SCIENCE PAPERS AND DISCUSSIONS

PREPARATION OF AMINOPHYLLINE TABLETS

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AMINOPHYLLINE was first included in the 7th Addendum to the 1932 British Pharmacopœia under the name of Theophylline with Ethylenediamine. Tablets of Theophylline with Ethylenediamine were included in the 1951 Addendum to the 1948 Pharmacopœia and are retained in the 1953 edition under the name of Aminophylline Tablets.

The pharmacopœial method of preparation is moist granulation and compression. Tablets made by this method become discoloured and develop an odour of ammonia within a few weeks of preparation. During discussion at the British Pharmaceutical Conference, 1954[1], Denston[2] suggested that the moist granulation method had been found to be satisfactory if drying is carried out thoroughly. However, discussion with several pharmacists reveals the widespread observation of the rapid deterioration of tablets prepared by the official method, and also, commercially available tablets vary appreciably in appearance and odour. For example, of six samples of tablets purchased on the open market from different sources, the colour varied from white to pale yellow and the odour from practically none to a marked odour of ammonia. It is noteworthy that no positive correlation exists between colour and odour. The properties of these tablets are shown in Table I.

TABLE I

PROPERTIES OF COMMERCIAL SAMPLES OF AMINOPHYLLINE TABLETS

Appearance	Odour
Pale cream colour with a few darker patches	Practically none
White	Faint odour of ammonia
Pale yellow colour	Faint odour of ammonia
White	Very faint odour of ammonia
Cream colour	Marked odour of ammonia
Very pale cream colour	Marked odour of ammonia

These six samples were purchased from different sources on the open market. It will be seen that there is no correlation between colour and odour.

EXPERIMENTAL

Samples of aminophylline powder were purchased from each of six manufacturers and their physical properties were noted. The colour varied from white to pale yellow and the odour from practically none to a marked odour of ammonia or acetamide. Again there was no correlation between colour and odour. The properties of these powders are shown in Table II. Batches of tablets were prepared from all of these samples of powder by each of three different methods.

Method A. Starch, talc and magnesium stearate were mixed with the

aminophylline in suitable proportions and granules were made by the moist granulation method. The granules were dried carefully and then compressed into tablets.

Method B. A base consisting of talc and starch was first prepared by moist granulation and subsequent drying, and the dry base was then mixed with the aminophylline and a small amount of magnesium stearate and the mixture was compressed into tablets.

Method C. Aminophylline, starch, talc and magnesium stearate were mixed in suitable proportions and the mixture was compressed into "slugs". These were broken up through a 16 mesh sieve and the 36 mesh dust was recompressed. The dry granules obtained were mixed with more starch and magnesium stearate and the mixture was then compressed to give the finished tablets. Recompression of the dust was necessary because the formula does not bind well and much "fines" are produced.

TABLE II

PROPERTIES OF BULK AMINOPHYLLINE POWDER

Colour	Odour
Cream	Marked odour of ammonia
White	Faint odour of ammonia
Very pale cream ..	Practically none
Cream	Faint odour of ammonia
Pale yellow ..	Strong odour of acetamide
Cream	Odour of acetamide

These six samples were also purchased from different suppliers on the open market. Again there is no correlation between colour and odour.

The tablets thus prepared were examined on preparation and at the end of storage for six months and one year in glass containers with metal screw caps and waxed wads which were stored at room temperature in the dark. When freshly prepared the tablets were all practically white or pale cream in colour and were almost odourless or did not have more than a faint odour. This was surprising, in view of the properties noted in Table II, but may be due to some of the odour dissipating during preparation and the colour may be masked by the addition of other ingredients.

TABLE III

PROPERTIES OF SAMPLES OF AMINOPHYLLINE TABLETS AFTER STORAGE

Sample	After storage for 6 months	After storage for 1 year
A 1	Deep cream colour. Strong odour of ammonia	Brown colour. Strong odour of ammonia
A 2	Pale cream colour. Strong odour of ammonia.	Brown colour. Strong odour of ammonia
A 3	Deep cream colour. Strong odour of ammonia.	Brown colour. Strong odour of ammonia
A 4	Very deep cream colour. Strong odour of ammonia	Brown colour. Strong odour of ammonia
A 5	Deep cream colour. Strong odour of ammonia	Brown colour. Strong odour of ammonia
A 6	Pale cream colour. Strong odour of ammonia	Brown colour. Strong odour of ammonia
B 1	White. Practically no odour	White. Practically no odour
B 2	White. Practically no odour	White. Practically no odour
B 3	White. Practically no odour	White. Practically no odour
B 4	White. Practically no odour	White. Practically no odour
B 5	Slightly mottled. Practically no odour	Slightly mottled. Practically no odour
B 6	Pale cream. Practically no odour	Pale cream. Practically no odour
C 1	White. Practically no odour	White. Practically no odour
C 2	White. Practically no odour	White. Practically no odour
C 3	White. Practically no odour	White. Practically no odour
C 4	White. Practically no odour	White. Practically no odour
C 5	Very mottled. Strong odour of acetamide	Very mottled. Strong odour of acetamide
C 6	White. Practically no odour	White. Practically no odour

Samples A, 1–6 were made by Method A from the different samples of aminophylline powder listed in Table II.
Samples B, 1–6 were made by Method B.
Samples C, 1–6 were made by Method C.

The properties of these tablets after storage for six months and one year are given in Table III. It will be seen that, after six months, those made by moist granulation varied in colour from pale cream to very deep cream and all smelled strongly of ammonia. Most of the tablets prepared by the other two methods were white in colour and practically odourless. One was pale cream and another slightly mottled, these two samples being practically odourless. One sample (C 5), however, had become very mottled and smelled strongly of acetamide. The cause of this is unknown.

After one year's storage the colour of the tablets made by moist granulation had become brown, whereas those made by the other two methods remained as they had appeared after 6 months.

Samples of all these tablets after 6 months' storage were assayed by Dr. G. E. Foster and the results are listed in Table IV. These show

TABLE IV

ANALYSIS OF AMINOPHYLLINE TABLETS AFTER SIX MONTHS' STORAGE AT ROOM TEMPERATURE

Sample	Time of disintegration at 37° C. (min.)	Average weight (g.)	Ethylenediamine per cent.		Theophylline per cent.	
			In products	Label strength	In products	Label strength
A 1	13	0·2438	5·53	108·0	31·5	102·5
A 2	9	0·2464	6·16	121·5	33·9	111·5
A 3	12	0·2374	6·1	116·0	36·5	115·5
A 4	16	0·2309	5·11	94·5	32·0	98·5
A 5	11	0·2436	5·59	109·0	30·2	98·0
A 6	12·5	0·2377	5·50	104·5	31·1	98·5
B 1	5	0·1313	10·1	106·0	55·2	96·5
B 2	3	0·1390	9·36	104·0	54·5	101·0
B 3	4	0·1318	10·75	114·0	63·0	110·5
B 4	3·5	0·1318	11·1	109·5	60·5	99·5
B 5	2·5	0·1280	10·5	108·0	57·0	97·0
B 6	2·25	0·1295	11·5	119·0	66·0	114·0
C 1	4	0·1327	10·2	108·0	55·2	98·0
C 2	2	0·1229	9·84	97·0	56·1	92·0
C 3	1·25	0·1356	6·75	73·0	41·1	74·0
C 4	3	0·1336	10·2	109·0	54·5	97·0
C 5	6	0·1308	0·72	7·9	5·7	10·4
C 6	3·5	0·1339	10·3	109·0	60·0	107·0

Samples A, 1–6 were made by Method A from the different samples of aminophylline powder mentioned in Table II. Samples B, 1–6 were made by Method B. Samples C, 1–6 were made by Method C. Label strengths have been calculated on the basis of an average B.P. tablet containing ethylenediamine 0·0125 g. and theophylline 0·075 g.

that the samples prepared by moist granulation were unfit for use after six months because of their physical properties although they still complied with the pharmacopœial requirements for theophylline and for ethylenediamine content. Those made by method B were all reasonably satisfactory in physical properties, after one year and complied with the requirements for strength of active ingredients. With the exception of sample C 5, the tablets made by method C were satisfactory in physical properties after storage for one year. The faulty sample was also very low in strength and sample C 3 was also low in strength when assayed after 6 months. The cause of this is unknown. A sample of tablets made by the dry granulation process (method C) sent to me by I. C. Edmundson is in perfect condition over two years after the date of their preparation.

Effect of Various Conditions of Storage

It is stated in the International Pharmacopœia that aminophylline should be stored protected from light, and Bull[3] also recommended that aminophylline tablets should be protected from light. Since many compounds containing amino groups darken in colour on exposure to light, six different samples of tablets enclosed in screw-capped white glass bottles were exposed to direct sunlight for three months. At the end of this time their appearance was compared with samples from the same batches which had not been exposed to sunlight and no darkening was noted. Some of each sample were assayed by Dr. G. E. Foster and the results are given in Table V. The results show that within the experimental error of the assay, no loss of strength had occurred.

TABLE V

ANALYSIS OF AMINOPHYLLINE TABLETS BEFORE AND AFTER EXPOSURE TO SUNLIGHT

Sample	Average weight (g.)	Ethylenediamine per cent.		Theophylline per cent.	
		In products	Label strength	In products	Label strength
1 Before exposure ..	0·2235	7·47	133·6	32·7	97·4
After " ..	0·2235	7·80	139·5	31·4	93·6
2 Before " ..	0·2293	5·74	105·3	35·0	107·0
After "	0·2293	5·74	105·3	34·8	106·4
3 Before " ..	0·2294	5·45	99·99	36·5	111·6
After " ..	0·2294	5·51	100·1	35·7	109·1
4 Before " ..	0·2503	6·26	125·5	42·0	140·1
After " ..	0·2503	6·20	124·4	41·1	138·8
5 Before " ..	0·2330	6·82	127·2	30·7	95·4
After " ..	0·2330	6·87	131·1	32·7	101·6
6 Before " ..	0·2065	6·10	100·8	35·7	98·3
After " ..	0·2065	6·07	100·3	36·1	97·1

Five of these samples were purchased on the open market and the sixth was manufactured. Label strength have been calculated on the basis of an average B.P. tablet containing ethylenediamine 0·0125g.and theophylline 0·075 g. It appears that, having regard to the experimental error of the assays, exposure to light has not had any appreciable effect on the composition of the tablets.

One sample prepared by moist granulation and one by preliminary compression were stored in screw-capped bottles with cork wads at 37° C. in an electrically-heated oven for 6 months. The former had become pale cream in colour with brown spots and had a faint odour of ammonia. The latter had remained white and had a faint odour of ammonia. Similar samples were stored in loosely closed bottles over water to give an atmosphere with maximum moisture content. At the end of 7 months the tablets made by moist compression had become deep brown in colour and had a strong odour of ammonia. Those made by preliminary compression were still white and practically odourless. This is surprising since both samples had absorbed sufficient water to become very soft.

DISCUSSION

Aminophylline obtained from different commercial sources varies in colour and odour. The pharmacopœial description states that the colour is either white or yellowish-white. The colour darkens on storage but the rate of darkening does not appear to be increased by direct sunlight.

The Extra Pharmacopœia (Martindale) Vol. I, 1952, and the United States Dispensatory, Vol. I, 1950, state that aminophylline develops a yellow or brown colour on contact with lactose. Bull[3] (British Pharmaceutical Conference, 1954) states that sugars should be avoided in the formulation of aminophylline tablets and our experience confirms this, as does that of I. C. Edmundson of Dunedin, New Zealand, and N. J. Van Abbé of Loughborough, with whom I have corresponded during this work.

If granules containing lactose are made by the moist process a yellow colour develops within an hour or so of preparation and with dextrose a deep brown colour appears in about the same time. In addition, tablets containing glucose prepared by granulation by preliminary compression become lemon yellow in colour within three days of preparation. With sucrose a yellow colour develops within about 12 hours of the preparation of moist granules. Discoloration also occurs in tablets made by moist granulation containing a high proportion of starch but is slower in developing. Edmundson suggested that the colour may be due to caramelisation of the carbohydrates in the presence of the alkaline ethylenediamine, but we have found some discoloration in tablets entirely free from carbohydrates. Another possible source of discoloration is contamination with metals. Ethylenediamine is, of course, a chelating agent and readily reacts with metals. For example, aminophylline gives a yellowish-brown colour with ferrous iron, a chocolate colour with ferric iron and a vivid purple colour with cupric salts. In each case the theophylline is precipitated. Yet another cause of discoloration may be oxidation. If 100 volumes hydrogen peroxide is added to aminophylline a yellow colour develops within about 10 minutes.

Tablets of aminophylline prepared by the official method of moist granulation have always, in our experience, deteriorated fairly rapidly, often becoming unfit for use in a few months or even weeks. Tablets which have become markedly discoloured and strongly odorous may still comply with the official assay for theophylline and for ethylenediamine content. Van Abbé, however, has told me that in his experience the discoloration is usually, if not always, accompanied by a fall in ethylenediamine content.

Satisfactory tablets can be prepared by two methods in which moistening of the aminophylline is avoided. Samples made by these two methods have remained in perfect condition on storage for at least a year.

SUMMARY

1. The discoloration of aminophylline tablets is discussed and the official method of moist granulation is criticised.

2. Two methods of preparation in which the aminophylline is not moistened are suggested.

I wish to thank Mr. I. C. Edmundson for many helpful suggestions, including methods B and C; Dr. G. E. Foster for carrying out assays on several samples; Mr. N. J. Van Abbé for exchange of information and Mr. A. J. Pearson for technical assistance.

REFERENCES

1. Whittet, *J. Pharm. Pharmacol.*, 1954, **6**, 1074.
2. Denston, *ibid.*, 1954, **6**, 1080.
3. Bull, *ibid.*, 1954, **6**, 1077.

DISCUSSION

The paper was presented by the AUTHOR.

PROFESSOR K. BULLOCK (Manchester) said that the figures in Tables IV and V would be much more valuable if some information had been given about the errors and their possible sources particularly in sampling.

Dr. G. E. FOSTER (Dartford) said that Mr. Whittet had purchased samples of aminophylline and compressed them. If he had taken theophylline and ethylenediamine and purified them, he might have found that another factor involved was some impurity in the material used. The samples tested in his laboratory consisted of about 25 tablets each, and it had been assumed that the author had sent a representative sample.

MR. H. GRAINGER (London) pointed out that aminophylline was a sequestering agent, for metallic ions which might be the cause of discoloration rather than the sugars.

MR. V. REED (London) asked whether tablets with an odour of ammonia should be used.

MR. N. J. VAN ABBÉ (Loughborough) said he had found that when compressed dry, aminophylline often caused binding in the dies and mechanical damage. Had the author experienced this difficulty?

MR. T. C. DENSTON (London) said that as the official moist granulation process was a general method which permitted a great deal of latitude to the operator, precise details of the method used by the author should be stated.

DR. F. HARTLEY (London) said that although aminophylline was an established drug it was difficult to understand why the ethylenediamine compound of theophylline should be used in tablets since it was the theophylline which exerted the therapeutic action. Did the discoloration reduce the therapeutic effect of the tablets? He suggested that a critical therapeutic evaluation of theophylline and of ethylenediamine was desirable.

MR. WHITTET, in reply, agreed that samples of aminophylline varied greatly. Because ethylenediamine was a sequestering agent, moist granules put through a metal sieve became discoloured.

He did not think that an odour of ammonia indicated any great deterioration in the tablets. He had had no damaged punches and dies.

In regard to incompatibility with sugars, he had found that it was the ethylenediamine which reacted, samples of theophylline with sugars not being discoloured after several months.

He appreciated that it might be possible to obtain a better solubilising agent for theophylline. There was no evidence of great loss of activity in discoloured tablets, but pharmaceutically they looked bad.