Stability of Phenylpropanolamine Hydrochloride in Liquid Formulations Containing Sugars

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ABSTRACT □ Stability studies with a decongestant syrup formulation containing phenylpropanolamine hydrochloride in a sugar vehicle indicated a loss of phenylpropanolamine hydrochloride. To ascertain the biological significance of this indicated chemical loss, the degraded formulation was administered to human volunteers and the urinary excretion of phenylpropanolamine hydrochloride was determined. The excretion and chemical assay patterns were in good agreement, indicating that the sugar vehicle was both chemically and biologically incompatible with phenylpropanolamine hydrochloride. A control formulation made with phenylpropanolamine hydrochloride in a sorbitol vehicle showed good chemical stability and urinary excretion patterns. Further studies showed chemical losses with phenylpropanolamine hydrochloride in the presence of fructose, dextrose, and 5-(hydroxymethyl)-2-furaldehyde but not with levulinic acid. Possible mechanisms for the sugar–phenylpropanolamine hydrochloride interaction are discussed.

Keyphrases □ Phenylpropanolamine hydrochloride—stability in liquid formulations containing sugars □ Stability—of phenylpropanolamine hydrochloride in liquid formulations containing sugars □ Adrenergic agents—phenylpropanolamine hydrochloride, stability in liquid formulations containing sugars

While formulating a decongestant syrup containing phenylpropanolamine hydrochloride, it was observed that the stability pattern indicated a loss of phenylpropanolamine hydrochloride. Initial formulations contained sucrose with either corn syrup or an invert sugar composition in the vehicle.

Since it was surmised that the sugars had interacted with the phenylpropanolamine hydrochloride, stability experiments were done with phenylpropanolamine hydrochloride in aqueous vehicles containing dextrose, fructose, and sucrose–corn syrup, with a sorbitol vehicle as the control. In addition, 5-(hydroxymethyl)-2-furaldehyde and levulinic acid were tested since these compounds are produced from the hydrolysis of dextrose and fructose.

To ascertain the biological significance of the indicated chemical loss of phenylpropanolamine hydrochloride, a urinary excretion study was performed using the initial formulation in the sucrose–corn syrup vehicle. After storage at 5 and 55° for 1 month, comparisons were made with a formulation containing sorbitol.

EXPERIMENTAL

Analytical Methods—Initially, the phenylpropanolamine hydrochloride[1] in the sucrose[2]–corn syrup[3] formulations was determined using the ion-pair–methyl orange procedure (1, 2). For subsequent experiments using dextrose[4], fructose[4], 5-(hydroxymethyl)-2-furaldehyde[5], and levulinic acid[5], phenylpropanolamine hydrochloride was determined by the ninhydrin procedure of Burke *et al.* (3). A periodate oxidation method (4) was used for the determination of phenylpropanolamine hydrochloride in urine.

Urinary Excretion Tests—All preparations were given orally to nonfasted subjects. Pooled urine samples were collected for 24 hr prior to dosage for measurements of blank excretion values. After the morning dosage, urine was collected for 24 hr. Urinary phenylpropanolamine hydrochloride was determined by a reported method (4).

In agreement with earlier results (4), the present experiments indicated that 90–100% of a 50-mg phenylpropanolamine hydrochloride dose was excreted by humans in the urine. With the 15–25-mg doses administered in the present experiment, only 70–80% was excreted. A relatively constant amount of phenylpropanolamine hydrochloride apparently is metabolized and not recovered in the urine (*e.g.*, 10% of a 50-mg dose equals 5 mg, which is 20% of a 25-mg dose).

Table I—Effect of Sucrose and Corn Syrup on Phenylpropanolamine Hydrochloride Stability

	Formula			
	1	2	3	4
Phenylpropanolamine hydrochloride, % (w/v)	0.15	0.15	0.15	0.15
Sucrose, % (w/v)	40	—	—	40
Corn syrup, % (w/v)	—	40	—	—
Sorbitol, % (w/v)	—	—	40	—
Initial pH	6.0	6.0	5.9	4.5
Retention of phenylpropanolamine hydrochloride (3 days/70°), %	93	54	97	67

RESULTS

The assay data in Table I show that the phenylpropanolamine hydrochloride losses in the presence of sucrose and corn syrup were significant after 3 days at 70°. The sucrose effect was much greater at pH 4.5 than at pH 6. Practically no change occurred with sorbitol.

The data in Table II compare the effect of dextrose and fructose (the hydrolytic cleavage products of sucrose) on phenylpropanolamine hydrochloride stability at pH 4, 6, and 7. As pH increased, the degradation rate and degree of color development increased. At pH 4, there was only a slight rise in pH, whereas pH decreased at pH 6 and 7. Precipitation was noted in all samples after 1 week of storage at 70° and was visibly greater at pH 6 and 7 than at pH 4. The magnitude of these changes was significantly greater for dextrose than for fructose. Formula 5, containing 5 mg of phenylpropanolamine hydrochloride/ml, 35% sucrose, 15% corn syrup, 11% ethanol, and 20% propylene glycol, was the formulation used for the human excretion studies reported in Table III.

Table IV shows the effects of 5-(hydroxymethyl)-2-furaldehyde and levulinic acid on phenylpropanolamine hydrochloride stability at pH 4, 6, and 7 and on sorbitol at pH 6. Sorbitol had no effect, and levulinic acid had no significant effect. In contrast, there was a loss of phenylpropanolamine hydrochloride from interaction with 5-(hydroxymethyl)-2-furaldehyde. While no pH changes occurred, the solution darkened and a dark precipitate developed. Recovery of this precipitate by centrifugation indicated that it was water insoluble, methanol soluble, and very slowly soluble in chloroform. By comparison, precipitates from dextrose–phenylpropanolamine hydrochloride solutions were water insoluble and methanol soluble but appeared to be chloroform insoluble.

Table III shows the urinary excretion data from formulations containing phenylpropanolamine hydrochloride. The first formulation (A-5°) initially contained 24.4 mg of phenylpropanolamine hydrochloride/5 ml in the sugar vehicle already described. After 1 month at 55° (A-55°), ~38% of the phenylpropanolamine hydrochloride was lost with 15.2 mg/5 ml retained. Formulation B, which assayed 26.8 mg of phenylpropanolamine hydrochloride/10 ml, was made in a sorbitol vehicle and was stable.

In all three cases, the amount of phenylpropanolamine hydrochloride recovered in the 24-hr urine samples was in proportion to the amount of "undegraded" phenylpropanolamine hydrochloride administered, or ~71–78% of the dose.

[1] NF XIV, Ganes Chemical Works.
[2] USP XIX.
[3] Globe 1132, Corn Products Division, CPC International
[4] Anhydrous, Aldrich Chemical Co.
[5] Ninety-nine percent, Aldrich Chemical Co.

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Table II—Effect of Sucrose–Corn Syrup, Dextrose, Fructose, and pH on Phenylpropanolamine Hydrochloride Stability

	Formula						
	5	6	7	8	9	10	11
Ingredients[a]							
Phenylpropanolamine hydrochloride, % (w/v)	0.5	1.0	1.0	1.0	1.0	1.0	1.0
Sucrose, % (w/v)	35	—	—	—	—	—	—
Corn syrup, % (w/v)	15	—	—	—	—	—	—
Dextrose, % (w/v)	—	10	10	10	—	—	—
Fructose, % (w/v)	—	—	—	—	10	10	10
Buffer type	Citrate	Citate	Phosphate	Phosphate	Citrate	Phosphate	Phosphate
Normality	0.29	0.25	0.28	0.23	0.25	0.28	0.23
Physical stability							
Changes in optical density after 1 week at 70°[b]	—	0.414	1.745	1.832	0.2	0.85	1.438
Chemical stability							
pH							
Initial	6	4	6	7	4	6	7
1 week/70°	—	4.2	4.55	4.35	4.1	5.2	5.3
4 weeks/55°	5.25	4.2	4.8	4.6	4.2	5.7	6.05
Percent retention of phenylpropanolamine hydrochloride after							
1 week/70°	—	84	55	45	91	71	63
1 month/55°	65	87	57	43	87	79	73
16 weeks/45°	—	93	64	55	—	84	77
3.5 months/45°	65	—	—	—	—	—	—
3.5 months/37°	85	—	—	—	—	—	—
Percent loss of phenylpropanolamine hydrochloride per week at room temperature[c]	0.26	0.09	0.62	1.37	0.07	0.17	0.46

[a] The vehicles also contained 20% propylene glycol, 11% ethanol, 5% glycerin, and distilled water. [b] Measured at 315 nm using the 5° sample as a blank. Changes were due to formation of colored degradation products. [c] Calculated from losses observed at elevated temperatures using Arrhenius plots.

Table III—Assay and Urinary Excretion of Phenylpropanolamine Hydrochloride

Formulation	Phenylpropanolamine Hydrochloride Assay	24-hr Urinary Excretion Pattern			
		Percent Phenylpropanolamine Retained	Amount Given, ml	Amount Excreted, mg	Percent of Retained Dose Excreted[a]
A-5° (sucrose–corn syrup vehicle, Formula 1 of Table I), 1 month 5°	24.4 mg/5 ml	100	5	19	78
A-55° (same as A-5°), 1 month 55°	15.2 mg/5 ml	62	5	10.8	71
B (sorbital vehicle)	26.8 mg/10 ml	100	10	19	71

[a] Five subjects.

Table IV—Effect of 5-(Hydroxymethyl)-2-furaldehyde, Sorbitol, and Levulinic Acid on Phenylpropanolamine Hydrochloride Stability

	Formula								
	12	13	14	15	16	17	18	19	20
Phenylpropanolamine hydrochloride, % (w/v)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
5-(Hydroxymethyl)-2-furaldehyde, % (w/v)	0.142	0.142	0.142	0.142	—	—	—	—	—
Sorbitol, % (w/v)	—	—	—	—	10	—	—	—	—
Levulinic acid	—	—	—	—	—	0.18	0.18	0.18	0.18
Buffer type	Phosphate	Citrate	Phosphate	Phosphate	Phosphate	Phosphate	Citrate	Phosphate	Phosphate
Normality	0.42	0.25	0.28	0.23	0.28	0.43	0.34	0.3	0.39
Initial[a] pH	6	4	6	7	6	5.65	4	6	7
Percent retention after									
7 days 70°	79	95	100	100	101	—	100	100	100
14 days 70°	—	85	76	97.5	—	—	—	95	—
4 weeks 55°	—	93	87	87	98	100	—	—	98
3.5 months 55°	85	—	—	—	—	—	—	—	—

[a] No significant changes observed after storage at elevated temperatures.

DISCUSSION

The analytical data reported here indicate that there was an interaction of phenylpropanolamine hydrochloride with sugars containing aldose or ketose functional groups or with 5-(hydroxymethyl)-2-furaldehyde, a degradation product of dextrose or fructose. Levulinic acid, another possible degradation product, was unreactive. Sucrose *per se* is not expected to be reactive with phenylpropanolamine hydrochloride until hydrolysis to carbonyl-containing cleavage products occurs as a function of time, temperature, and pH of the vehicle. As expected, there was no chemical loss of phenylpropanolamine hydrochloride in sorbitol solutions.

If phenylpropanolamine hydrochloride combines with the carbonyl groups of the aldose or ketose sugars or with a reactive carbonyl degradation product, the resulting interaction product may or may not undergo biological transformation after ingestion to release phenylpropanolamine hydrochloride. The urinary excretion data, although limited, appear to suggest that the interaction product does not revert to free phenylpropanolamine hydrochloride after ingestion. If degraded phenylpropanolamine hydrochloride were converted *in vivo* to free phenylpropanolamine hydrochloride, the group ingesting this dose (containing 62% of the amount found in A-5°, the refrigerated control) would have excreted ~19 mg of phenylpropanolamine hydrochloride rather than 10.8 mg.

Possible Interaction Mechanisms—While the present study did not attempt to elucidate the nature of the interaction of phenylpropanol-

amine hydrochloride with the aldose or ketose sugars, the literature was reviewed with regard to the various possibilities concerning this interaction.

Oxazolidine Formation—β-Amino alcohols, such as ephedrine (5–8), pseudoephedrine (5, 7–9), phenylpropanolamine (9–11), and phenylephrine (12, 13), can form oxazolidines with aliphatic and aromatic aldehydes and ketones. The elimination of water from the reaction between the carbonyl group and the vicinal amino and hydroxyl groups of the amino alcohol is usually accomplished by azeotropic distillation (9, 10) or with a dehydrating agent (13) but can occur in an aqueous medium (11). Oxazolidine formation depends on thermodynamic and steric factors. In some cases, the product may exist as a mobile tautomeric system with the corresponding Schiff base (9, 11).

Stability of oxazolidines to hydrolysis is reportedly variable (6, 9). However, oxazolidines usually can be cleaved by heating with acids to yield the amino alcohol and the carbonyl compound (5, 6, 11, 13). The oxazolidine from the interaction of ephedrine and benzaldehyde was marketed in an oily nasal inhalant and was presumably active topically (6). Oxazolidine formation from interaction of sympathomimetic β-amino alcohols with aldose and ketose sugars or with 5-(hydroxymethyl)-2-furaldehyde has not been reported. 5-(Hydroxymethyl)-2-furaldehyde is readily formed by the acid-catalyzed hydrolysis of glucose or fructose (14) or by heating glucose in water (15).

Tetrahydroisoquinoline Formation—Cyclization of norphenylephrine [1-(3-hydroxyphenyl)-2-amino-ethanol] with various carbonyl compounds (*via* a Pictet–Spengler type of reaction but requiring no acidic catalyst) was reported (16) to yield tetrahydroisoquinolines and not oxazolidines as previously reported. The reaction probably proceeds *via* a Schiff base intermediate and appears to be characteristic of β-amino alcohols with a phenolic hydroxyl *para* to the site of cyclization. Similarly, tetrahydroisoquinolines can be formed in sucrose-coated tablets of norphenylephrine (17) from 5-(hydroxymethyl)-2-furaldehyde and levulinic acid, products of the thermal decomposition of sucrose.

The formation of isoquinolines from interaction of phenylpropanolamine and aldose or ketose sugars or their decomposition products has not been reported. This possibility seems remote since a phenolic group in the benzene nucleus is apparently required to promote cyclization.

Browning (Carbonyl–Amine) Reactions—Nonenzymic browning reactions involving the carbonyl group of aldose or ketose sugars with primary or secondary amines are well known (18, 19). The browning of lactose, galactose, dextrose, dextrates, and 5-(hydroxymethyl)-2-furaldehyde with *dl*-amphetamine, its *N*-methyl derivatives, and *d*-amphetamine was studied extensively (20–26). The carbonyl group of the sugar or 5-(hydroxymethyl)-2-furaldehyde and the amine presumably form colored products *via* a Schiff base-type reaction or by formation of glycosyl amines, *N*-glycosides, or certain compounds formed by Amadori rearrangement (27). Isoglucosamines (amino ketones, not Schiff base), if formed by rearrangement, would be expected to be resistant to hydrolysis unlike the glycosamines, most of which easily darken and undergo further decomposition (27).

No experimental data indicate which of the foregoing interaction possibilities is the principal one involved in the phenylpropanolamine hydrochloride–sugar interaction. It is felt that Schiff base formation probably occurred under the test condition with further rearrangement(s) to produce a compound(s) that did not revert to free phenylpropanolamine hydrochloride either *in vivo* or *in vitro*.

REFERENCES

(1) T. Higuchi and J. I. Bodin, "Pharmaceutical Analysis," Interscience, New York, N.Y., 1961, pp. 413–418.

(2) K. A. Connors, "Textbook on Pharmaceutical Analysis," 2nd ed., Wiley–Interscience, New York, N.Y., 1961, p. 514.

(3) D. Burke, V. S. Venturella, and B. Z. Senkowski, *J. Pharm. Sci.*, **50,** 232 (1961).

(4) K. R. Heimlich, D. R. MacDonnell, T. L. Flanagan, and P. D. O'Brien, *ibid.*, **50,** 232 (1961).

(5) E. H. Stuart, U.S. pats. 1,749,361 and 1,749,452 (1930).

(6) L. H. Welch, *J. Assoc. Off. Ag. Chem.*, **30,** 467 (1947).

(7) L. Neelakantan, *J. Org. Chem.*, **36,** 2253, 2256 (1971).

(8) L. Neelakantan and J. A. Molin-Case, *ibid.*, **36,** 2761 (1971).

(9) E. Bergmann, *Chem. Rev.*, **53,** 310 (1953).

(10) M. Senkus, *J. Am. Chem. Soc.*, **67,** 1515 (1945).

(11) L. Neelakantan and H. Kostenbauder, *J. Pharm. Sci.*, **65,** 740 (1976).

(12) H. Bretschneider, *Monatsch.*, **77,** 117 (1947).

(13) S. Yuan and N. Bodor, *J. Pharm. Sci.*, **65,** 929 (1976).

(14) M. L. Wolfram, R. D. Schuetz, and L. Cavalieri, *J. Am. Chem. Soc.*, **70,** 514 (1948).

(15) B. Scallet and J. Gardner, *ibid.*, **67,** 1934 (1945).

(16) T. Kametani, K. Fukumoto, H. Agui, H. Yagi, K. Kigasawa, H. Sugahara, M. Hiragi, T. Hayasaka, and H. Ishimaru, *J. Chem. Soc. C*, **1968,** 112.

(17) K. Kigazawa, N. Ikari, K. Ohkubo, H. Iimura, and S. Haga, *J. Pharm. Soc., Jpn.*, **93,** 925 (1973).

(18) W. Pigman, "The Carbohydrates: Chemistry, Biochemistry, Physiology," Academic, New York, N.Y., 1957, pp. 406, 412.

(19) R. S. Shallenberger and G. G. Birch, "Sugar Chemistry," AVI Publishing, West Port, Conn., 1975, p. 169.

(20) R. A. Castello and A. M. Mattocks, *J. Pharm. Sci.*, **51,** 106 (1962).

(21) C. A. Brownley and L. Lachman, *ibid.*, **53,** 452 (1964).

(22) R. N. Duvall, K. T. Koshy, and J. W. Pyles, *ibid.*, **54,** 607 (1965).

(23) R. N. Duvall, K. T. Koshy, and R. E. Dashiell, *ibid.*, **54,** 1196 (1965).

(24) K. T. Koshy, R. N. Duvall, A. E. Troup, and J. W. Pyles, *ibid.*, **54,** 549 (1965).

(25) S. M. Blaug and W. Huang, *ibid.*, **61,** 1770 (1972).

(26) *Ibid.*, **63,** 1415 (1974).

(27) J. Stanek, "The Monosaccharides," Academic, New York, N.Y., 1963, pp. 451, 454, 456.

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