient to suggest which of the two concepts describes the adsorption properties of I.

Stability Evaluation of Aspirin–Silica Tablets—The results of the stability study (Figs. 7 and 8) indicate that the desiccant effect of silica is not the only factor that helps stabilize aspirin in these formulations. The precise mechanism by which this effect occurs is not based on simple retention of water vapor by silica to limit its access to aspirin particles *per se* but probably involves a complex of considerations such as: (*a*) the state of equilibrium between the bound and free water within the microporous structure of the tablets, (*b*) changes in the tablet structure that affect the pore size distribution, and (*c*) the occlusion of pores by silica-bound water or by partial deposition of sublimed salicylic acid on the surfaces of aspirin or silica particles (3, 19).

These phenomena could be explained further by the following hypothesis. Within the micropores of the tablets, the water remaining in association with silica mainly consists of strongly bound water directly bound to the silanol groups in the monolayer and, possibly, in some successive layers. This water probably exists in a polarized oriented form because of its permanent dipole. However, receding from the silica surface, the state of water progressively reaches "liquid water," which is essentially free water, available for the hydrolytic degradation of aspirin.

In a situation of limited moisture supply, an equilibrium is established between the bound and free water within the tablet, and thus, silica effectively stabilizes aspirin after the free moisture within the tablet reaches a negligible level. However, with an essentially unlimited moisture supply, as in the present study, the silica must also limit the access of water to aspirin and/or prevent the release of degradation products. Consequently, the hydrolytic reaction could approach equilibrium and also be diffusion rate limited due to an inability of water to reach the tablet interior. The "strongly bound water" itself may perform this function through occlusion of the tablet pores. However, the possibility of pore occlusion by the subliming salicylic acid cannot be overlooked.

To define these mechanisms, a subsequent study (19) involved the determination of the pore size distribution of aspirin–silica tablets by mercury intrusion porosimetry. The results (19) revealed that, at lower concentrations, silica functioned primarily to reduce the size and volume of coarse pores, presumably representing the spaces between the aggregates of the starch and aspirin particles. This effect was optimum at a concentration of 3% silica, which was also the optimum level of aspirin

stabilization in the present study. At this level, the tablets consistently exhibited the smallest average pore size irrespective of the relative changes in the size and volume of pores resulting from the swelling of starch grains or deposition of salicylic acid in the tablet pores. The role played by subliming salicylic acid and its contribution to the occlusion of the micropores were also evident in this study from the reduction in pore volumes and the size of the pores with increased periods of exposure to water vapor.

SUMMARY AND CONCLUSIONS

Silica I was studied with respect to its physicochemical and surface properties and its ability to stabilize a hydrolabile drug (aspirin) in tablet matrixes. The major findings of the investigation were:

1. Silica I exhibited an adsorption behavior characteristic of adsorbents with limited pore volume. The monolayer capacity and the specific surface area, determined by both water vapor and nitrogen adsorption isotherms employing the BET theory of multilayer adsorption, revealed the superior moisture adsorption capacity of I as compared to the other silicas tested.

2. The void volume of aspirin–silica tablets compressed under constant compressional force was proportional to the silica content of the tablets. Silica contributed approximately six times as much to the void volume as did aspirin on an equal weight basis. Therefore, it was necessary to control the void space of the tablets to eliminate the effect of the void volume variable in the interpretation of stability data.

3. The stability of aspirin tablets containing I at concentration levels of 0–15% was investigated under storage conditions of a continuous moisture supply (82% RH) at 40°. At the end of 120 days, tablets containing up to 5% I exhibited improved aspirin stability in comparison to control tablets. An optimum concentration of 3% silica, however, showed maximum stabilization; the tablets containing 10 and 15% silica showed progressively poorer stability, approaching that of the control tablets at the end of 120 days.

4. Silica I, with superior moisture adsorption properties, proved to be of significant value in enhancing the stability of the hydrolabile test drug (aspirin) by acting as an internal moisture scavenger. This study also demonstrated the importance of controlling the tablet void space in studies involving stability evaluation of drugs prone to moisture hydrolysis in solid drug dosage systems.

REFERENCES

(1) B. K. Martin, in "Advances in Pharmaceutical Sciences," vol. 3, H. S. Bean, A. H. Beckett, and J. E. Carless, Eds., Academic, London, England, 1971, p. 107.

(2) S. R. Byrn, *J. Pharm. Sci.*, **65**, 1 (1976).

(3) A. Y. Gore, K. B. Naik, D. O. Kildsig, G. E. Peck, V. F. Smolen, and G. S. Banker, *ibid.*, **57**, 1850 (1968).

(4) J. A. Hockey, *Chem. Ind. (London)*, **Jan. 9, 1965**, 57.

(5) R. K. Iler, "The Colloid Chemistry of Silica and Silicates," Cornell University Press, Ithaca, N.Y., 1955, pp. 87, 158, 233.

(6) D. S. Carr and B. L. Harris, *Ind. Eng. Chem.*, **41**, 2014 (1949).

(7) R. H. Stokes and R. Robinson, *ibid.*, **41**, 2013 (1949).

(8) "International Critical Tables," 1st ed., vol. III, McGraw-Hill, New York, N.Y., 1928, p. 270.

(9) N. R. Patel and R. E. Hopponen, *J. Pharm. Sci.*, **55**, 1065 (1966).

(10) I. Ingram and W. Lowenthal, *ibid.*, **57**, 393 (1968).

(11) S. Brunauer, P. H. Emmett, and E. Teller, *J. Am. Chem. Soc.*, **60**, 309 (1938).

(12) L. E. Osipow, "Surface Chemistry, Theory and Industrial Applications," Reinhold, New York, N.Y., 1962, p. 26.

(13) S. J. Gregg, "The Surface Chemistry of Solids," 2nd ed., Reinhold, New York, N.Y., 1961, p. 48.

(14) A. N. Martin, J. Swarbrick, and A. Cammarata, "Physical Pharmacy," 2nd ed., Lea & Febiger, Philadelphia, Pa., 1970, p. 482.

(15) P. H. Emmett and S. Brunauer, *J. Am. Chem. Soc.*, **59**, 1553 (1937).

(16) K. S. W. Sing and J. D. Madeley, *J. Appl. Chem.*, **3**, 549 (1953).

(17) *Ibid.*, **4**, 365 (1954).

(18) S. P. Zhdanov, *Dokl. Akad. Nauk, USSR*, **68**, 99 (1949).

(19) H. Gucluyildiz, G. S. Banker, and G. E. Peck, *J. Pharm. Sci.*, **66**, 407 (1977).

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Metal-Binding Abilities of Radioprotective Aminoalkyl Disulfides and Thiosulfates

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Abstract □ Metal-binding stability constants for several heterocyclic aminoalkyl disulfides and thiosulfates with Ni(II) and Al(III) were determined. The data obtained indicated that both classes of compounds were acting as bidentate chelating agents and that the heterocyclic rings apparently prevented tridentate behavior of the disulfides because of steric hindrance. The magnitude of the constants indicated that metal complexes of these compounds could exist in a cellular environment, but no correlation with radiation-protective activity was apparent.

Keyphrases □ Disulfides, aminoalkyl—metal-binding stability constants determined, relation to radiation-protective activity □ Thiosulfates, aminoalkyl—metal-binding stability constants determined, relation to radiation-protective activity □ Metal binding—stability constants determined for various aminoalkyl disulfides and thiosulfates, relation to radiation-protective activity □ Binding, metal—stability constants determined for various aminoalkyl disulfides and thiosulfates, relation to radiation-protective activity □ Radiation-protective activity—various aminoalkyl disulfides and thiosulfates, relation to metal-binding stability constants

Aminoalkyl disulfides and thiosulfates have strong radiation-protective properties in animals (1, 2). The fact that the protective compounds all have a two- or three-carbon distance between the amino and sulfur functions, which confers potential metal-chelating ability to them, suggests that metal binding may be important in their

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