Complexation of Procainamide with Dextrose

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Abstract □ The percent of procainamide complexed with dextrose was determined to be directly related to the concentration per mole fraction of dextrose in the solution. The complexation process was reversible and did not proceed at lower pH (~1.5). The rate of formation of complex was dependent on the initial pH value of the solution and the pH decreased as the concentration of the complex increased. The increase in the concentration of procainamide did not change the equilibrium concentration of the complex. The addition of sodium chloride or edetate disodium did not alter the rate of formation of the complex or its equilibrium concentration. The addition of hydrochloric acid prevented the formation of the complex and on adding hydrochloric acid after the formation of the complex, procainamide was completely freed.

Keyphrases □ Dextrose—complexation of procainamide □ Procainamide—complexation, with dextrose □ Complexation—procainamide with dextrose

Procainamide (I) is often mixed with 0.9% NaCl or 5% dextrose solution in water. The mixture is usually administered by continuous intravenous infusion for the treatment of certain cardiovascular diseases.

Procainamide is stable when mixed with sodium chloride solution (1) but in 5% dextrose solution, the stability is doubtful (1, 2). For example, one such solution lost ~12% of potency after 24 hr of storage (1). It has been predicted that procainamide may be forming a reversible association complex with dextrose (2). Procainamide is considered unusually stable towards hydrolysis in the pH range of 2–7 (3) even at higher temperatures.

The separation of procainamide from *p*-aminobenzoic acid (the major product of degradation) using high-pressure liquid chromatography (HPLC) has been reported (2). The other product of degradation, diethylethylenediamine, did not absorb light to record a peak in the chromatogram. An additional peak from the interaction of dextrose and I was observed in the chromatogram.

The purpose of this investigation was to study the complexation of procainamide with dextrose. The study was conducted using an HPLC method similar to that previously reported (2) in the literature.

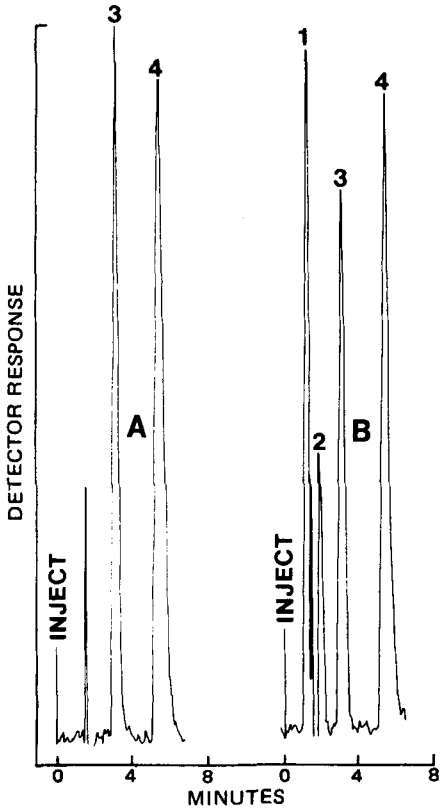

Figure 1—*Sample chromatograms: Peaks 1–4 are from* p-*aminobenzoic acid, complex of I with dextrose, free procainamide and methapyrilene (internal standard), respectively. Chromatogram A is from a standard solution and B from a 27-hr-old solution of procainamide (Solution 9 in Table I) to which 10.0 μg/ml of* p-*aminobenzoic acid was added before final dilution. For chromatographic conditions, see text.*

EXPERIMENTAL

Chemicals and Reagents—All chemicals and reagents were USP, NF, or American Chemical Society grade and were used as received. Procainamide hydrochloride[1] was used without further purification.

Apparatus—A high-pressure liquid chromatograph[2] equipped with a multiple wavelength detector[3], a recorder[4], and a digital integrator[5] was used.

Column—A semipolar column[6] (30 cm long × 4-mm i.d.) consisting of a monomolecular layer of cyanopropylsilane permanently bonded to silica gel was used.

Chromatographic Conditions—The mobile phase was 40% (v/v) acetonitrile in water containing 0.02 *M* ammonium acetate (pH ~7)[7], and

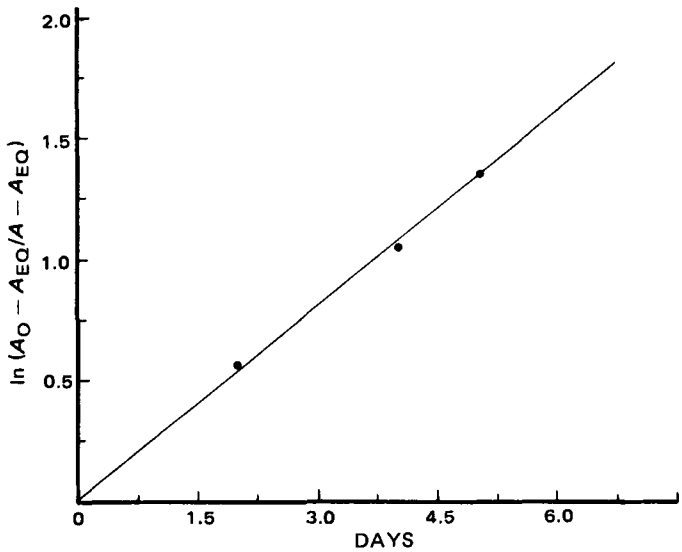

Figure 2—*A plot of complexation of dextrose with procainamide (Solution 6 in Table I) using the equation for a reversible reaction.*

[1] E. R. Squibb & Sons, Princeton, N.J.
[2] ALC 202 equipped with U6K universal injector, Waters Associates, Milford, Mass.
[3] Schoeffel SF770, Westwood, N.J.
[4] Omniscribe 1513-12, Houston Instruments, Austin, Tex.
[5] Autolab minigrator, Spectra Physics, Santa Clara, Calif.
[6] μBondapak/CN, Waters Associates, Milford, Mass.
[7] Zeromatic (SS-3) pH meter, Beckman, Fullerton, Calif.

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Table I—Procainamide Hydrochloride Aqueous Solutions Prepared

Solution Number	Procainamide HCl, %	Dextrose, %	Other Ingredients (Final Conc)
1	0.1	0	—
2	0.1	0.2[a]	0.01 *N* HCl
3	0.1	0.2[a]	—
4	0.1	0.2[a]	0.45% NaCl[b]
5	0.1	1.0[a]	—
6	0.1	2.0[a]	—
7	0.1	3.0[a]	—
8	0.1	4.0[a]	—
9	0.1	5.0[a]	—
10	0.2	5.0[a]	—
11	0.4	5.0[a]	—
12	0.1	3.0[a]	0.18% NaCl[b]
13	0.1	3.0[a]	0.36% NaCl[b]
14	0.1	3.0[a]	0.54% NaCl[b]
15	0.1	3.0[a]	0.01 *N* HCl
16	0.1	0	0.5 *M* KH_2PO_4
17	0.1	1.0[a]	as above
18	0.1	2.0[a]	as above
19	0.2	2.0[a]	as above
20	0.1	3.0[a]	as above
21	0.1	5.0[a]	0.05% edetate disodium
22	0.1	5.0[c]	—
23	0.1	6.5[c]	—
24	0.1	8.0[c]	—
25	0.1	11.0[c]	—

[a] From dextrose 5% in water, Travenol Laboratories, Deerfield, Ill. [b] From sodium chloride, 0.9% in water, Travenol Laboratories, Deerfield, Ill. [c] From dextrose anhydrous, USP, J. T. Baker Chemical Co., Phillipsburg, N.J.

the flow rate was 2.0 ml/min. The detector was set at 280 nm (wavelength of maximum absorption), sensitivity was 0.04, the temperature was ambient, and the chart speed was 30.5 cm/hr.

Preparation of Solutions—The stock solutions of procainamide hydrochloride (1.0 mg/ml) and the internal standard, methapyrilene hydrochloride (5.0 mg/ml) in water, were prepared daily. A standard solution was prepared by transferring a 1.5-ml quantity of the stock solution of I and a 4.0-ml quantity of the stock solution of methapyrilene hydrochloride (II) to a 100-ml volumetric flask and then diluting with water to volume.

All solutions prepared for investigations of procainamide–dextrose

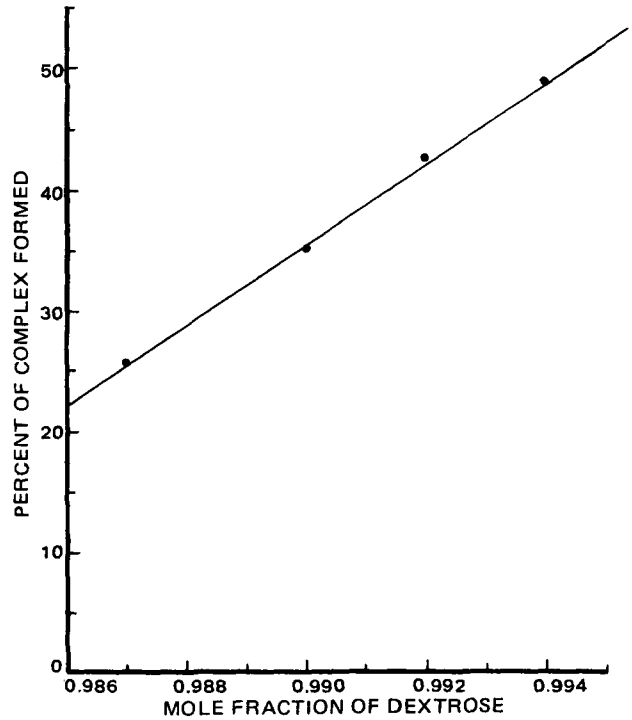

Figure 3—*A plot of mole fraction of dextrose* versus *percent of the complex formed after 4 days of storage (Solutions 22–25, Table I).*

Table II—Assay Results

Solution Number[a]	Percent of Label Claim Remaining, days							
	1	2	3	4	5	6	7	11
1	—	—	99.8	—	—	—	—	—
2	—	—	100.2	—	—	—	—	—
3	—	—	99.6	—	—	—	—	—
4	—	—	99.9	—	—	—	—	—
5	—	94.3	—	91.5	88.1	85.6	85.6	—
6	—	86.9	—	79.6	76.7	68.7	69.2	—
7	—	80.2	—	66.7	60.8	59.0	59.3	—
8	—	73.5	—	53.8	49.3	47.2	48.2	—
9	—	64.3	—	48.3	42.3	42.5	42.7	42.5
10	—	65.3	—	49.1	43.5	—	—	—
11	—	64.6	—	51.5	42.7	—	—	—
12	—	—	—	65.9	—	60.1	—	—
13	—	—	—	67.4	—	58.2	—	—
14	—	—	—	65.1	—	60.1	—	—
15	—	99.2	—	100.4	—	99.8	99.7	—
16	100.2	99.8	—	100.4	—	—	—	—
17	78.9	78.6	—	79.0	—	—	—	—
18	60.6	61.2	—	61.4	—	—	—	—
19	62.0	60.8	—	62.2	—	—	—	—
20	49.3	50.2	—	51.2	—	—	—	—
21	—	65.2	—	48.8	—	—	—	—
22	97.3	—	—	74.2	—	—	—	—
23	96.4	—	—	64.8	—	—	—	—
24	94.8	—	—	57.4	—	—	—	—
25	91.3	—	—	52.2	—	—	—	—

[a] For composition of the solution, see Table I.

complex are reported in Table I. All were prepared using a simple solution method. The solutions were assayed (see procedure following) and transferred to amber-colored bottles[8] and stored at room temperature (24 ±1°). They were reassayed after appropriate intervals and pH values were also determined.

Preparation of Assay Solution—All the solutions were diluted with water to contain 15.0 μg/ml of I (based on the label claim) and 200.0 μg/ml of II (internal standard).

Assay Procedure—A 20.0-μl aliquot of the assay solution was injected into the chromatograph using the described conditions. For comparison, an identical volume of the standard solution was injected after the assay solution eluted.

Calculations—The results were calculated using:

$$\frac{Ph_a}{Ph_s} \times 100 = \text{Percent of the label claim}$$

Where Ph_a is the ratio of the peak heights of procainamide and methapyrilene of the assay solution and Ph_s that of the standard solution of an identical concentration.

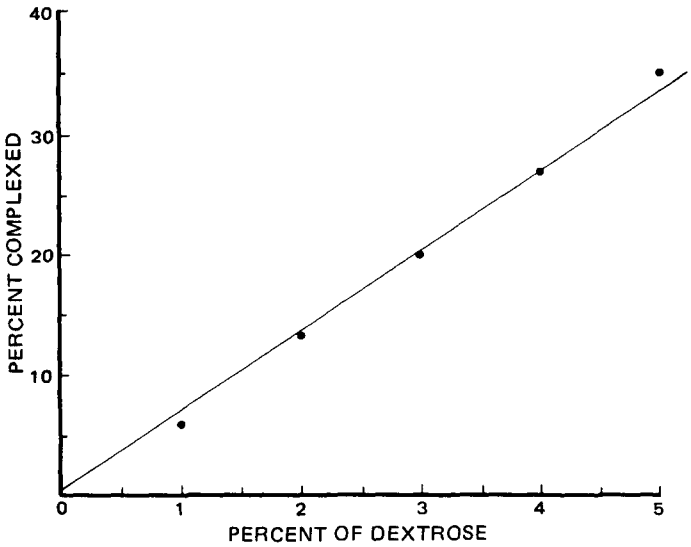

Figure 4—*A plot of dextrose concentration* versus *percent of procainamide–dextrose complex formed after 2 days of storage (Solutions 5–9 Table I).*

[8] Brockway Glass Co., Brockway, Pa.

Table III—pH Values of Solutions

Solution Number[a]	pH Value Remaining[b]						
	0	1	2	3	4	8	11
1	5.6	—	—	5.6	—	—	—
2	1.2	—	—	1.4	—	—	—
3	5.3	—	—	5.1	—	—	—
4	5.4	—	—	5.1	—	—	—
5	5.0	—	4.8	—	4.5	4.0	—
6	4.6	—	4.4	—	3.8	3.7	—
7	4.6	—	4.4	—	3.6	3.4	—
8	4.6	—	4.4	—	3.1	3.0	—
9	4.6	—	4.4	—	3.2	3.0	2.9
10	4.6	—	4.4	—	3.2	3.0	—
11	4.6	—	4.4	—	3.2	3.0	—
12	4.6	—	4.4	—	3.6	3.4	—
13	4.6	—	4.5	—	3.7	3.4	—
14	4.9	—	4.5	—	3.7	3.4	—
15	1.4	—	1.3	—	1.3	1.3	—
16	4.4	—	4.4	—	4.5	—	—
17	4.4	—	4.4	—	3.9	—	—
18	4.4	—	4.4	—	3.8	—	—
19	4.4	—	4.4	—	3.8	—	—
20	4.4	—	4.4	—	3.8	—	—
21	4.8	—	4.5	—	—	—	—
22	6.0	6.0	—	—	5.0	—	—
23	6.0	6.0	—	—	5.0	—	—
24	6.0	6.0	—	—	5.0	—	—
25	6.0	6.0	—	—	5.2	—	—

[a] For composition of the solution, see Table I. [b] Accuracy ± 0.1.

Other Experiments—A 1.5-ml quantity of a 4-day-old solution in 3% dextrose (Solution 7 in Table I) was mixed with 2 ml of ~5 *N* HCl. The mixture was allowed to stand for ~20 min, then 4.0 ml of the stock solution of the internal standard was added, the mixture was brought to volume (100.0 ml) with water, and assayed.

In another experiment, 50.0 mg of *p*-aminobenzoic acid was dissolved in enough 5% aqueous solution of dextrose to make 50.0 ml. This solution was assayed after 0-, 2-, and 4-day intervals to determine if there was a reaction between dextrose and *p*-aminobenzoic acid. The assay was conducted using the HPLC method described previously since *p*-aminobenzoic acid separated (Peak 1 in Fig. 1) from I, II, and the complex between I and dextrose. Before injecting, the solution was diluted to a ratio of 1.0:100 with water. The concentration of *p*-aminobenzoic acid was determined by comparing the peak heights of the assay solution with a standard solution of an identical concentration (10.0 μg/ml).

RESULTS AND DISCUSSION

The results indicated that procainamide and dextrose formed a reversible complex (Fig. 2). This complexation could be completely prevented by adding 0.01 *N* HCl (Solution 15 in Table II). Furthermore, procainamide could be completely released from the complex by treating with hydrochloric acid (see Other Experiments). On treatment with ~5 *N* HCl, all of the procainamide was freed from the complex formed over a 4-day period in 3% aqueous solution of dextrose (Solution 7 in Table II). Preliminary investigations indicated that aged solutions of dextrose with procainamide did not interfere with the assay procedure for procainamide and its complex.

The rate of complex formation was dependent on the initial pH value of the solution. For example, in Solutions 22–25 that had higher initial pH values (Table III), the formation of complex was slower than in Solutions 5–8 (initial pH value 4.6). A direct comparison was possible between Solutions 9 and 22, since both contained 5% dextrose. In Solution 9, a commercial sterile solution was used (Table I) and in Solution 22, anhydrous dextrose was used. The sterile solution of dextrose had a lower pH (~4) *versus* a fresh solution made from the powder (pH ~6). The pH values after adding 0.1% of procainamide hydrochloride were 4.6 and 6 for Solutions 9 and 22, respectively. It is well-known (4) that solutions of dextrose become acidic on autoclaving.

A new set of solutions (16–20 in Table I) were prepared containing 0.05 *M* phosphate buffer. The rate of complexation in these solutions was slightly higher than those without buffer (Table II) which might be an experimental error. There is also a possibility of interaction of phosphates with dextrose (5), which is under investigation.

The pH values of the solutions on storage were decreasing (Table III), which is probably due to release of hydrogen ions upon the formation of complex. The concentration of the complex formed was directly related to the mole ratio of dextrose (Fig. 3) in the solution. However, at lower concentrations of dextrose (~2–4%), especially after 2 days of storage, dextrose concentrations were directly related (Fig. 4) to the concentrations of the complex.

Keeping the dextrose concentration constant and increasing the concentration of procainamide did not affect the rate of formation of complex or the equilibrium concentration (Solutions 9–11, Table II). Also, the increase in the ionic strength with sodium chloride did not alter the equilibrium or rate of formation of the complex (Solutions 7, 12–14, Table II). The addition of 0.05% edetate disodium did not affect the process of complexation (Solutions 9 and 21, Table II).

The process of complexation (a reversible reaction, Fig. 2) is slow and the time required for the equilibrium to establish is dependent on the initial pH of the solution (see above and data in Table II). The equilibrium concentration itself depended on the initial concentration of dextrose and pH of the solution.

For Solution 6, the K, k_f, and k_r values for the complexation (reversible process) were estimated to be 0.456, 0.0858, and 0.188 day^{-1}, respectively.

None of the solutions showed any peak in the chromatogram due to *p*-aminobenzoic acid even with a complex concentration of 50%. This compound could be easily separated from I, II, and the complex (Fig. 1). Moreover, in a separate experiment (see Other Experiments), it was determined that *p*-aminobenzoic acid did not form a complex with dextrose. Letting *p*-aminobenzoic acid stand in the presence of dextrose (≤4 days) did not change its concentration or peak(s) in the chromatogram.

Since all of procainamide could be released from the complex (see above) by treating with hydrochloric acid (see Other Experiments), the drug probably did not decompose. The complex itself may be as active as procainamide[9]. If so, there may be no stability problem on mixing I with dextrose. Since blood also contains dextrose, the implications of this process in biosystems requires further investigation.

The possibility of formation of 5-hydroxymethylfurfural rather than the complex is ruled out since it is a reversible reaction (Fig. 2), the hydrolysis of glucose to 5-hydroxymethylfurfural cannot be reversed (6), and the hydrolysis of glucose to 5-hydroxymethylfurfural usually occurs at higher temperatures (no heat was used in these studies).

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[9] This needs to be proven.