THE STABILITY OF PENICILLIN IN SUGAR-COATED TABLETS

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SODIUM and potassium benzylpenicillin tablets for oral use have been available for several years. These penicillin salts have an unpleasant bitter taste, difficult to disguise in compressed products; the obvious solution is a sugar-coated product, but this has not until recently made its appearance.

Soluble benzylpenicillin salts are known to be unstable in the presence of moisture: the importance of controlling the free moisture in penicillin tablets has been stressed by the Ministry of Health in presenting data collected from British penicillin tablet manufacturers[1]. It appears to have been assumed that tablets of soluble penicillin could not be sugar-coated by the conventional coating process, and the new British process of compression-coating, an anhydrous method, has been announced as scoring a success by making possible for the first time the manufacture of sugar-coated penicillin tablets[2].

Experiments carried out in these laboratories have demonstrated the feasibility of sugar-coating soluble penicillin tablets by the conventional process and the stability studies being reported here show that such tablets are at least as stable as uncoated ones over a 2-year period. Further, we have evidence that in temperate climates the sugar-coating gives protection to the tablet against careless handling after dispensing from the original container.

Some fears might be expressed that the sugar-coating could, by delaying the disintegration or solution time of the tablet, interfere with the absorption and utilisation of the penicillin. Maximum utilisation of oral penicillin is said to occur in the duodenum[3,4] and Boger and Beatty[5] have stressed the importance of a short solution time for oral penicillin tablets. We have shown that our pan coated penicillin tablets dissolve completely in well under 15 minutes *in vitro*, but we also considered it desirable to show by clinical tests on human volunteers that the penicillin in sugar-coated tablets was as readily absorbed as from uncoated ones.

PART I

Stability studies.

All assays were made by crushing the tablet, dissolving it in sterile solution of standard *p*H 7 and determining the penicillin content biologically with *Bacillus subtilis*. Each result reported is the mean of 3 separate assays.

Free moisture content was determined by finely powdering 5 tablets and determining the weight loss of 1 g. of the well-mixed powder after it had reached constant weight in a vacuum desiccator over phosphorus pentoxide.

In the first series of experiments a number of small batches of 200,000 unit potassium benzylpenicillin tablets (2000 to 5000 per batch) were

sugar-coated in a normal sugar-coating pan. In the first few batches the free moisture content of the tablets was above 1 per cent. and the coating split away from the tablet after a few weeks, but in subsequent experiments, when the free moisture content was low, satisfactory coating was obtained. These tablets were packed in glass screw-capped bottles fitted with a waxed cork shive. Samples were stored in a cupboard in a part of the laboratory reserved for keeping samples at room temperature and also in a cabinet thermostatically controlled at 38° C. The temperature of the laboratory throughout the test varied from 18° to 24° C.

TABLE I

STABILITY OF POTASSIUM PENICILLIN IN SUGAR-COATED TABLETS IN CLOSED CONTAINERS AT 38° C.—1ST SERIES

Units per tablet

Experimental batch	Free moisture, per cent.	Original assay	1 Month	2 Months	3 Months
E	1·2	207,000	183,000	Discontinued, coating split	
F	0·3	194,000	201,000	205,000	200,000
G	0·3	201,000	203,000	212,000	196,000
H	0·4	200,000	202,000	203,000	200,000
I	0·45	190,000	190,000	200,000	188,000

TABLE II

STABILITY OF POTASSIUM PENICILLIN IN SUGAR-COATED TABLETS IN CLOSED CONTAINERS AT ROOM TEMPERATURE (18° TO 24° C.)—1ST SERIES

Units per tablet

Experimental batch	Free moisture, per cent.	Original assay	1 Month	3 Months	2 Years
E	1·2	207,000	185,000	185,000	174,000*
F	0·3	194,000	200,000	201,000	203,000
G	0·3	201,000	212,000	208,000	208,000
H	0·4	200,000	202,000	197,000	199,000
I	0·45	190,000	191,000	208,000	197,000

* Many of the tablets of batch E had split coatings after 3 months at room temperature.

Periodic assays for penicillin were carried out on the tablets. Table I gives the results obtained on 5 batches of tablets stored for 3 months at 38° C. Table II gives the results obtained on the same 5 batches of tablets stored for 2 years at room temperature. Batch E with a free moisture content over 1 per cent. showed signs of instability after a few weeks at 38° C.; even at room temperature the coating on some of the tablets in this batch began to split off after about 3 months. The tablets of the remaining 4 batches remained unchanged throughout the tests.

The successful sugar-coating of these experimental batches of 200,000 unit potassium benzylpenicillin tablets prompted us to extend the investigation to sodium benzylpenicillin, to cover potencies other than 200,000 unit and to scale up the process to batches of production size. Table III gives the results of stability tests on this second series stored for 2 months at 38° C. The coating and stability have so far proved satisfactory.

It is well known that uncoated soluble-penicillin tablets dispensed from

bulk packs into unsuitable containers will deteriorate rapidly under adverse climatic conditions. Exposure to the atmosphere of a room in the Home Counties does not necessarily produce the adverse conditions such tablets might meet in coastal or other humid areas of the British Isles. A standard condition of 25° C. and 75 per cent. relative humidity

TABLE III

STABILITY OF POTASSIUM AND SODIUM PENICILLIN IN SUGAR-COATED TABLETS STORED IN CLOSED CONTAINERS AT 38° C.—2ND SERIES

Units per tablet

Batch and salt	Free-moisture, per cent.	Original assay	1 Month	2 Months
1 Potassium	0·6	49,000	48,000	44,000
2 ,,	0·6	202,000	200,000	199,000
3 ,,	0·7	211,000	213,000	203,000
4 ,,	0·8	420,000	424,000	418,000
5 ,,	0·6	510,000	527,000	535,000
6 Sodium	0·6	50,000	54,000	51,000
7 ,,	0·6	205,000	203,000	202,000
8 ,,	0·8	207,000	200,000	202,000
9 ,,	0·8	529,000	510,000	519,000

was therefore adopted for testing the effect of exposure to the atmosphere under fairly severe conditions of humidity. The tablets were exposed on open Petri dishes in an air-tight cabinet maintaining these conditions over a saturated salt solution. Uncoated tablets of penicillin from production batches were used as controls.

Table IV gives the result of this test and shows that the effective life of uncoated penicillin tablets under these conditions does not exceed some 14 days, whereas the sugar-coated tablets are perfectly stable for at least 2 months. The experiment is continuing.

An experiment exposing the tablet to a relative humidity of 90 per cent.

TABLE IV

STABILITY OF PENICILLIN IN TABLETS EXPOSED IN AN OPEN PETRI DISH TO A RELATIVE HUMIDITY OF 75 PER CENT. AT 25° C.—UNCOATED PENICILLIN TABLETS USED AS CONTROLS

Batch, sugar coated	Initial		After 7 days		After 14 days		After 21 days		After 1 month		After 2 months	
	Assay	Free moisture, per cent.	Assay and appearance	Free moisture, per cent.	Assay and appearance	Free moisture, per cent.	Assay and appearance	Free moisture, per cent.	Assay and appearance	Free moisture, per cent.	Assay and appearance	Free moisture, per cent.
2	202,000	0·6	206,000	—	203,000	0·5	207,000	—	214,000	0·6	189,000	0·6
3	211,000	0·7	209,000	—	199,000	1·0	208,000	—	208,000	0·6	199,500	0·8
4	420,000	0·8	430,000	—	430,000	0·9	418,000	—	430,000	0·8	420,000	0·9
Uncoated penicillin tablets used as controls												
Uncoated X	200,000	0·7	196,000 No change in appearance	2·1	190,000 Off white tablets. Few yellow speckles	3·5	Tablets damp yellow shapeless mass, impossible to assay					
Y	415,000	0·9	401,000 No change in appearance	2·4	366,000 Darker tablets. Speckled surface	3·1	357,000 Speckling heavier. Tablets yellow		Sticky mass, impossible to assay			

at 38° C. (extreme tropical conditions) resulted after 3 days in an unassayable sticky mass from the sugar-coated tablets: a similar state of the uncoated tablets was produced in 16 to 24 hours.

PART II

Penicillin blood levels and urinary excretion in human volunteers.

In view of the claimed need for oral penicillin tablets to dissolve rapidly[4], the disintegration time for our sugar-coated tablets was determined. Batch H had a solution time of 5½ minutes when first prepared; this time was found to be substantially unaltered 2 years later. The

TABLE V

BLOOD LEVELS AND URINARY EXCRETION OF PENICILLIN AFTER ORAL ADMINISTRATION OF 2 × 200,000 I.U. TABLETS TO HUMAN VOLUNTEERS.

Tablets	Volunteer	Penicillin blood levels (I.U./ml.) at: ½ hour	1 hour	2 hours	4 hours	6 hours	Total units excreted in 6 hours
Sugar-coated penicillin tablets	1	0·25	0·55	0·12	<0·03	0	excluded*
	2	0·55	0·51	0·22	<0·03	0	23,700
	3	1·14	0·73	0·30	<0·03	0·08	40,600
	4	2·33	0·97	0·31	0·09	0·09	66,600
	5	0·56	0·32	0·08	<0·03	0	20,000
	6	0·73	0·73	0·28	0·03	0	33,600
	7	0·88	1·20	0·57	0·26	0·02	52,400
	8	2·05	2·11	0·56	0·11	0·02	123,900
	9	1·35	1·28	0·75	0·11	0	58,100
	10	1·27	0·73	0·22	<0·03	0	41,900
	Average	1·11	0·91	0·34	0·06	0·02	51,200
Uncoated penicillin tablets	A	0·50	1·04	0·56	0·12	0·03	58,200
	B	0·85	0·25	0·58	0·10	0·04	91,100
	C	1·25	0·95	0·25	0·06	0	68,200
	D	0·98	1·45	0·42	0·10	0·05	51,300
	E	1·48	1·00	0·53	0·06	0	22,200
	F	1·30	1·00	0·28	<0·03	0	31,200
	G	2·00	0·74	0·18	<0·03	0	80,600
	H	0·87	0·89	0·21	0·03	0	54,300
	I	0·55	0·91	0·28	<0·03	0	31,200
	J	0·94	0·82	0·50	0·13	0·06	91,200
	Average	1·07	0·91	0·38	0·06	0·02	57,960

0 indicates less than 0·02 I.U./ml.
* some loss of sample probable.

solution time for batches 3 to 11 (second series) were found to range from 6 to 11 minutes. The average solution time of production batches of uncoated penicillin tablets is 6 minutes: the results on our sugar-coated tablets indicate no appreciable increase in the time of solution of the tablets due to the sugar-coating.

Besides these *in vitro* solubility tests, an experiment was carried out to study the absorption of penicillin from the sugar-coated tablets by human volunteers, as shown by urinary excretion and blood levels.

10 volunteers were each given 2 × 200,000 unit pan sugar-coated penicillin tablets. Blood samples were taken from each at ½, 1, 2, 4 and 6 hours after administration. These were assayed for penicillin by plate bioassay with *Sarcina lutea* (strain CPI–1001) as test organism.* Each

* Standard methods U.S. Food and Drug Administration Laboratories, Washington, U.S.A.

volunteer collected all urine passed during the 6 hours of the test and the bulked sample from each was titrated for penicillin in a similar manner.

The results, shown in Table V and compared with those of a similar experiment on uncoated tablets, show no significant differences between penicillin blood levels or excretion after administration of the two types of tablet.

SUMMARY

1. Figures have been presented to show the stability for 3 months at 38° C. and at room temperature (18° to 24° C.) for 2 years of penicillin tablets sugar-coated by conventional pan methods.

2. Such sugar-coated penicillin tablets have been shown to withstand a relative humidity of 75 per cent. at 25° C. for at least 2 months.

3. The results presented show that conventional sugar-coating does not interfere with the *in vivo* absorption of the penicillin from the tablets.

The authors are indebted to Mr. L. J. Hamilton, Mr. B. I. Helliwell, and Mr. W. R. Long for analytical assistance and recording of stability figures.

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DISCUSSION

The paper was presented by MR. F. TAYLOR.

DR. D. C. GARRATT (Nottingham) suggested that details of the methods of coating should have been given.

MR. F. BERRY (Nottingham) said that the keeping properties and the stability of the tablets depended largely on the method of manufacture. What was the nature of the diluent used? Was the process moist granulation or dry granulation? What was the nature of any subcoating used?

MR. R. LEVIN (Liverpool) asked whether there had been any variation from batch to batch in the formulation of the tablets. Were the authors satisfied that their method of estimating free moisture was satisfactory? By crushing 5 tablets and mixing them it seemed that they exposed the tablets to the atmosphere, and changes in the free moisture condition may have taken place. Had they attempted to estimate the moisture in an uncrushed tablet so as to compare the figures with those after crushing? Could they give additional information on the free moisture after a period of storage? It would be interesting to see whether a relationship existed between moisture picked up and loss of penicillin content. From the blood level figures it seemed that an unsatisfactory level existed after four hours. Was that so?

MR. A. W. BULL (Nottingham) said it was an established fact that if penicillin tablets could be prepared in conditions of low humidity and low moisture content, and if they were placed into sealed containers, then stability would be achieved. The solution to the problem seemed to lie in the subcoating of the tablet, and it would have been valuable if details of the subcoating techniques—the moisture protection techniques—had been included in the paper.

MR. D. STEPHENSON (Dartford) said that batches would have to be much more rigorously examined when prepared by this method than by methods where the use of moisture could be entirely avoided. It seemed unlikely that there would ever be a large use for sugar-coated penicillin tablets because children, who were the principal consumers of penicillin oral tablets, could not be persuaded to swallow them whole.

MR. TAYLOR, in reply, said that the tablets were coated by someone skilled in the art of sugar-coating. In regard to batch variation, so far as sugar-coating was concerned there was no variation but there was variation in some batches in the basic formula of the uncoated tablet. This did not seem to affect the problem, which was whether such tablets could be sugar-coated satisfactorily. The method for determining moisture content was the best they could devise and appeared to give reasonably reproducible results, but he agreed it was a difficult problem. With a sugar-coated tablet, a determination of the loss by storing over phosphorus pentoxide meant very little. It was assumed from the humidity studies that the water did not go through the coating to the penicillin tablet, and it therefore seemed unlikely that it would come out of the core through the coating. It was doubtful whether determination on the whole tablet would yield any information. It was true that to sugar-coat tablets which were very sensitive to moisture, rigorous batch control was necessary. In reply to the question about the blood levels, he said that for soluble penicillin the figure of 0·06 I.U./ml. was twice what was considered to be a reasonable therapeutic level, and in any case tablets were taken at four-hourly intervals.