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Systematic Error Associated with Apparatus 2 of the USP Dissolution Test IV: Effect of Air Dissolved in the Dissolution Medium

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Abstract □ Acceptable concentrations of gases in a medium are not well defined in USP dissolution tests. A sample of 10-mg prednisone tablets, known to be sensitive to dissolved gases, was tested with batches of purified water that contained different concentrations of air. The data suggest that results from Apparatus 2 can be influenced by the concentration of air in the dissolution medium unless the medium remains unsaturated with air for the duration of the test. The repeatability of means of six results was markedly improved when the air concentration in the medium was accurately controlled at the beginning of the test.

Keyphrases □ USP dissolution test—correlation of air concentration in medium to dissolution results, Apparatus 2 □ USP Apparatus 2—repeatability of dissolution results, prednisone tablets, effect of dissolved air in medium □ Prednisone—dissolution, USP Apparatus 2, effect of dissolved air in medium

The USP (1) recognizes that gases dissolved in the dissolution medium may influence dissolution test results. In such cases the analyst is directed to remove the dissolved gases before conducting the test; however, no guidance concerning acceptable gas concentrations is given. Since purified water is used to prepare dissolution media, the dissolved gases are those found in air. Complete removal of air from water is not easy; even if "air-free" water were available, air would begin to redissolve as soon as the water again contacted the atmosphere. Thus, one must assume that the air in the dissolution medium is to be reduced to a concentration that no longer influences the dissolution results—a concentration which can be determined only by experiment.

In addition to the USP calibrator tablets, this laboratory has used a sample of commercial 10-mg prednisone tablets, identified as Tablet 2 in previous papers of this series (2, 3), as a "performance standard" for Apparatus 2. Tablet 2, which was also used as a practice sample in a recent collaborative study (4), is very sensitive to excess air in the dissolution medium. A dissolution medium whose air concentration does not influence dissolution results was desired. Various methods for controlling the concentration of dissolved air were studied, and the data are presented in this paper.

BACKGROUND

The first USP dissolution test for prednisone tablets (5) specified the use of deaerated water. Deaerated water (6) is purified water that has been treated to reduce the content of dissolved air by suitable means, such as by boiling it vigorously for 5 min and cooling or by applying ultrasonic vibration. This laboratory interpreted (7) the specification to mean that the water could not be supersaturated with air at 37°, the temperature at which the dissolution test is conducted, because this condition might result in the gradual formation of bubbles on all immersed solid objects, including the product being tested. For several years, dissolution media were prepared from purified water which was boiled, cooled to room temperature, and used within a 24-hr period. A vacuum technique (3) was then developed and used. The two treatments appeared to give equivalent results; however, boiling was less convenient and was gradually replaced by the vacuum treatment.

When the dissolution test for prednisone tablets was revised (8), the specification for the medium was changed from deaerated water to purified water. The USP monograph on purified water does not specify the quantity of dissolved air allowed. Freshly prepared purified water obtained by distillation contains only a fraction of the air contained in freshly prepared purified water obtained by ion-exchange or by reverse osmosis. Dissolution results for certain products are substantially changed when purified water obtained by ion-exchange treatment is substituted for deaerated water (9). The USP later inserted the current specification for dissolved gases in the dissolution medium in the general chapter on dissolution.

EXPERIMENTAL

The test conditions were those used in a recent collaborative study (4) with these exceptions. The six-spindle dissolution drive[1] was not commercially available. The volumes of dissolution medium were measured in volumetric flasks[2]. The dissolution test system was allowed to equilibrate for only 1–2 min before the test was started. Purified water was

[1] Built by the Winchester Engineering and Analytical Center, Food and Drug Administration, Winchester, MA 01890.
[2] 500-ml flasks marked T.D./T.C.; Kimble Products, Vineland, NJ 08360.

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Table I—Dissolution Results (Percent of Label Claim) for Tablet 2 from Water Equilibrated [a] with Air at Various Temperatures and then Brought to 37°

Equilibration Temperature, °	Uncorrected Barometric Pressure, mm Hg	Mean[b]	SD[b]
	754	78.8[c]	3.5
23	754	71.4[d]	4.2
23	754	70.9[e]	5.6
25	754	61.4	3.5
27	754	57.6	3.8
29	754	50.3	3.3
31	744	46.3	1.4
33	745	41.8	2.7
35	745	40.4	2.7
37	748	39.0	1.6
39	748	38.5	2.8
41	748	37.5	1.3
43	746	38.2	1.9
45	741	37.2	2.2
47	740	39.8	2.3
47	—[f]	36.8	2.5
49	742	35.2	1.6
49	—	36.3	3.1

[a] For 45 min unless otherwise indicated. [b] $n = 6$. [c] Result obtained from deionized water at 23° that had not been equilibrated with air. [d] Result obtained from deionized water that had been equilibrated with air for 90 min. [e] Result obtained from deionized water that had been equilibrated with air for 30 min. [f] — Not recorded.

obtained by reverse osmosis. A 19-liter carboy was filled daily and served as a reservoir. Before the water was subjected to the treatments described below, portions were siphoned into 500-ml volumetric flasks. The contents of the flasks were heated to 38° and transferred to the dissolution vessels. Six dissolution results were obtained with this water.

Control of Air Concentration by Temperature—Approximately 800 ml of water was added to each of six 900-ml volumetric flasks which were then placed in a water bath at room temperature. A 4-mm o.d. glass tube was inserted to the bottom of each flask and connected through a manifold to an air pump that delivered air at a rate of 4 liters/min. Air was bubbled through the water for 90 min. The temperature of the water and the barometric pressure were recorded. Six 500-ml volumetric flasks were filled to volume with the treated water from the 900-ml flasks and placed in a holding bath at 38°. After 30 min the contents of the 500-ml flasks were transferred to the dissolution vessels. In this way the temperature of the treated water was kept between 36.5° and 37° at the beginning of the dissolution test. Six dissolution results were obtained for Tablet 2.

This procedure was repeated under the same experimental conditions except that air was bubbled through the water for 30 min. The results from six tablets agreed closely with those obtained when the water was equilibrated with air for 90 min. Thereafter, air was bubbled through the water for a minimum of 45 min.

The temperature of the water bath holding the 900-ml flasks was increased from 23° to 49° in increments of 2° for each test of six tablets. Additional data were collected by equilibrating the water with air in the same manner over a narrow range of temperatures from 37.4° to 38.4°.

Ten units of Tablet 2 were dissolved in 17 liters of water. The tablet excipients were allowed to settle, and the clear solution was siphoned into a container. Portions of this solution were equilibrated with air at 37.1° and transferred to the dissolution vessels for testing of Tablet 2. Additional portions were used in the determinative step as solvent for the standard solution and as reference for the spectrophotometer. The experiment was then repeated with a solution prepared by dissolving 20 units of Tablet 2 in 20 liters of water.

The air pump was then replaced with a cylinder of compressed nitrogen with minimum purity of 99.7%. The nitrogen was bubbled for 1 hr through 3500 ml of water heated to 37.0°. Portions of the water were siphoned into six 500-ml flasks that had been flushed with nitrogen. The flasks were placed in a water bath at 38° for 30 min, and the contents of the flasks were then transferred to dissolution vessels that also had been flushed with nitrogen. During dissolution, a nitrogen atmosphere was maintained over the water in the vessels.

Control of the Air Concentration by Pressure—Approximately 3500 ml of water was added to a 4-liter reagent bottle equipped with a two-hole rubber stopper. A long tube (6-mm i.d.) was inserted through one hole of the stopper so that its end was close to the bottom of the bottle. A short tube was inserted through the other hole so that the end of the tube was flush with the lower side of the stopper. The air pump was connected to the long tube with the stopper in place in the bottle, and air was bubbled up through the water. A piece of rubber tubing connected to the short tube in the stopper was partially closed, and a positive pressure was developed over the water in the bottle while the water was agitated by the air bubbles. The bottle was placed in a water bath at 37.6° for 1 hr, and a positive pressure of 50 mm Hg above that of the prevailing atmosphere was maintained over the water. The water was then siphoned into 500-ml flasks, and the flasks were returned to the water bath for 10 min before being emptied into the dissolution vessels. Six units of Tablet 2 were tested. The experiment was then repeated with water prepared by maintaining a positive pressure of 10 mm Hg over the water instead of 50 mm Hg.

To obtain pressures below ambient, the short tube in the stopper was connected to a vacuum, and air was drawn down through the long tube (now open to the atmosphere) and up through 3500 ml of water. The vacuum over the water was adjusted by partial closure of a piece of rubber tubing connected to the long tube. The water in the bottle was heated to 37.5° for 1 hr under a pressure ~30 mm Hg below that of the prevailing atmosphere. The water in the bottle was then siphoned into the 500-ml flasks, the flasks were reheated, and the contents of the flasks were then transferred to the dissolution vessels. Six dissolution results were obtained. The experiment was conducted again at the same pressure and then repeated with the pressure adjusted to 57 mm Hg below ambient. The experiment was then conducted at pressures of 145, 80, 70, and 50 mm Hg. Dissolution results obtained in this manner were compared with dissolution results obtained with the use of water as it was routinely prepared in this laboratory, *i.e.*, the water was sprayed into a 19-liter carboy at room temperature under a pressure of ~145 mm Hg.

RESULTS AND DISCUSSION

The saturated concentration of air in water in a container open to the atmosphere depends on the temperature of the water and the pressure of the air above the water. Ideally, the equilibrium concentration of a gas in a liquid is proportional to the pressure of the gas over the liquid at a constant temperature (Henry's Law). Thus, the concentration of air in

Table II—Dissolution Results (Percent of Label Claim) for Tablet 2 from Water Equilibrated with Gas [a] under Various Conditions

Equilibration Temperature, °	Uncorrected Barometric Pressure, mm Hg	Mean[b]	SD[b]	Equilibration Temperature, °	Pressure, mm Hg[c]	Mean[b]	SD[b]
37.5	750	39.3	2.7	37.6	AP +50	56.3	4.3
37.5	750	41.2	2.5	37.6	AP +10	39.9	1.8
38.4	—[d]	39.1	2.0	37.6	AP −30	38.8	2.7
37.6	747	38.8	2.6	37.5	AP −30	37.3	2.4
				38.0	AP −57	37.8	1.8
37.4	—	39.7	4.0	36.8	145	35.6	1.8
				36.4	80	35.0	3.6
37.1	749	37.1[e]	3.0	39.0	70	35.2	2.2
37.1	751	38.3[f]	3.0	37.6	50	35.1	2.5
				RT[g]	~145	35.2	2.1
37.0	749	38.7[h]	3.0	RT	~145	35.6	2.7
				RT	~145	35.3	1.5

[a] Air in all instances except where otherwise indicated. [b] $n = 6$. [c] AP = atmospheric pressure. [d] — Not recorded. [e] Medium contained 10 tablets dissolved in 17 liters. [f] Medium contained 20 tablets dissolved in 20 liters. [g] RT = medium was sprayed into a carboy under reduced pressure at room temperature. [h] Medium was treated with nitrogen at atmospheric pressure instead of air.

water can be controlled over a very wide range by changing the air pressure over the water. Although there is no general relationship between temperature and the concentration of a gas in a liquid, the equilibrium concentrations in water of the four major components of air decrease as the temperature of the water increases (10). These four components are nitrogen, oxygen, argon, and carbon dioxide (78.08, 20.95, 0.93, and 0.03% by volume, respectively). Combined, they make up 99.99% of the gases found in air (11). Because the solubility (v/v) of air in water under 1 atm at 100° is ~65% of the solubility of air at 25° (10), the concentration of air in water can be controlled only over a narrow range by changing the temperature of the water.

The dissolution results obtained for Tablet 2 when the air concentration in the water was controlled by temperature at prevailing atmospheric pressures are given in Table I and Fig. 1. The means of six results agreed closely when batches of water equilibrated with air for 30 and 90 min at room temperature were used; this agreement indicated that the water was being equilibrated in a repeatable manner. These means were significantly lower ($p < 0.025$) than the mean of six results obtained when freshly drawn deionized water that had not been equilibrated with air at room temperature was used. Thus, the equilibration treatment had a definite effect on the air concentration in the water.

Since the dissolution test was carried out at 37° in all cases, the dissolution media equilibrated at <37° became supersaturated with air when heated to 37° and those equilibrated at >37° became unsaturated with air when cooled to 37°. Because of the manipulation of the medium after the original equilibration, the degree of saturation at the beginning of the dissolution test was related to, but probably not equal to, the difference in the equilibrium concentration of air at the equilibration temperature and at 37°.

The relationship (Fig. 1) between the amount of prednisone dissolved from Tablet 2 and the air concentration in the medium may be explained in terms of sorption of air by the tableted formulation after tablet disintegration takes place. Normally, the tablet particles stay on the bottom of the dissolution vessel and collect into a cone of material during the dissolution test. Sorption of air decreases the density of the particles so that they may be agitated to a greater extent by the dissolution medium. The cone is disrupted by this agitation, and shielding of the inner particles is lessened. The sorption of air can also partially block the medium from contact with the particles. In this case the dissolution results decrease as the quantity of excess air increases. This effect has been observed with another tableted formulation (3) whose disintegrated particles are normally lifted and circulated by the dissolution medium. The decrease in dissolution results was small when air prevented contact of the medium with the particles. However, the increase in dissolution results was large when air bubbles increased the agitation of the particles.

The curve in Fig. 1 appears to approach a lower limit of 35% of label claim. This lower limit does not coincide with the equilibrium concentration of air in water at 37°, but is obtained from water that has a lower concentration of air. Additional tests of Tablet 2 with water equilibrated with air at temperatures near 37° confirmed that mean dissolution results between 39 and 41% of label claim were obtained (Table II). One explanation is that the equilibrium concentration of air in the water is shifted downward when the tablet is introduced to the medium. Thus, excess air from the medium would be available for sorption. This explanation is not well supported by the slightly lower results obtained when the tablets were introduced to equilibrated solutions that already contained some dissolved tablet material (Table II). The decrease in results is not large enough to account for the total difference. Another explanation is that the tablet particles are in "competition" with the water for the dissolved air. In this case the sorption process could be described as a true equilibrium of air between the water and the tablet particles.

To see if one or more of the minor components of air could be preferentially sorbed by Tablet 2, the test was conducted under a nitrogen atmosphere. The dissolution results obtained by this procedure compare closely with those obtained by equilibrating water with air (Table II). Preferential sorption was not indicated.

The dissolution results obtained when the equilibrium air concentration was controlled by pressure (Table II) follow a predictable pattern. Dissolution medium equilibrated at 37° with air at a positive pressure of 50 mm Hg above atmospheric pressure gave results that indicated that the medium was supersaturated with air. Dissolution medium equilibrated with air at a positive pressure of 10 mm Hg gave results that were equivalent to those obtained from dissolution medium equilibrated at atmospheric pressure. Media equilibrated at pressures of 30–57 mm Hg below atmospheric pressure gave results that were equivalent to or slightly below those obtained at atmospheric pressure. When the pressure over the water was reduced to ≤145 mm Hg, sufficient air was removed to cause the dissolution results (means of six) to level off between 35 and 36% of label claim. This is the lower limit that the curve in Fig. 1 appears to approach. Results between 35 and 36% of label claim were also obtained when the test was conducted with water that had been sprayed into a carboy under a pressure of 145 mm Hg at room temperature.

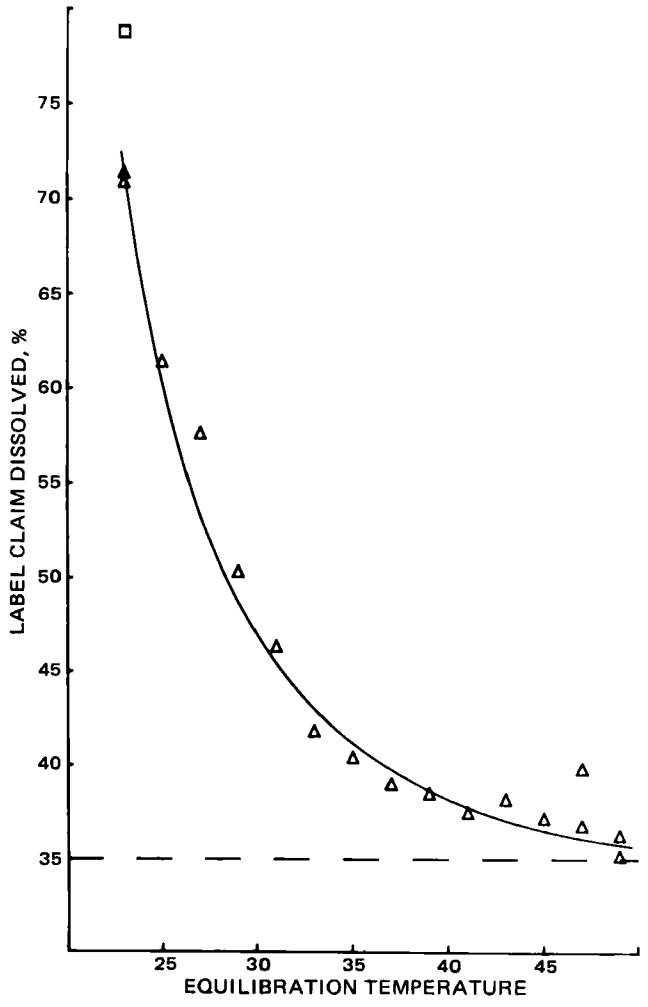

Figure 1—*Dissolution results for Tablet 2* versus *the temperature at which the dissolution medium was equilibrated with air; all results were obtained at 37°; (□) deionized water at room temperature.*

CONCLUSIONS

It is known that excess air from the dissolution medium can change the dissolution results obtained for certain tablets. The data presented in this paper show that results can be changed not only by air concentrations that exceed the saturation point in the dissolution medium but also by concentrations of air at the saturation point and below. To ensure that dissolved air does not influence dissolution results, the USP dissolution test should be conducted with dissolution media that contain different concentrations of air until a range of concentrations has been established that will not change the results. Although the concentration of air can be reduced to a low value at the beginning of a test, it is difficult to specify an air concentration below which no dissolution result could possibly be changed because of the variety of products subjected to the test, the conditions under which the test is made, and the differences in time requirements for the test. Nevertheless, repeatable dissolution results can be obtained by control of the air concentration. Thus, if the air concentration in the dissolution medium is repeatably controlled at the beginning of the test, the effect of the air on the solid dosage form should be reasonably constant from one laboratory to the next.

This laboratory has routinely reduced the air concentrations in the dissolution medium to low, but unknown, values by use of vacuum at room temperature. The medium thus treated has been considered adequate for dissolution tests within 8 hr of its preparation. When water prepared in this manner was used to test Tablet 2, an intralaboratory acceptance range of 35–43% of label claim was established for means of

six results[3]. From the data presented in this paper, a range of 35–41% of label claim is obtained from the use of water that contains air concentrations that do not exceed the saturation point of air in water at 37°. Thus, it should be possible to narrow the present acceptance range for these tablets, or at least to make the range more meaningful, if the air concentration in the water is controlled at the beginning of the test.

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[3] This acceptance range was calculated from data obtained by this laboratory.

Drug Interactions I: Detection of Inorganic Nitrite in Organic Nitrate Esters Under Acidic Conditions Simulating the Human Stomach

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Abstract □ Both unformulated (bulk) and formulated (drugs) organic nitrate esters (isosorbide dinitrate, nitroglycerin, and pentaerythritol tetranitrate) were studied in the presence and absence of hydrochloric acid to determine if they could be sources of nitrite (and therefore lead to nitrosamine formation) under acidic conditions similar to those found in the stomach. The presence and generation of nitrite ion was detected by a modification of the Griess reaction. Bulk isosorbide dinitrate and nitroglycerin were found to be contaminated with 13.8–121.4 μmoles of inorganic nitrite per mole of nitrate ester. In addition, in the presence of hydrochloric acid, these preparations generated 0.52–1.18 μmoles of inorganic nitrite/mole of nitrate ester/min. Unformulated nitroglycerin generated nitrite at a rate roughly twice that of isosorbide dinitrate. In contrast, no evidence for nitrite contamination or generation by pentaerythritol tetranitrate was found. Tablets and capsules of isosorbide dinitrate contained ~27–216 μmoles of nitrite/mole of nitrate ester and, in the presence of hydrochloric acid, generated an average of 0.55 μmole nitrite/min. For isosorbide dinitrate, this rate was similar for bulk and formulated drug. In comparison to isosorbide dinitrate, the amount of nitrite initially present in tablets and capsules of nitroglycerin varied more widely (~25–2290 μmoles nitrite/mole of nitrate ester), and in this case nitrite was generated at higher rates than unformulated drug averaging ~4.7 μmoles nitrite/mole of nitrate ester/min. Contrary to a literature report, we found that nitrate ion is not reduced to nitrite by hydrochloric acid (pH 1–3). These data suggest that the continuous production of nitrite ion from isosorbide dinitrate and nitroglycerin is due to the hydrolysis of nitrite ester impurities, a reaction known to be strongly catalyzed by the chloride ion. Although the generation of inorganic nitrite from organic nitrate esters is of interest, the low levels of nitrite produced are unlikely to lead to intragastric nitrosamine formation.

Keyphrases □ Isosorbide dinitrate—presence and generation of inorganic nitrite, simulated gastric conditions, Griess reaction □ Nitroglycerin—presence and generation of inorganic nitrite, simulated gastric conditions, Griess reaction □ Pentaerythritol tetranitrate—presence and generation of inorganic nitrite, simulated gastric conditions, Griess reaction □ Inorganic nitrite—presence in and generation from the nitrate esters isosorbide dinitrate, nitroglycerin, and pentaerythritol tetranitrate, simulated gastric conditions, Griess reaction

Organic nitrate esters such as nitroglycerin have been used for many years on an intermittent basis to relieve the symptoms of angina pectoris. Recently, organic nitrates have been used on a continuing basis to prevent anginal attacks; they are often ingested with other medications such as tranquilizers or are prescribed concomitantly with β-adrenergic blocking drugs such as propranolol hydrochloride for an additive pharmacological effect (1). Since these medications are taken for many years, often for the lifetime of the patient, it is important to evaluate the safety of simultaneous ingestion of such drugs (2).

There has been much discussion regarding the potential hazards of nitrosamines formed from therapeutic drugs during their passage through the GI tract (3, 4). In fact, in studies where animals are fed inorganic nitrite along with various drugs such as chlordiazepoxide, the formation of carcinogenic nitrosamines has been demonstrated (5). To form nitrosamines, an acidic milieu, the presence of amines, and a source of nitrite are required. The human stomach provides such an appropriate acidic environment (6), and most antihypertensive, β-adrenergic blocking, and tranquilizing drugs are secondary or tertiary amines. Nitrosamine formation can occur from a tertiary amine, but an oxidative cleavage to a secondary amine is required first (7). Nitrosation of secondary amines is a well-established reaction (7).

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