Effect of Silica Gel on Stability and Biological Availability of Ascorbic Acid

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Abstract □ The alleged interaction of silica gel and ascorbic acid has been investigated in model experiments and in practical tablet trials, using wet granulation procedures. In simple mixtures stored for 3 weeks at 45° in closed tubes, losses of ascorbic acid increase progressively with increasing moisture content, whether or not silica gel is present, although losses are higher in the presence of silica gel. At an equivalent percentage of water in such mixtures, the amount of silica gel or the prior adsorption of 1½ times its weight of vitamin E on the silica gel, did not influence the loss of ascorbic acid. The data show that silica gel binds a certain fraction of the water present and that the loss of ascorbic acid is directly proportional to the amount of unbound water in the system. Sodium ascorbate is more sensitive than ascorbic acid to aerobic oxidation in the presence of moisture. Other commonly used tablet excipients, as well as silica gel, enhance losses of ascorbate. However, proper technology applied to wet granulation procedures yields excellent recoveries and stability of ascorbic acid or sodium ascorbate in dried granulations and in finished multivitamin tablets. The human bioassay technique, in which extra urinary excretion of ascorbic acid after tablet dosage is compared to that after dosage of ascorbic acid in water, has been used to demonstrate the full physiological availability of ascorbic acid in the presence of silica gel. Storage of such tablets for 3 months at 45° did not alter the complete bioavailability of the ascorbic acid.

Keyphrases □ Ascorbic acid—stability, biological availability □ Stability, ascorbic acid—humidity, excipient effects □ Silica gel effect—ascorbic acid stability, bioavailability □ Moisture concentration—ascorbic acid stability □ Biological availability, ascorbic acid—silica gel effect

Diffuse reflectance spectroscopy has been used by Lach and Bornstein (1–3) to study interactions of a number of drugs with various adjuvants after treatment of the mixtures by equilibration in aqueous or nonaqueous media, by compression, and by exposure to controlled humidity conditions. Such an interaction of ascorbic acid and silica gel has been claimed by Lach (4). Since silica gel is a useful adsorbent for converting liquid vitamins such as vitamin E and panthenol into free-flowing, dry powders, it became important to evaluate this alleged interaction of silica gel with ascorbic acid. This has been done in model experiments with simple mixtures and under practical conditions of formulating multivitamin dosage forms. In addition, physiological availability tests in humans have been utilized to check for possible influence of silica gel contained in multivitamin tablets on the biochemical behavior of ascorbic acid.

EXPERIMENTAL

Model Experiments—(*a*) *Effect of Graded Moisture Levels*—Experimental mixtures of ascorbic acid with silica gel[1] and with 60% adsorbate of *d,l*-α-tocopheryl acetate on silica gel were prepared both at normal use ratios and at an eightfold higher than normal adsorbent/vitamin ratio. Ascorbic acid alone and the various mixtures were adjusted with distilled water to graded moisture levels up to 40% and stored in closed tubes for 21 days at 45°. The percentage of water added was based in each case on the total weight of the tube contents, except for the vitamin E adsorbate mixtures where the weight of the oil phase was not included. The compositions of the mixtures before addition of water are shown in the legend of Fig. 1. Ascorbic acid was determined after storage by titration with about 0.1 *N* standard iodine solution and starch indicator.

(*b*) *Rate of Loss of Ascorbic Acid and Sodium Ascorbate at 45° with 11.6% Water*—The stress conditions used in *Experiment* (*a*), namely 3 weeks at 45° at high moisture levels, are obviously much more strenuous than those normally encountered in pharmaceutical manufacturing operations, such as wet granulation procedures, in which drying is completed in a much shorter period. It was of interest, therefore, to check the rate of decomposition of ascorbic acid in similar mixtures stored for 1, 2, and 3 days at 45° at one of the lower levels of moisture, namely 11.6%.

Ascorbic acid and the ascorbic acid plus silica gel mixture used in this test, when shaken with water at a concentration of about 20 mg. of vitamin C per ml., yielded a pH of 2.3 and 2.4, respectively. Sodium ascorbate with and without silica gel, at similar dilutions in water, gave a pH of 6.7 with silica gel and 7.2 without. The same stability tests were set up with sodium ascorbate with and without silica gel at 11.6% water.

(*c*) *Effect of Other Tablet Excipients*—The relative effect of other excipients commonly used in tablets has been compared to that of silica gel in a test similar to that in (*b*). Three hundred milligrams of sodium ascorbate were mixed with 80 mg. of the particular excipient and water added to give 11.6% by weight. The mixtures were stored in closed tubes for 3 days at 45° and ascorbate determined by iodine titration.

Granulation and Tablet Trials—Multivitamin mixtures containing ascorbic acid or sodium ascorbate and silica gel adsorbates of vitamin E were made by wet granulation procedures with and without iron. To minimize exposure to moisture stress, the granulations were milled through a No. 6, round-hole screen to the minimum practical particle size and dried in layers of 1.27 cm. (0.5 in.) or less with rapidly moving, 45° air. Vitamin C recoveries were determined for the granulations and finished tablets made from these granulations, using iodometric titrations. Stability of vitamin C was determined similarly after accelerated and room temperature storage.

Availability Studies in Men—It has been pointed out (1–3) that drug-adjuvant interactions possibly may result in significant altera-

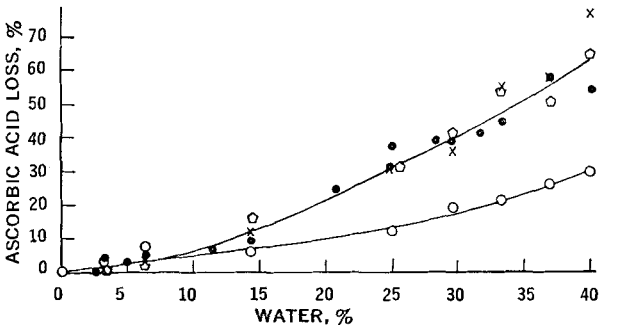

Figure 1—*Effect of silica gel on stability of ascorbic acid at graded percent moisture levels; mixtures stored in closed tubes for 3 weeks at 45°. Key:* ○, *300 mg. ascorbic acid alone;* ●, *300 mg. ascorbic acid + 80 mg. silica gel;* ⌓, *300 mg. ascorbic acid + vitamin E adsorbate (80 mg. silica gel + 120 mg.* d,l-α-*tocopheryl acetate);* ×, *300 mg. ascorbic acid + 640 mg. silica gel.*

[1] Syloid 244, W. R. Grace & Co., Davison Chemical Div., Baltimore, Md.

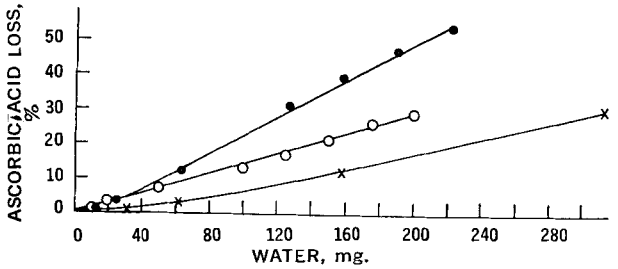

Figure 2—*Effect of silica gel on stability of ascorbic acid with graded weights of water added; mixtures stored in closed tubes for 3 weeks at 45°. Key: ○, 300 mg. ascorbic acid alone; ●, 300 mg. ascorbic acid + 80 mg. silica gel; ×, 300 mg. ascorbic acid + 640 mg. silica gel.*

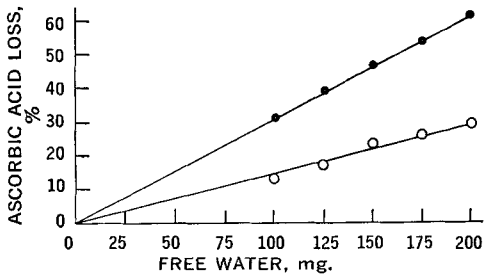

Figure 3—*Effect of free water level on stability of ascorbic acid in mixtures with or without silica gel; storage in closed tubes for 3 weeks at 45°. Key: ○, 300 mg. ascorbic acid alone; ●, 300 mg. ascorbic acid + 80 or 640 mg. silica gel.*

tions of the biochemical behavior of a medicament. Although such effects are more likely to occur at low drug to adjuvant ratios, the possible existence of the excipient as a chemisorbed layer on the drug has been mentioned as a factor that might cause similar effects at high drug to adjuvant ratios (2). To determine whether silica gel in a tablet would influence the physiological availability of ascorbic acid, the human bioassay technique described by Melnick *et al.* (9) was applied to several tablet formulations. In this test, comparison is made between the extra urinary excretion of the vitamin following dosage with the test sample and that following administration of the vitamin in pure form.

Five male subjects were saturated with ascorbic acid by daily dosing with 500 mg. for 3 weeks. Dosing with test samples and standard was not initiated until a stable plateau had been obtained for the 24-hr. urinary excretions following a 500-mg. dose, given after 2 days without dosing. Two different tablet formulations as listed in Table VI were tested, both containing vitamin E at a level of 30 mg. per tablet in the form of silica gel adsorbate. The standard dose of pure ascorbic acid taken in water was 450 mg. For the initial test, the dose taken was six tablets (453 and 466 mg. ascorbic acid for the Lot Nos. 73-69/1 and 73-69/3, respectively). For the aged sample, seven tablets (430 mg. ascorbic acid) were given.

One test was performed each week with basal urine collected on the day prior to taking each test dose. After dosage with ascorbic acid alone or in tablets, respectively, urine was collected for the periods 0–6 hr. and 6–24 hr., except for Dose 2 of ascorbic acid where only total 24-hr. collections were made. Basal urines were collected in each case according to the same schedule. Ascorbic acid in urine was determined by the dichlorophenol–indophenol–xylene extraction method, as previously described (10). In each case the extra excretion due to dose was calculated by subtracting the corresponding basal excretion value from the value after dose.

RESULTS AND DISCUSSION

Model Experiments—*Effect of Graded Moisture Levels*—The results of storage tests on the ascorbic acid plus silica gel mixtures at graded moisture levels for 3 weeks at 45° are shown in Fig. 1. Ascorbic acid alone shows progressively increasing storage losses with increasing moisture content. At low moisture levels (below 6%), no significant difference could be determined between samples with or without silica gel. At higher moisture levels, the losses increase with increasing moisture content in mixtures containing silica gel and are higher than those found with ascorbic acid alone. It is noteworthy, however, that at any percentage moisture level, an eightfold increase in the ratio of silica gel to ascorbic acid caused no further increase in the ascorbic acid loss above that observed at the lower silica gel level in the 3 weeks at 45° storage tests. This lack of concentration effect of silica gel suggests strongly that the degradation of ascorbic acid is not due to surface interaction. Further, when 60% vitamin E oil was adsorbed on the silica gel, no change in the stability of ascorbic acid was observed. Thus is due undoubtedly to the strongly hydrophilic nature of this adsorbent.

It is of interest to examine the data in Fig. 1 in terms of the losses of ascorbic acid found at equivalent weights of water in the mixtures, rather than at equivalent percentages of water. This type of plot is given in Fig. 2. The circumstance that the higher proportion of silica gel exerts a protective effect indicates that some binding of water by the silica gel is taking place and suggests that the ascorbic acid losses are related to the amount of unbound or free water in the various mixtures. If this is true, then the equivalence of the ascorbic acid losses at the high and low silica gel levels at any particular percentage of moisture would indicate an equivalent amount of free water in these two mixtures.

Assuming that the silica gel binds water as a fixed fraction of its own weight at any given percentage of water, calculation has been made of the fraction that must be bound at both the 80 and 640-mg. silica gel levels in order to yield equal weights of free water at these two levels. A typical calculation is given below for the 25% water level in both mixtures, the compositions of which are as follows: (*a*) 80 mg. silica gel, 300 mg. ascorbic acid, and 127 mg. water; (*b*) 640 mg. silica gel, 300 mg. ascorbic acid, and 313 mg. water. If X = bound water level (expressed as percent of silica gel weight) which will yield the same weight of free water for both mixtures, then in both cases the total water minus bound water = free water, and

$$127 - 80 \times \frac{X}{100} = 313 - 604 \times \frac{X}{100}$$

from which $X = 33.2$. Then milligrams of bound water are: (*a*) $80 \times 0.332 = 26.6$ and (*b*) $640 \times 0.332 = 212.6$, and milligrams of free water are: (*a*) $127 - 26.6 = 100.4$ and (*b*) $313 - 212.6 = 100.4$.

These percentages of bound water and the corresponding weights of free water at the various total water levels are listed in Table I, together with the respective losses of ascorbic acid taken from the curve in Fig. 1. Values at the lower moisture levels are not included in Table I since the magnitude of the ascorbic acid losses in this range of water content is not sharply defined, due to the difficulty of mixing the small quantities of water uniformly, the greater error inherent in the small differences in titrations before and after storage, and the possible effect in some cases of a moisture loss during storage.

Table I—Effect of Moisture Content on Stability of Ascorbic Acid in Presence of Silica Gel[a]

H_2O Added, %	H_2O Added, mg. 80 mg. S.G.	H_2O Added, mg. 640 mg. S.G.	80 or 640 mg. S.G. Bound H_2O S.G. wt., %	80 or 640 mg. S.G. Free H_2O, mg.	Loss A. A., %
25.0	127	313	33.2	100.4	31.3
29.4	159	392	41.6	125.7	39.7
33.3	190	470	50.0	150.0	47.0
36.9	222	550	58.6	175.0	54.6
40.0	254	627	66.6	200.7	62.3

[a] Ascorbic acid (A.A.), 300 mg. + 80 or 640 mg. silica gel (S.G.) + indicated percent H_2O—storage in closed tubes for 3 weeks at 45°.

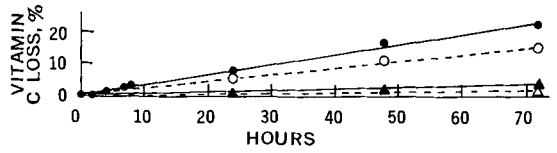

Figure 4—*Rate of loss of vitamin C in presence of silica gel; storage in closed tubes at 45° with 11.6% water. Key: △, 300 mg. ascorbic acid alone; ▲, 300 mg. ascorbic acid + 80 mg. silica gel; ○, 300 mg. sodium ascorbate alone; ●, 300 mg. sodium ascorbate + 80 mg. silica gel.*

The excellent correlation between weights of free water in the mixtures and losses of ascorbic acid is shown by the plot of Fig. 3. The losses of ascorbic acid are directly proportional to the calculated amounts of free water in the mixtures. For the sake of comparison, the data on the ascorbic acid plus water mixtures without silica gel are plotted in Fig. 3. The slope of the latter line is smaller than that of the ascorbic acid + silica gel + water mixtures. Again, in view of the fact that equal losses are found with a given weight of ascorbic acid over an eightfold range of silica gel plus bound water weights, it appears highly unlikely that surface reaction is a significant factor responsible for the higher losses of ascorbic acid in the presence of silica gel. It is believed more likely that trace metals such as iron and copper, which are present in silica gel to the extent of 110 and 1 p.p.m., respectively, are dissolved by the water and exert their well-known catalytic effect on ascorbic acid decomposition in solution (5, 6). Trace metals in the ascorbic acid (less than 10 p.p.m.) are present to the same extent in the tubes with or without silica gel. This mode of decomposition of ascorbic acid is in contrast to that reported by Carstensen *et al.* (7) for thiamine in solid dosage forms, where losses occur in an adsorbed surface monolayer of thiamine dissolved in water.

Rate of Loss of Ascorbic Acid and Sodium Ascorbate at 45° with 11.6% Water—These data are shown in Fig. 4. The loss of ascorbic acid alone in 3 days at 45° is only about 1%; in the mixture with silica gel the loss in this period is 3.6%. This small effect of silica gel in the 3-day test shows the same trend as described previously for the 3-week test.

The losses of sodium ascorbate, both with and without silica gel, are considerably higher than those found with ascorbic acid. This is to be expected in view of the fact that aerobic oxidation of ascorbic acid in the presence of metallic catalysts proceeds more slowly in acid solution than in neutral solution (8).

Effect of Other Tablet Excipients—The losses of ascorbate in the presence of the various excipients at 11.6% water are listed in Table II. Like silica gel, all these other excipients also increase the loss of ascorbate. The magnitude of the effect is undoubtedly dependent on the factors discussed above, including pH, water-binding capacity of the adjuvant, and trace metal content.

Granulation and Tablet Trials—Table III shows the excellent recoveries of ascorbic acid in dried granulations properly formulated with high levels of vitamin E in the form of silica gel adsorbates. Table IV similarly shows the excellent stability of sodium ascorbate in two dried granulations.

Finished tablets prepared by suitable techniques also show good stability of vitamin C in the presence of silica gel. This is demonstrated by the data in Table V on ascorbic acid stability in tablets prepared with 33 and 60% adsorbates of *d,l*-α-tocopheryl acetate on silica gel.

It has long been known that the sensitivity of vitamin C to oxidation in the presence of moisture is a factor that must be considered in the preparation of multivitamin tablets by wet granulation procedures. This is true whether or not silica gel is present in the granulation. In granulations containing appreciable quantities of silica gel and/or excipients, which are also potential contributors to vitamin C breakdown, it is possible to obtain excellent recovery of either ascorbic acid or sodium ascorbate by suitable wet granulation procedures. However, it is essential that the moisture level be held to the minimum level for effective granulation and that drying be carried out promptly and efficiently.

Table II—Influence of Various Excipients Plus Water on Stability of Sodium Ascorbate[a]

Excipient	Loss of Ascorbate, %
None	14.5
Cornstarch	16.4
Dicalcium phosphate anhydrous	17.7
Dicalcium phosphate dihydrate (milled)	19.0
Avicel	18.3
Silica gel	22.0
Tricalcium phosphate	25.3

[a] Excipient 80 mg. + 300 mg. sodium ascorbate + 11.6% water; storage for 3 days at 45°.

Table III—Recovery of Ascorbic Acid in Granulation and Tablets[a]

Lot No.	Vitamin E,[b] %	Excipient Added	Recovery Theoretical, % Granulation	Tablets
73-69/1	33	Dicalcium phosphate dihydrate	98	98
73-69/3	60	Same	100	100
73-69/5	60	Dicalcium phosphate anhydrous	100	100
73-69/6	60	Tricalcium phosphate	100	99

[a] Theoretical content: vitamin C = 77 mg.; vitamin E = 30 mg. [b] Adsorbate of *d,l*-α-tocopheryl acetate on silica gel.

Table IV—Stability of Na Ascorbate in Granulation with Vitamin E Containing Silica Gel

Storage Test	Na Ascorbate, Theoretical, % Lot 811-58	Lot 811-59
Initial	97	98
3 weeks at 25°	98	96
3 weeks at 45°	96	96
3 weeks at 55°	96	96

Table V—Stability of Ascorbic Acid in Coated Multivitamin Plus Iron Tablets

Storage Test	Ascorbic Acid, Theoretical, % Maintenance Formula[a]	Therapeutic Formula[b]
1 month at 55°	100	91
3 months at 45°	100	94
6 months at 37°	97	88
12 months at 25°	100	94

[a] Contains 30 mg. of *d,l*-α-tocopheryl acetate per tablet as a 33% adsorbate on silica gel. [b] Contains 30 mg. of *d,l*-α-tocopheryl acetate per tablet as a 60% adsorbate on silica gel; both formulas have a theoretical ascorbic acid content of 77 mg. per tablet.

Table VI—Physiological Availability of Ascorbic Acid from Tablets Containing Silica Gel—24-hr. Test

	Dose (about 450 mg.) Excreted, %				
			Multivitamin Tablets, Vitamin E, 30 mg.		
Subject	Standard Ascorbic Acid Dose 1	Dose 2	Lot No. 73-69/1 (33% E Adsorbate) Initial	3 mo./45°	Lot No. 73-69/3 (60% E Adsorbate) Initial
BM	45	28	33	32	25
MO	52	57	36	37	46
RG	24	34	41	36	51
JS	39	40	41	53	41
ED	38	36	43	46	39
Average	39.3		38.3	40.8	40.4
Availability ±*SE*, %			99 ± 9	103 ± 14	104 ± 13

Table VII—Physiological Availability of Ascorbic Acid from Tablets Containing Silica Gel—6-hr. Test

Subject	Dose (about 450 mg.) Excreted, %: Standard Ascorbic Acid	Lot No. 73-69/1 (33% E Adsorbate) Initial	Lot No. 73-69/1 (33% E Adsorbate) 3 mo./45°	Lot No. 73-69/3 (60% E Adsorbate) Initial
BM	28	27	27	17
MO	35	25	27	28
RG	18	26	26	37
JS	23	33	28	29
ED	26	29	28	24
Average	26.0	28.0	27.2	26.8
Availability ±*SE*, %		108 ± 13	105 ± 11	103 ± 17

Experiences with wet granulation formulations containing ascorbic acid or sodium ascorbate indicate that excellent stability can be achieved if the wet granulation is dried to about 10% moisture within a few hours and to the final, low moisture content within 24 hr.

Order of mixing of ingredients and especially the mode of addition of water can be important. The vitamin C stability may be influenced by the presence of adsorbents that bind water or soluble ingredients that serve as emulsifiers or influence the solubility or reactivity of vitamin C.

Availability Studies in Men—The results of bioavailability tests in men of ascorbic acid in tablets containing silica gel have been calculated on the basis of 24-hr. excretions of test doses. These results are summarized in Table VI. Both lots of tablets show complete bioavailability of the ascorbic acid, and this was not changed by storage for 3 months at 45°. In order to provide information on the question of whether or not silica gel reduces the rate of absorption of ascorbic acid *in vivo*, calculations of physiological availability also were made on the basis of urinary excretions in the first 6 hr. after dose. These data are given in Table VII. Again, the results show complete availability of ascorbic acid in all three tablet trials, indicating that the ascorbic acid is absorbed normally in the presence of silica gel.

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Interfacial Barriers in Interphase Transport II: Influence of Additives upon the Transport of Diethylphthalate Across the Hexadecane-Gelatin-Water Interface

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Abstract □ The authors recently described a novel method for investigating the effects of an interfacial barrier in interphase transport. The procedures, both theoretical and experimental, were applied to the study of the effects of an adsorbed gelatin at the hexadecane-water interface upon the transport of diethylphthalate between the two phases. The present paper describes the influences of surfactants, electrolyte type, and concentration upon the permeability coefficient for the interfacial barrier. Experiments were conducted as before, employing diethylphthalate as the solute. The transport data were analyzed by the physical model described earlier. The results showed that the two ionic surfactants, sodium lauryl sulfate and dodecylpyridinium chloride, markedly decreased (2 to 12 times) the interfacial barrier even at low concentration (0.001–0.10% in the stock emulsion). Furthermore, the analysis showed that neither the electrolyte type nor concentration influenced the permeability coefficients, although they significantly altered the interphase transport rates themselves by changing the partition coefficients. These findings are particularly interesting as they may represent types of nonspecific situations that give rise to important barriers in *in vivo* drug transport.

Keyphrases □ Transport, interphase—interfacial barriers □ Diethylphthalate transport—hexadecane-gelatin-water interface □ Electrolyte effect—diethylphthalate transport, hexadecane-gelatin-water interface □ Surfactant effect—diethylphthalate transport, hexadecane-gelatin-water interface □ Permeability coefficients, interfacial barriers—surfactant, electrolyte type, concentration effect.

Recent studies from these laboratories (1, 2) involving the use of a novel method for investigating interfacial barriers in interphase transport have shown that substances adsorbed at the oil-water interface may control the interphase transport rates of solutes. Gelatin adsorbed at the hexadecane-water interface has been shown (1) to give an interphase transport rate for diethylphthalate that is about 1×10^4 times slower than diffusion controlled. A significant reduction in the aqueous to lipid transport rate of cholesterol by an