Stability of Crystalline Sodium Penicillin G

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A study of solution stability of crystalline preparations of penicillin G indicated that pH and potency dropped rapidly when such solutions (5,000 units/ml.) were stored at either 15° or 24°C.; this behavior is in sharp contrast to the greater stability of earlier, cruder preparations. As this was probably due to the removal during the crystalline process of certain impurities having buffering capacity, a study was initiated to find some substance which would protect the solutions of crystalline penicillin without detriment to the stability of the dry powder when stored in open containers at 100°C.

TABLE 1

Buffer	5,000 units/ml. solution at 24°C.—potency losses*							Solid at 100°C.
	Initial pH	4 days		5 days		7 days		6 days
		% loss	pH	% loss	pH	% loss	pH	% loss
Sodium phosphate	7.2			12.7	6.95			98.6†
" bicarbonate	7.0			33.5	5.1			41.0†
" oleate	7.0			12.4	6.5			100.0†
" acetate	6.7			13.2	5.7			42.0†
" borate	6.7			65.5	4.6			100.0†
" succinate	6.6			21.2	5.8			97.2†
" tartrate	6.6			50.8	4.8			100.0†
" citrate	7.0			8.5	6.5			100.0†
" sulfanilate	5.2	78.4	4.9					7.8
" phthalate	6.1	35.1	4.9			73.7	4.8	1.4
" mandelate	6.1	71.0	4.5					6.3
" benzoate	5.7	60.4	4.6					8.1
" nicotinate	6.0	27.2	5.0			62.1	4.8	10.4
" salicylate	5.9	83.4	4.5					19.6
" sulfamate	6.0	85.7	4.6					18.0
" tartrate	6.1	71.1	4.6					23.9
" gluconate	6.0	81.4	4.5					20.0
" succinate	6.4	7.4	5.3			26.2	5.2	16.8

* Based on values obtained by the spectrophotometric method outlined by R. M. Herriott (*J. biol. Chem.*, 1946, **164**, 725–736).

† Samples were dried in such a manner as to yield amorphous mixtures; the others are all crystalline.

Table 1 indicates the results obtained using various buffers to the extent of 5 per cent by weight of the crystalline sodium penicillin co-dried to yield in some cases a crystalline mixture and in others an amorphous mixture, depending upon the procedure employed in the drying process.

For a more detailed study we chose sodium bicarbonate, sodium acetate, sodium succinate, and sodium citrate. The effect of temperature of storage, buffer concentrations, and starting batch material are clearly indicated in Table 2.

It appears that about 5 per cent by weight of penicillin of the buffers studied will protect solutions of crystalline penicillin for at least 4 days at 24°C. and for at least 7 days at 15°C. Those solutions which contain 1 per cent or less buffer exhibit lack of stability comparable to unbuffered solutions, losing over 50 per cent at 24°C. in 4 days.

When applied to plant batches, the average loss in potency[1] of solutions stored at 15°C. for 7 days for 10 unbuffered batches is 26 per cent, while the average loss of potency in these batches buffered with sodium citrate under the same conditions of storage is only 1 per cent.

[1] Based on values obtained by the iodometric method outlined by Joseph F. Alicino (*Ind. eng. Chem.* (Anal. ed.), 1946, **18**, 619).

TABLE 2

Buffer	Batch No.	Conc. buffer (%)	5,000 units/ml. solution—potency losses					Solid at 100°C.
			Initial pH	4 days—24°C.		7 days—15°C.		6 days
				% loss	pH	% loss	pH	% loss
Sodium bicarbonate	1	4.5	7.4	9.3	6.7	3.2	7.2	0.6
		2.25	7.1	10.8	5.8	9.7	6.1	0.1
		0.90	6.8	31.4	4.9	6.8	5.7	0.3
		0.43	6.4	58.9	4.5	15.2	4.8	2.1
Sodium acetate	1	10.0	6.4	3.4	5.7	0.3	5.9	5.0
		5.0	6.5	4.0	5.7	5.3	5.7	8.8
		1.0	6.3	43.4	4.7	7.4	5.3	6.8
		0.1	6.1	76.0	4.4	38.5	4.8	6.0
" succinate	1	10.0	6.3	4.2	5.9	1.7	5.6	3.5
		5.0	6.2	3.4	5.4	11.3	5.7	6.0
		1.0	6.0	62.0	4.6	19.3	5.3	7.0
		0.1	5.8	83.0	4.6	40.5	4.9	7.1
" citrate	1	10.0	6.6	+4.3	5.7	+1.6	6.4	0.3
		5.0	6.6	+6.3	5.3	2.1	6.1	+0.1
		1.0	6.5	65.1	4.4	2.2	5.2	5.9
		0.1	6.2	81.0	4.4	43.9	4.7	8.0
" citrate	2	5.0	6.5	6.2	5.2	+2.3	5.9	4.4
	3	5.0	6.6	+4.0	5.7	+1.3	6.1	14.6
	4	5.0	6.7	+10.1	5.6	1.3	6.0	1.1
	5	5.0	6.5	13.5	4.7	+0.3	5.8	2.4
	6	5.0	6.6	2.3	5.6	2.7	6.2	15.4

From the results obtained it would appear that the decomposition of sodium penicillin in solution is autocatalytic and that, once decomposition starts, it is difficult to control. The rate of inactivation increases rapidly with increases in temperature.

An Operative Approach to the Treatment of *Schistosomiasis mansoni* Infections

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With the finding of a new method for the simple removal of adult *Sch. mansoni* from experimentally infected animals (*1*), a series of interesting observations were made, among which were the following:

(1) The use of heparin simplified the removal of the adult worms from the blood vessels of the experimentally infected animal.

(2) The number of adult worms recovered from the portal vein proper was far greater in animals heparinized before death than in those that had not been heparinized.

(3) A striking number of adult *Sch. mansoni* could be recovered from the livers of animals heparinized before death,