STUDIES IN THE KEEPING QUALITIES OF UNCOATED TABLETS OF PROCAINE BENZYLPENICILLIN

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Uncoated tablets of the soluble salts of benzylpenicillin have been available in this country for several years. For much of this time it was believed that these preparations were stable for lengthy periods if stored under dry conditions. This assumption was shaken rather rudely by Bagnall[1] who claimed that an appreciable loss of potency may occur under these conditions within the anticipated life of the product, especially if they are stored in bulk containers from which samples were frequently withdrawn or in containers which did not provide an adequate barrier against moisture. In the light of these findings a comprehensive investigation of the keeping qualities of tablets of the soluble salts of benzylpenicillin was carried out by the Ministry of Health, using information supplied by the laboratories of several manufacturing houses. From the results of this investigation Davis[2] concluded that tablets of the soluble salts of benzylpenicillin could be considered to be stable for eighteen months provided that they had a low initial moisture content (i.e. not more than 1 per cent.) and were packed only in small bulk containers fitted with tight closures.

Procaine benzylpenicillin is relatively insoluble and might for this reason be expected to show greater resistance to decomposition due to the presence of moisture than do the soluble salts. The literature on the clinical efficacy of oral procaine benzylpenicillin shows it to compare favourably in all respects, with the soluble salts of penicillin[3–10].

The information now presented was obtained by preparing a batch of tablets to a simple formulation and subjecting them to various storage conditions for a period up to nine months. The keeping qualities were assessed by examining the important characteristics of the tablets, namely potency, disintegration, appearance and firmness, at frequent intervals. The moisture content was determined initially and on completion or near completion of each storage test.

Experimental

1. *Formulation* (250,000 units = 0·276 g.)

Granulation mixture		*Compression mixture*	
Procaine benzylpenicillin, 200 mesh powder (1000 units per mg.)	100·0 g.	Granulation mixture as above, dried	
Corn starch, 80 mesh powder	5·0 g.	Corn starch, 80 mesh powder	5·0 g.
Solution sodium carboxymethyl cellulose 1 per cent. w/v	26 ml.	Magnesium stearate, 80 mesh powder	0·5 g.

The granulation mixture was passed through a No. 12 sieve and dried at 37° C. for twelve hours. The dried granules were passed through a No. 16 sieve and mixed with the lubricating agents to form the compression mixture. This was compressed by means of a Manesty Type "E" tabletting machine fitted with 11/16 in. concave punches into tablets each containing 250,000 units of procaine benzylpenicillin.

2. *Storage*

The prepared tablets were divided into three batches A, B and C which were stored as described below, all being protected from light.

Batch A. The tablets were packed 20 each into 2 oz., screw-cap glass jars, fitted with metal caps complete with waxed card inserts. The jars were sealed with Sellotape and set aside at 4° C., 18° ± 5° C. (i.e., room temperature) and at 37° C.

Sufficient samples were prepared to enable one jar to be removed from each place of storage every month over the test period of nine months. Assays and disintegration tests were carried out at monthly intervals. Moisture determinations were made initially and after seven months.

Batch B. One hundred tablets were placed in a 16 oz. wide mouth, screw cap, glass jar, with an unlined loose fitting cap, and set aside at room temperature for nine months. Assays and moisture determinations were carried out at the end of the test period.

Batch C. Fifty tablets were placed in an open 2 oz. glass jar and exposed to the atmospheric conditions of the laboratory for four weeks during the month of May (temperature 18° ± 5° C.; relative humidity 50 to 80 per cent.). Assays and moisture determinations were carried out at the end of this period.

3. *Assessment of Keeping Qualities*

(i) *Determination of weight variation in the initial tablets.* The weight variation of the tablets was determined by the method of the British Pharmacopœia 1953.

Theoretical weight per tablet = 0·276 g.
Observed average weight per tablet = 0·2844 g.
Weight variation = ±1·86 per cent.

(ii) *Determination of the free moisture content.* The free moisture content was determined by crushing the tablets and sampling without delay; the powdered sample was dried under vacuum for 5 hours at 60° C. Determinations were duplicated and the average recorded. Results are shown in Table I.

(iii) *Determination of penicillin content.* The penicillin content of the tablets was determined by dissolving each tablet in 250 ml. of water and assaying the solution iodometrically by the method of Alicino[11]. The assay was repeated twice and the average recorded. The assay variation within each group of three readings was not greater than ±1 per cent.

After storage for six months samples removed from Batch A were

assayed in addition by the microbiological method using a cavity plate diffusion technique with *Staphylococcus aureus* as the test organism.

Results are shown in Table II.

(iv) *Test for disintegration.* Since the initial disintegration time was short, small changes would have been difficult to detect. The pharmacopœial method permits the presence of an appreciable air bubble, which by impact can speed the disintegration. A technique was therefore used which excluded the presence of an air bubble of significant proportion, thus disintegration took place more slowly.

TABLE I

MOISTURE CONTENT (PER CENT. W/W)

Initial moisture content	=	1·74
Batch A: After 7 months at 4° C.	=	2·13
After 7 months at 18° ± 5° C.	=	2·11
After 7 months at 37° C.	=	1·89
Batch B: After 9 months at 18° ± 5° C.	=	1·86
Batch C: After 4 weeks at 18° ± 5° C.	=	2·01

A tablet was dropped into a 1 in. test tube full of water at 37° C. The tube was stoppered, ensuring that no air bubble was present. The tube was inverted frequently so that the tablet passed to and fro but did not touch the glass. Disintegration was taken to be complete when the largest remaining granule was not greater than No. 8 mesh, as judged by eye. The test was repeated twice and the average of the three readings taken. These were usually quite close and in no case varied by more than ±10 per cent. from the average. After eight and nine months comparative readings were obtained using the official test method.

TABLE II

PENICILLIN CONTENT (UNITS PER TABLET)

Storage period (months)	No. of samples averaged	Storage temperature 4° C.	18° ± 5° C.	37° C.
Batch A: 0	6	252,000	252,000	252,000
1	3	247,000	241,000	246,000
2	3	245,000	242,000	245,000
3	3	236,000	241,000	243,000
4	3	238,000	239,000	236,000
5	3	241,000	247,000	241,000
6	3	241,000	244,000	239,000
6	3	238,000*	244,000*	246,000*
7	3	237,000	235,000	230,000
8	3	242,000	239,000	242,000
9	3	246,000	241,000	240,000
Batch B: 9	9	—	238,000	—
Batch C: 1	3	—	241,000	—

* Microbiological assay.

TABLE III

TIME FOR DISINTEGRATION IN WATER (SECONDS)

Average time for three samples

Storage period (months)	Storage temperature 4° C.	18° ± 5° C.	37° C.
1	80	90	120
2	76	103	130
3	80	70	139
4	85	105	155
5	83	85	145
6	130	128	197
7	112	134	160
8	60*	60*	94*
9	73	121	155
9	44*	70*	113*

* B.P. test method.

(v) *Examination for appearance and firmness.* The appearance and firmness of the initial tablets

were assessed by eye and by fracture between fingers and thumb. These observations were repeated on all samples during and at the completion of their test. It was found that the tablets showed no change in appearance or firmness during or after their respective periods of test.

Discussion and Conclusions

This experiment shows that when stored at temperature of 4° C., 18° ± 5° C. and 37° C., the tablets showed a potency loss not greater than 4 per cent. after nine months. This loss is not increased by storing the tablets in a large insecurely sealed bulk container. The evidence appears to suggest that potency losses brought about by the presence of free moisture are due rather to residual moisture in the original tablets than to that taken up during subsequent storage. If this be so, a lower initial free moisture content might be expected to reduce or eliminate the small potency loss sustained by the test samples. A slight increase in the time for disintegration was noted with ageing, this being greater as the temperature of storage increases. Tablets stored for nine months at 37° C. disintegrated completely within two minutes. The free moisture content showed very small increases, the greatest taking place at the lowest storage temperature. Differences in degree between the moisture content increases appear to have been without significance. Procaine benzylpenicillin tablets have been stored in sealed jars, in a large loosely capped jar and in an open jar, in an effort to detect a tendency to deterioration either by potency loss or in other respects. Within the limitations of the test, namely time and condition of storage, it would appear that tablets of procaine benzylpenicillin are relatively stable in atmospheric conditions normal to this country, even where they are not packed in a tightly sealed container.

Summary

1. Tablets of procaine benzylpenicillin have been prepared to a simple formulation and subjected to various conditions of storage.

2. Data on the keeping qualities of the tablets are presented, as assessed by examining the important characteristics of the tablets, namely potency, disintegration, appearance and firmness.

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DISCUSSION

The paper was presented by THE AUTHOR.

MR. A. R. ROGERS (Brighton) asked whether the authors had determined the free and combined moisture content by the Karl Fischer method. Had the combined moisture any effect on the keeping qualities of the tablets?

MR. T. C. DENSTON (London) suggested that the sentence in the first paragraph "This assumption was shaken rather rudely" might be reconsidered as, in his view, the assumption referred to had been completely confirmed. The material investigated by Bagnall had not, in fact, been stored under dry conditions.

MR. D. JACK (Harrow) asked why the author differentiated between the effect of initial moisture, and moisture taken up during storage. It was difficult to see that there would be any great difference between the effects of the two as there was nothing in the granulation to protect the procaine penicillin from moisture absorbed.

MR. G. SYKES (Nottingham) said that the paper appeared to omit any confirmation of the stability of the powder or granulation mixture. He reminded the author that there was an aqueous suspension of procaine penicillin on the market.

DR. R. A. WEBB (Hull) said he had noticed that tablets of penicillin had a mottled appearance after long storage. Had the author noticed this with other penicillin preparations, and was it a sign of deterioration?

MR. R. LEVIN, in reply, said that the Karl Fischer method had not been used. He was interested only in the free moisture content to see whether any potency losses might be related to the free moisture present. He was aware that the instability which developed in the samples examined by Bagnall occurred only because of incorrect conditions of storage, and agreed with Mr. Denston's comment. He found that development of slight mottling after twelve months did not indicate potency losses. He was aware that aqueous suspensions of procaine penicillin existed, but those products relied on the presence of buffering agents for their stability.