Stabilization of Oxygen-Sensitive Formulations via a Secondary Oxygen Scavenger

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The ability to stabilize dopamine hydrochloride formulations via the utilization of a secondary bag containing an antioxidant has been established. By physically separating the drug formulation from the stabilization solution, the chemistry of both solutions can be optimized independently so as to ensure product efficacy. Factors controlling the effectiveness of the proposed stabilization strategy are discussed in the context of actual experimental results. Such a strategy is effective in terms of protecting the formulation during processing/storage only if the product is stored in an oxygen barrier overpouch.

KEY WORDS: dopamine hydrochloride; oxygen-sensitive drugs; premixed products; product stabilization; antioxidants.

INTRODUCTION

Stabilization of oxygen-sensitive premixed formulations over the course of their shelf life is complicated and costly. Steps taken to minimize the formulation's exposure to oxygen during preparation, packaging, and storage include (i) direct addition of antioxidant, (ii) control of processing operations (e.g., use of nitrogen sparging to eliminate dissolved oxygen), (iii) development of stricter manufacturing tolerances (headspace volumes and composition, sterilization conditions), and (iv) use of oxygen-impermeable overpouches (e.g., foil). These steps impact the product's market acceptability and manufacturing cost.

An alternate approach for stabilizing oxygen-sensitive formulations involves the physical separation of the formulation's drug-containing and oxygen-controlling components. This product configuration consists of two compartments, one which contains the drug formulation and the other which contains the oxygen scavenger. This two-compartment configuration can take a variety of forms including

(a) a secondary O_2 scavenger container placed within the primary drug container (direct contact between the scavenger container and the formulation),
(b) a secondary O_2 scavenger container placed outside of the primary drug container with both containers being enclosed in an overpouch, and
(c) a single container with two side-by-side compartments, one for the formulation and one for the scavenger solution.

The ability to separate physically the drug formulation and the scavenger solution permits the optimization of each solution to perform its desired function and therefore maximize product stability.

This report describes the application of the proposed concept to the stabilization of formulations of dopamine hydrochloride, of which the solution phase chemistry is well-known.

MATERIALS AND METHODS

Materials

Dopamine hydrochloride was obtained from Knoll Fine Chemicals, Inc. (New York). Other materials used to prepare formulations, mobile phases, diluents, and other solutions were HPLC or reagent grade as appropriate. Water was obtained from a Barnstead (Boston, MA) NANOpure II water polishing system.

Preliminary Evaluation

Two formulations containing 1.6 mg/mL dopamine hydrochloride in 5% dextrose were prepared at pH 3.5; additionally, one formulation contained 50 mg/100 mL sodium bisulfite. The scavenger solution contained 500 mg/100 mL sodium bisulfite at pH 5.0. Test systems included glass bottles and 50-mL plastic bags made from a multilayer, oxygen-permeable material. Four types of test articles were made. Test article 1, the negative control, was the dopamine formulation without bisulfite. Replicates of test article 1 were prepared by adding 50 mL of the dopamine formulation without bisulfite to either the glass bottle or the bag and then sealing the system. Test article 2, the positive control, was the dopamine formulation with the bisulfite in it and replicates were prepared as per test article 1. Test article 3 was the alternate stabilization design with the scavenger container inside the primary formulation container. The scavenger container was prepared by adding 10 mL of the antioxidant solution to a 10-mL bag made from 1-mm-thick polypropylene. This scavenger bag was then placed inside containers (glass bottles or bags) containing 50 mL of the dopamine formulation without bisulfite. In the cases discussed so far, the bag test articles were placed into high-density polyethylene (HDPE) overpouches. Test article 4, applicable only for the bags, was a formulation bag and a scavenger bag outside one another but constrained as a system by a HDPE overpouch. The primary bag contained the dopamine formulation without bisulfite and the scavenger bag was made as per test article 3. In this case, both bags were independently sealed and placed into the same overpouch.

Replicate test articles of all four types were subjected to one, two, or three autoclave cycles (121°C for 45 min, 45-min cooldown to ambient temperature) and both the formulation and the scavenger solutions were chemically analyzed.

Stability Evaluation

Two compartment bags were made in the following manner. A single piece of 1-mm-thick polypropylene was placed between two pieces of the multilayer primary bag material. Three ends of the three-layer system were heat-

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sealed together, producing a two-compartment pouch (compartments separated by the polypropylene material). One compartment was filled with 40 mL of a drug formulation containing 1.6 mg/mL dopamine hydrochloride in 5% dextrose at pH 3.5. The other compartment was filled with 40 mL of a scavenger solution containing 7.5 mg/mL sodium bisulfite in a 0.08 *M* citrate buffer at pH 5.0. After filling, the test articles were closed by heat-sealing the final side and then placed in HDPE overpouches. Negative control samples were prepared by adding 40 mL of the dopamine formulation to single compartment bags made from the multilaminate material. Test articles were autoclaved (121°C for 45 min) and then stored at either 25, 45, 55, or 65°C for up to 13 weeks. At various times during storage, replicate test articles were chemically characterized.

Analysis

Dopamine concentration was determined in the primary formulation by HPLC via a USP XXI method (1). The HPLC system consisted of the following components: Kratos Analytical (Ramsey, NJ) Spectroflow 400 Solvent Delivery System and Model 757 UV Detector, Micromertics (Norcross, GA) Model 728 Autosampler, Scientific Services, Inc. (State College, PA) Model 235 electronically actuated injector, and Hewlett Packard (Avondale, PA) LAS data collection system. The concentration of bisulfite and sulfate in both the primary and the secondary solutions was determined by ion chromatography (2). The color of the dopamine formulations was determined with a Klett-Summerson Model 800-3 Colorimeter (Klett MFG Co., Inc., New York). Solution pH was also measured.

RESULTS AND DISCUSSION

General Chemistry

The generally accepted degradation mechanism for dopamine-like compounds is shown in Fig. 1 (3–5). The principal reactions include oxidation, cyclization of the aliphatic amino side chain, and polymerization to highly colored compounds. Degradation starts by oxidation to form a quinone, cyclization to a colored adrenochrome-type molecule and indoles, and finally, polymerization to high molecular weight melanin-like polymers (6). Dopamine stability is pH dependent and is greatest at pH's lower than 5 (6).

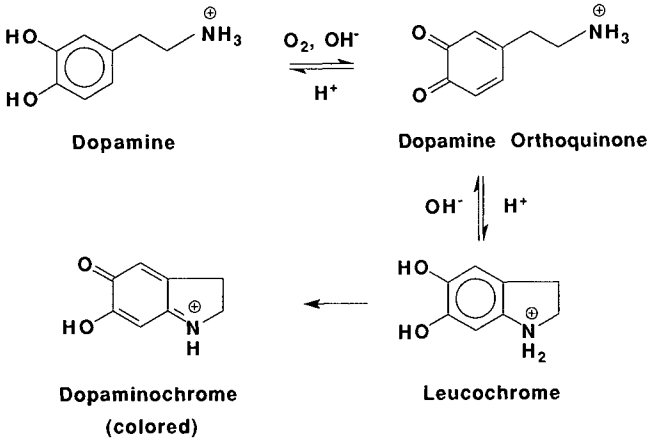

Fig. 1. Degradation pathway of dopamine hydrochloride.

Sodium bisulfite is used as a stabilizer (antioxidant) in dopamine formulations to prevent the formation of colored products. Sulfurous acid has pK_a's of 1.76 and 7.2 (7). The bisulfite ion reacts with oxygen to form the sulfate ion:

$$2HSO_3^- + O_2 \leftrightarrow 2SO_4^{-2} + 2H^+$$

At low pH, SO_2 (aq) outgasses from solution as SO_2 (g) under autoclave conditions (8).

Preliminary Evaluation

Chemical analysis of the test articles prepared in glass bottles is shown in Table I. While the dopamine loss is not large in any sample, the non-bisulfite-containing controls were already highly colored after the first autoclave cycle. As a general rule of thumb, solutions with a Klett number greater than 50 are considered to be inappropriate for use. Thus we observe that the product's utility is driven not by loss of drug potency but, rather, by the striking physical manifestation of a degradation product. Bisulfite-containing formulations remain essentially colorless, thus establishing

Table I. Composition of the Glass Bottle Test Articles[a]

(A) Composition of the drug formulation

Formulation	No. of cycles	Concentration[b] Dopamine	SO_3^{-2}	SO_4^{-2}	Klett no.
Control, no bisulfite	0	1.78	—[c]	—	0
	1	1.74	—	—	62
	2	1.65	—	—	160
	3	1.62	—	—	258
Control, bisulfite in formulation	0	1.70	3.88	0	0
	1	1.56	3.71	0.51	10
	2	1.64	3.33	0.59	22
	3	1.51	2.91	0.74	24
Scavenger bag in the bottle	0	1.78	0	0	0
	1	1.82	0.26	0.08	6
	2	1.55	0.24	0.15	10
	3	1.57	42	0.30	24

(B) Composition of the scavenger solution

Cycle no.	Concentration[d] SO_3^{-2}	SO_4^{-2}	S_T	pH
0	30.3	21.5	51.8	5.0
1	22.3	24.2	46.5	3.5
2	23.8	24.6	48.4	4.0
3	27.8	15.7	43.5	3.8

[a] Results represent the mean of two test articles per interval. For the drug, sulfite, and sulfate determinations, multiple analyses were performed for each test article.
[b] Dopamine concentration, mg/mL; others, mmol/L.
[c] Not present in the sample.
[d] In mmol/L. S_T is the total sulfur-containing species concentration in the scavenger solution.

the need for bisulfite somewhere in this product configuration. Comparison of the test articles which have bisulfite in either the formulation or the scavenger bag indicates little difference in performance for the two stabilization strategies. Thus, oxygen readily migrates into the scavenger bag under the autoclave conditions, thereby protecting the dopamine-containing formulation from oxidation. As the pH of the scavenger solution decreases (especially during the third autoclave cycle), some SO_2 (g) is produced in the scavenger solution at the elevated temperature and migrates into the primary drug formulation (SO_3^{-2} and SO_4^{-2} are both found in the primary formulation and total sulfur is lost from the scavenger solution). The pH decrease is the direct result of the antioxidant action of the bisulfite. One anticipates that this undesirable outgassing of SO_2 could be minimized by adding a buffer to the secondary solution to control its pH. Finally, it is noted that the bisulfite levels of all formulations remain high after three autoclave cycles and, thus, that these formulations could survive additional storage stress.

The glass bottle test article represents a closed system, somewhat similar to a premixed solution stored in an oxygen-impermeable (foil) overpouch. The plastic bag test articles, stored in an oxygen-permeable overpouch, represent an open system in that the total available pool of oxygen is unlimited. Chemical analysis of the solutions associated with the bag test articles are summarized in Table II. While the dopamine level in all test articles was essentially the same (all greater than 90% of the preparation value), the non-bisulfite-containing controls were highly colored (as was the case with the previous experiment). For the test articles containing the scavenger bag, sulfite ingress into the primary formulation during autoclaving was observed regardless of whether the scavenger bag had direct contact with the formulation or not. Again, the sulfite ingress results from outgassing of SO_2 (g) from the secondary solutions as its pH decreases because of the bisulfite oxidation.

The sulfite/sulfate species distribution in the scavenger bags indicates that in the open system the product's oxygen-scavenging ability is depleted after the third autoclave cycle. Thus additional storage of these test articles would result in eventual formulation discoloration. Similarly, the test articles with bisulfite dissolved in the formulation exhibit considerable bisulfite loss after the third autoclave cycle, although it appears that these test articles have a somewhat greater residual stability than do the scavenger bag-containing samples.

Table II. Composition of the Plastic Bag Test Articles, No Buffer in the Scavenger Solution

(A) Composition of the drug formulation[a]

Formulation	No. of cycles	Concentration[b] Dopamine	SO_3^{-2}	SO_4^{-2}	Klett no.
Control					
No bisulfite	0	1.60	—[c]	—	0
	1	1.53	—	—	74
	2	1.47	—	—	132
	3	1.44	—	—	198
Control					
With bisulfite	0	1.65	3.88	0	0
	1	1.52	2.68	1.48	15
	2	1.43	1.81	1.85	22
	3	1.48	1.10	2.05	35
Scavenger bag					
Inside primary bag	0	1.60	0	0	0
	1	1.52	0.39	0.13	11
	2	1.52	0.46	0.20	15
	3	1.46	0.46	0.26	22
Outside primary bag	0	1.60	0	0	0
	1	1.54	0.54	0.07	11
	2	1.52	0.88	0.13	12
	3	1.43	0.65	0.44	22

(B) Composition of the scavenger solution[d]

Cycle no.	Concentration[e] SO_3^{-2}	SO_4^{-2}	S_T	pH
Scavenger bag inside primary formulation container				
0	36.9	13.3	50.3	5.0
1	29.7	15.6	45.3	3.0
2	22.1	20.6	42.8	3.0
3	7.5	22.5	29.8	2.5
Scavenger bag outside primary formulation container				
0	36.9	13.3	50.3	5.0
1	17.5	24.4	41.9	2.4
2	10.6	26.1	36.6	2.4
3	2.3	30.4	32.7	2.4

[a] Results represent the mean of duplicate test articles per interval. For the drug, sulfite, and sulfate determinations, replicate analyses were performed for each test article.
[b] Dopamine concentration, mg/mL; others, mmol/L.
[c] Not present.
[d] Results represent the mean of duplicate test articles per interval. For the sulfite and sulfate determinations, replicate analyses were performed for each test article.
[e] In mmol/L. S_T is the total sulfur-containing species concentration in the scavenger solution.

Stability Study

The composition of the dopamine-containing portions of the stability test articles is shown in Table III. The non-bisulfite control exhibited unacceptable color after autoclaving, while the scavenger bag-containing test articles remained colorless. During the autoclave cycle, bisulfite was lost from the secondary solution by both oxidation and outgassing (into the primary solution). As a result of the oxidation process, the pH of the bisulfite solution decreased somewhat during the autoclave process.

The bisulfite in the secondary bags was completely depleted at the first analysis interval for all temperatures studied. The rate of oxygen ingress through the HDPE overpouch is so high that complete bisulfite loss occurs within 8 weeks of storage at 25°C and 2 weeks of storage at 65°C. Thus it was anticipated that at the later time intervals the test articles would develop a significant discoloration. While significant discoloration of the dopamine formulations was observed after 8 weeks of storage at 55 and 65°C, the rate of

Table III. Composition of the Bag Test Articles, Buffered Scavenger Solution

(A) Drug formulation

Storage temp. (°C)	Storage duration (weeks)	Concentration[a]			Klett no.
		Dopamine	SO_3^{-2}	SO_4^{-2}	
Control sample (no bisulfite)					
—	0[b]	1.54	—[c]	—[c]	120
Test articles with scavenger solution					
—	0[b]	1.57	0.37	ND[d]	12
25	8	1.59	ND	1.09	15
45	4	1.56	ND	1.23	7
	8	1.58	ND	1.50	12
	13	1.59	ND	1.70	29
55	2	1.56	ND	1.00	13
	4	1.60	ND	1.34	18
	8	1.59	ND	1.85	63
65	2	1.55	ND	1.15	14
	4	1.57	ND	2.19	66
	8	1.56	ND	2.25	102

(B) Scavenger solution

Storage temp. (°C)	Storage duration (weeks)	Concentration[e]			pH
		SO_3^{-2}	SO_4^{-2}	S_T	
—	0[f]	73.6	5.0	78.6	5.00
—	0[b]	56.2	14.8	71.0	4.66
25	8	ND	69.3	69.3	3.98
45	4	ND	72.2	72.2	3.98
55	2	ND	71.9	71.9	3.98
65	2	ND	70.5	70.5	3.97

[a] Dopamine concentration, mg/mL; other concentrations, mmol/L. Results are the mean of 4 determinations. The initial dopamine concentration (pre-autoclave) was 1.61 mg/L.
[b] Postautoclave results.
[c] Not present.
[d] Not detected.
[e] Concentrations are in mmol/L and represent the mean of four determinations.
[f] Initial preparation (preautoclave).

color formation was slower than for an unstabilized dopamine formulation at pH 3.5. Thus the dopamine formulation pH was measured during the later test intervals. Formulation pH dropped to approximately 2.6 at the 4-week and later test intervals, presumably due to the oxidation of bisulfite outgassed from the secondary solution during autoclaving. This pH drop was responsible for the enhanced dopamine stability observed.

In conclusion, sequestering an antioxidant in a secondary bag is an effective means of stabilizing dopamine HCL-containing formulations. Such a strategy minimizes the degree to which product manufacturing must be controlled and modified and provides the additional advantage that the antioxidant (or its degradation product) is not administered to the patient. As implemented in this study the strategy cannot stabilize a formulation packaged in an oxygen-permeable overpouch because the amount of bisulfite required over the desired product shelf life (18 months at ambient temperature) is prohibitively large.

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