THE OCCURRENCE OF METHYL COMPOUNDS IN GALENICALS

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The presence of traces of methyl alcohol in the galenicals prepared from certain vegetable drugs has been previously recorded, and the fact is of considerable interest since the Board of Customs and Excise prohibits its presence in rebateable preparations. Richardson[1] showed evidence of such a possibility and found amounts varying from 0·01 to 0·10 per cent (0·045 to 0·48 per cent. based on alcohol content) in simple preparations of orange peel, gentian root, lemon peel, buchu and compound preparations of orange, gentian and rhubarb. In his opinion, the derivation of the colour in the reaction obtained in the British Pharmacopœia's modification of the Denigés test[2] was not the presence of essential oils or methyl esters, but of methyl alcohol itself, since adequate means were employed for removal of the former[3]. It was suggested that the methyl alcohol was derived from the decomposition of pectin present in orange and lemon peels. No observations on the technique of distillation were given.

Our interest in this matter was renewed recently, because of a complaint by the Customs and Excise Authorities with reference to a rebate claim on a production batch of concentrated compound infusion of gentian. They accepted that certain drugs on distillation may produce small amounts of methyl alcohol or substances giving similar reactions, but maintained that the proportion found, 0·21 per cent., was abnormally high and that the preparation must, therefore, be considered to contain industrial methylated spirit. Since methylated spirit was not used in the manufacture of the concentrated compound infusion of gentian, this and subsequent batches, made with pure alcohol, were tested for methyl alcohol and compared with samples of material marketed by other pharmaceutical houses. The test used was the B.P. test for the presence of methyl alcohol in alcohol which, as stated in Appendix XII G may give a positive response to the presence of methyl compounds as well as to methyl alcohol in the preparation. The former are converted to methyl alcohol in the test and the figures for methyl alcohol in this paper include that derived from such compounds. The results are recorded in Table I.

Methyl alcohol determinations on a number of batches of other galenicals prepared with pure rectified alcohol carried out as routine control, are recorded in Table II.

These results substantiated our contention that methyl compounds can be present in galenicals prepared according to the British Pharmacopœia and justified our intention to reinvestigate the original observations of Richardson, to show whether amounts of methyl compounds which the Customs and Excise Authorities had stated to be inadmissible were, in fact, liable to be present and if possible to determine the source or reasons for their production.

TABLE I

METHYL ALCOHOL IN CONCENTRATED COMPOUND INFUSION OF GENTIAN

Sample No.	Alcohol content per cent.	Methyl alcohol in galenical per cent.	Methyl alcohol per cent. of alcohol content
1	21·9	0·088	0·41
2	20·8	0·046	0·22
3	22·6	0·041	0·18
4	22·0	0·044	0·20
5	22·2	0·089	0·40
6	21·8	0·12	0·55
7	21·8	0·12	0·55
8	21·6	0·10	0·46
9	21·6	0·05	0·22
10	18·2	0·05	0·28
11	18·4	0·05	0·28
12	19·5	0·05	0·26
13	21·3	0·05	0·23
14	22·4	0·025	0·11
15	21·3	0·05	0·24
16	20·2	nil	nil
17	21·4	0·10	0·47

Samples numbered 1 to 5, 8 and 9 are taken from normal manufacturing batches. Those numbered 6 and 7 are from manufacturing batches made with previously disintegrated orange and lemon peels. Numbers 10 to 13 were made on a laboratory scale. Numbers 14 to 17 were materials purchased in the normal way from other drug houses.

TABLE II

METHYL ALCOHOL IN NORMAL BATCHES OF GALENICALS
(Carried out as routine control)

Preparation	Alcohol content per cent.	Methyl alcohol in galenical per cent.	Methyl alcohol per cent. of alcohol content
Ammoniated tincture of valerian	50·1	0·10	0·20
Compound tincture of gentian	41·2	0·008	0·019
Concentrated compound tincture of gentian B.P. 1932, 5th addendum	35·2	0·008	0·023
Camphorated tincture of opium	58·0	0·0025	0·004
Tincture of belladonna	68·4	0·0055	0·008
Tincture of ipecacuanha	23·6	nil	nil
Tincture of orange	73·6	0·007	0·009
Tincture of squill	55·2	nil	nil
Tincture of calumba	58·4	nil	nil
Tincture of lemon (for syrup of lemon)	34·4	0·11	0·32
Tincture of hyoscyamus	66·4	0·007	0·011
Strong tincture of ginger	82·8	0·008	0·01
Tincture of aloes	39·6	0·008	0·02
Tincture of opium	42·8	0·008	0·019
Compound tincture of rhubarb	50·0	0·005	0·01
Tincture of serpentary	59·0	0·006	0·01
Tincture of myrrh	84·8	0·02	0·024
Tincture of strophanthus	67·6	0·001	0·001
Liquid extract of senega	39·6	0·44	1·1
Liquid extract of cascara	22·4	nil	nil
Liquid extract of liquorice	17·8	nil	nil
Liquid extract of ergot	48·4	0·005	0·010
Liquid extract of sarsaparilla	13·2	0·004	0·030
Concentrated infusion of orange peel	21·2	0·12	0·57
" " " "	22·0	0·12	0·55
" " " "	22·0	0·08	0·36
Concentrated infusion of valerian	23·0	0·033	0·14
Elixir of senna	12·8	0·08	0·62
Concentrated compound decoction of sarsaparilla	21·0	0·0018	0·009

EXPERIMENTAL

The alcohol content was obtained (a) by the British Pharmacopœial method or (b) by direct distillation; where ammonia was present, the distillate was neutralised to solid phenolphthalein and redistilled.

The method of the British Pharmacopœia for detection of methyl

alcohol was adapted to quantitative use by comparison against controls as follows:

An amount of the distillate obtained by method (a) or (b) calculated by preliminary experiment to contain the equivalent of between 0·0001 ml. and 0·001 ml. of methyl alcohol was taken, sufficient alcohol added to produce finally a 10 per cent. solution, and diluted to 5 ml. with water. The pharmacopœial test for methyl alcohol was carried out on this solution and controls containing 0·0001, 0·00015, 0·0002, etc., ml. of methyl alcohol in 5 ml. of 10 per cent. methyl alcohol-free ethyl alcohol, and the colour produced compared.

All alcohol used in the experiment and on production tests was checked for methyl alcohol content, and all results recorded were corrected for the trace of methyl alcohol present in the ethyl alcohol used. The results given in Tables I and II were obtained on distillates obtained by the British Pharmacopœial method.

In order to account for the high methyl alcohol content of liquid extract of senega recorded in Table II, a batch was examined at each stage of manufacture. The alcohol was determined by the method of the British Pharmacopœia (a) and by direct distillation (b), the tests being carried out on the distillates. The methyl alcohol content of the menstruum was not detectable by the method of the British Pharmacopœia. The results are given in Table III.

TABLE III

METHYL ALCOHOL FOUND DURING THE MANUFACTURE OF LIQUID EXTRACT OF SENEGA

	Methyl alcohol by method (*a*) per cent.	Methyl alcohol by method (*b*) per cent.
Reserve portion of the percolate	0·28	0·01
Soft extract from the remainder of the percolate...	0·74	0·02
Liquid extract of senega	1·40	0·01

The above results indicate that the methyl alcohol obtained was produced during the assay. To confirm this, water, ethyl alcohol and an excess of sulphuric acid were added to the residue from the distillation of the liquid extract by method (b), and a normal distillation performed. The methyl alcohol content of the distillate was 0·52 per cent. calculated to the liquid extract. Since this was insufficient to account for the high methyl alcohol content of the final product, this process was repeated, starting with a distillation from the liquid extract by method (b). When the acid, alcohol and water had been added to the residue, it was distilled very slowly. The distillate gave 0·88 per cent, methyl alcohol calculated to the liquid extract, a quantity greater than the previous figure, but less than that obtained for the galenical. A further addition of water and alcohol to the residue was again slowly distilled. The methyl alcohol content of the distillate was 0·48 per cent. calculated to the liquid extract. The sum of the percentages of methyl alcohol obtained from the residue is 1·36, an amount comparable with that given for the finished product in Table III. This shows that the length of time taken in the distillation

by the method of the British Pharmacopœia affects the amount of methyl alcohol formed, and, further, that its source is undoubtedly the senega.

A production batch of concentrated infusion of senega B.P. gave methyl alcohol when the method of the British Pharmacopœia for alcohol content by acid distillation was used, to the extent of 0·36 per cent., whereas by direct distillation the amount was only 0·04 per cent. This latter figure was higher than expected and suggested that some alkaline hydrolysis occurred during preparation.

Owing to our Tinctures Department finding the recovered alcohol from the preparation of this galenical to be contaminated with methyl alcohol, the process was examined in detail, using the same drugs. The schematic diagram indicates the method of production, points of control testing and amounts of methyl alcohol found at each stage of production.

The method of preparation used in our Tinctures Department differs from that described in the British Pharmacopœia by the use of ammonia in the percolation, the modification aiding preparation and giving a better final product. That this small deviation from the British Pharmacopœia directions does not affect the findings was shown by the results of testing a sample prepared strictly by the British Pharmacopœia procedure, in which closely similar figures for the final methyl alcohol content were obtained.

In conclusion we determined the methyl alcohol in the distillate from a mixture of powdered senega, pure ethyl alcohol and water:

	per cent. methyl alcohol calc. to senega
1. Direct distillation, adding no acid or alkali	0·10
2. Distilled in presence of acid	1·20
3. Distilled in presence of ammonia, neutralised and redistilled	0·80

Hence it is demonstrated that for senega root and its galenical preparations, a small amount of preformed methyl alcohol may be present, but alkaline or acid distillation produces considerable amounts probably due to hydrolysis, acid giving the greater. The presence of methyl alcohol was confirmed by the Riche and Bardy[4] test.

The presence of methyl salicylate in senega to an extent of 0·25 per cent has been recorded[5,6]. Distillation of small amounts of methyl salicylate with dilute alcohol and water showed that ammonia will hydrolyse this ester completely in dilute alcohol, but dilute acid has no effect.

Richardson[1] suggested that the methyl alcohol might be derived from the hydrolysis of pectin and the gelatinisation of senega preparations has been attributed to the occurrence of pectinous substances in the drug[6,7]. By distillation of pectin far in excess of the proportions likely to be present in the galenicals tested, some methyl alcohol was obtained, the

amount from acid distillation being comparable with that from alkaline distillation. Pectin should not be present in senega preparations to any extent, since alkaline distillation of senega produces much less methyl alcohol than acid. This suggests other substances to be the main source of the methyl alcohol.

In our opinion, the production of methyl alcohol by hydrolysis during distillation may not necessarily always account for its presence in galenicals. In support of this, we can quote some experiments on concentrated infusion of orange which was examined at all stages of manufacture, showing relatively high proportions of methyl alcohol on each test using the method of the British Pharmacopœia for alcohol determination (which does not require acid distillation and eliminates esters by light petroleum extraction of the distillate) but also showing similar results by a direct neutral distillation. These results suggest that in preparations of orange, the methyl alcohol may occur in the orange peel.

Conclusions

Based on our work with senega and the results given by routine examinations of other galenicals, it may be inferred that methyl compounds may occur in many galenicals in more than traces and that some of these may be hydrolysed to methyl alcohol. Since acid or alkaline media increase this hydrolysis, it would be desirable for the test for methyl alcohol to be made on a distillate from neutral solution. As considerable frothing impedes distillation of many galenicals, especially senega, unless acid is present, a correct alcohol content should be determined by the method of the British Pharmacopœia, and the methyl alcohol test carried out separately, distilling from neutral solution.

Summary

1. The presence of methyl alcohol in galenicals in more than traces is recorded and previous observations confirmed.

2. The source of the methyl alcohol in senega preparations has been closely investigated.

3. The method of the British Pharmacopœia for alcohol content has been shown to be the main contributory cause of the production of methyl alcohol by acid hydrolysis of the senega extractives.

4. In these and other galenicals some preformed methyl alcohol is present.

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