PHARMACOPOEIAL DISCUSSION GROUP

CORRECTION

CODE: E-03
NAME: BENZYL ALCOHOL

Correction 2 to Rev. 2 sign-off document
(previous sign-off on 2011-06-15)

Items to be corrected:
- CAS number: addition of CAS [100-51-6].
- Identification: addition of harmonised IR identification.
- Acidity: significant figures of maximum volume of titrant.
- Benzaldehyde and other related substances: editorial changes.
- Peroxide value: editorial change.
- Assay: deletion of "boiling".

Attribute	EP	JP	USP
Definition	+	+	+
Identification (IR)	+	+	+
Refractive index	+	+	+
Acidity	+	+	+
Benzylaldehyde and other related substances*	+	+	+
Peroxide value	+	+	+
Residue on evaporation	+	+	+
Assay	+	+	+

* Benzylaldehyde and other related substances: EP and USP do not stipulate the sentence: "Adjust the sensitivity of the detector so that the height of the peak due to ethylbenzene is not less than 30 per cent of the full scale of the recorder"

Legend

+ will adopt and implement ; – will not stipulate

Non-harmonised attributes

Characters, Appearance of Solution, Labelling, Storage

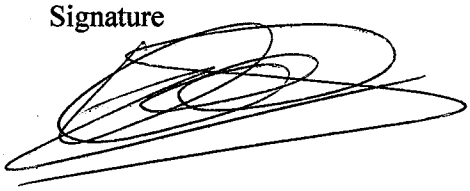
H.O.
CU
KM

Reagents and reference materials

Each pharmacopoeia will adapt the text to take account of local reference materials and reagent specifications.

Each pharmacopoeia will consider actual titrant concentration in equations according to their local rules of calculation for titration.

European Pharmacopoeia

Signature	Name	Date
	VIERCE [illegible]	22-[illegible]-2020

Japanese Pharmacopoeia

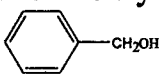
Signature	Name	Date
[illegible] Okuda for Y. Yoshida	Haruhiro Okuda	16 Dec / 2020.

United States Pharmacopoeia

Signature	Name	Date
[illegible] T. [illegible]	KEVIN MOORE	19-NOV-2020

E03 - BENZYL ALCOHOL

Alcohol Benzylicus



C_7H_8O M_r 108.1

[100-51-6]

DEFINITION

Benzyl alcohol contains not less than 98.0 per cent and not more than the equivalent of 100.5 per cent of phenylmethanol.

IDENTIFICATION

INFRARED ABSORPTION SPECTROPHOTOMETRY.

Record the infrared absorption spectrum of benzyl alcohol and compare with the Reference Spectrum or the spectrum obtained with the Reference Standard: the transmission minima correspond in position and relative size.

TESTS

Refractive index. 1.538 to 1.541.

Acidity. To 10 ml add 10 ml of *ethanol (96 per cent)* and 1 ml of *phenolphthalein solution.* Not more than 1.0 ml of *0.1 M sodium hydroxide* is required to change the colour of the indicator to pink.

Benzaldehyde and other related substances. Examine by gas chromatography, using *ethylbenzene* and *dicyclohexyl* as the standards.

Test solution. Use the substance to be examined.

Standard solution (a). Dissolve 0.100 g of *ethylbenzene* in 10.0 ml of the test solution. Dilute 2.0 ml of this solution to 20.0 ml with the test solution.

Standard solution (b). Dissolve 2.000 g of *dicyclohexyl* in 10.0 ml of the test solution. Dilute 2.0 ml of this solution to 20.0 ml with the test solution.

Reference solution (a). Dissolve 0.750 g of *benzaldehyde* and 0.500 g of *cyclohexylmethanol* in the test solution and dilute to 25.0 ml with the same solution. Add 1.0 ml of this solution to a mixture of 2.0 ml of standard solution (a) and 3.0 ml of standard solution (b) and dilute to 20.0 ml with the test solution.

Reference solution (b). Dissolve 0.250 g of *benzaldehyde* and 0.500 g of *cyclohexylmethanol* in the test solution and dilute to 25.0 ml with the same solution. Add 1.0 ml of this solution to a mixture of 2.0 ml of standard solution (a) and 2.0 ml of standard solution (b) and dilute to 20.0 ml with the test solution.

The chromatographic procedure may be carried out using:

— a column 30 m long and 0.32 mm internal diameter and a film-coating of *macrogol 20000 R* (1) (film thickness 0.5 µm),

— *helium for chromatography* as the carrier gas with a linear velocity of 25 cm/s at 50 °C,

— a flame-ionisation detector,

(1) DB-WAX, J&W is suitable.

EU 4.0 KTM

raising the temperature at a rate of 5 °C per minute from 50 °C to 220 °C and maintaining at 220 °C for 35 min and maintaining the temperature of the injection port at 200 °C and the detector at 310 °C.

Benzyl alcohol not intended for parenteral use

Inject without air-plug 0.1 µl of reference solution (a). When the chromatogram is recorded under the prescribed conditions the retention time of benzyl alcohol is about 26 min and the relative retention times are: about 0.28 for ethylbenzene, about 0.59 for dicyclohexyl, about 0.68 for benzaldehyde, about 0.71 for cyclohexylmethanol and 1.0 for benzyl alcohol.

The test is not valid unless: in the chromatogram obtained with reference solution (a), the resolution between the peaks corresponding to benzaldehyde and cyclohexylmethanol is not less than 3.0.

Adjust the sensitivity of the detector so that the height of the peak due to ethylbenzene is not less than 30 per cent of the full scale of the recorder.

Inject separately without air-plug 0.1 µl of the test solution and 0.1 µl of the reference solution (a).

If any peaks are present in the chromatogram obtained with the test solution which have the same retention times as the peaks due to ethyl benzene and dicyclohexyl, subtract the areas of any such peaks from the peak areas at these retention times in the chromatograms of reference solutions (a) or (b) (corrected peak areas of ethyl benzene and dicyclohexyl). Any such peaks in the test solution should be included in the assessments for total of other peaks.

In the chromatogram obtained with the test solution the area of any peak corresponding to benzaldehyde is not greater than the difference between the area of the peak due to benzaldehyde in the chromatogram obtained with reference solution (a) (0.15 per cent) and the area of the peak due to benzaldehyde in the chromatogram obtained with the test solution.

In the chromatogram obtained with the test solution the area of any peak corresponding to cyclohexylmethanol is not greater than the difference between the area of the peak due to cyclohexylmethanol in the chromatogram obtained with reference solution (a) (0.10 per cent) and the area of the peak due to cyclohexylmethanol in the chromatogram obtained with the test solution.

In the chromatogram obtained with the test solution, the sum of the areas of any peak with a retention time less than that of benzyl alcohol and apart from the peaks due to benzaldehyde and cyclohexylmethanol is not greater than 4 times the area of ethylbenzene in reference solution (a) corrected if necessary as described above (0.04 per cent).

In the chromatogram obtained with the test solution, the sum of the areas of any peak with a retention time greater than that of benzyl alcohol is not greater than the area of dicyclohexyl in reference solution (a) corrected if necessary as described above (0.3 per cent).

Disregard any peak with an area less than 0.01 times that of the peak due to ethylbenzene in the chromatogram of reference solution (a) corrected if necessary as described above.

Benzyl alcohol intended for parenteral use.

Inject without air-plug 0.1 µl of reference solution (b). When the chromatogram is recorded under the prescribed conditions the retention time of benzyl alcohol is about 26 min and the relativeretention times are: about 0.28 for ethylbenzene, about 0.59 for dicyclohexyl, about 0.68 for benzaldehyde, about 0.71 for cyclohexylmethanol and 1.0 for benzyl alcohol.

CV 17.0 KTM

The test is not valid unless: in the chromatogram obtained with reference solution (b), the resolution between the peaks corresponding to benzaldehyde and cyclohexylmethanol is not less than 3.0.
Adjust the sensitivity of the detector so that the height of the peak due to ethylbenzene is not less than 30 per cent of the full scale of the recorder.
Inject separately without air-plug 0.1 µl of the test solution and 0.1 µl of the reference solution (b).
If any peaks are present in the chromatogram obtained with the test solution which have the same retention times as the peaks due to ethyl benzene and dicyclohexyl, subtract the areas of any such peaks from the peak areas at these retention times in the chromatograms of reference solutions (a) or (b) (corrected peak areas of ethyl benzene and dicyclohexyl). Any such peaks in the test solution should be included in the assessments for total of other peaks.
In the chromatogram obtained with the test solution the area of any peak corresponding to benzaldehyde is not greater than the difference between the area of the peak due to benzaldehyde in the chromatogram obtained with reference solution (b) (0.05 per cent) and the area of the peak due to benzaldehyde in the chromatogram obtained with the test solution.
In the chromatogram obtained with the test solution the area of any peak corresponding to cyclohexylmethanol is not greater than the difference between the area of the peak due to cyclohexylmethanol in the chromatogram obtained with reference solution (b) (0.10 per cent) and the area of the peak due to cyclohexylmethanol in the chromatogram obtained with the test solution.
In the chromatogram obtained with the test solution, the sum of the areas of any peak with a retention time less than that of benzyl alcohol and apart from the peaks due to benzaldehyde and cyclohexylmethanol is not greater than 2 times the area of ethylbenzene in reference solution (b) corrected if necessary as described above (0.02 per cent).
In the chromatogram obtained with the test solution, the sum of the areas of any peak with a retention time greater than that of benzyl alcohol is not greater than the area of dicyclohexyl in reference solution (b) corrected if necessary as described above (0.2 per cent).
Disregard any peak with an area less than 0.01 times that of the peak due to ethylbenzene in the chromatogram of reference solution (b) corrected if necessary as described above.

Peroxide value. Not more than 5.
Place 5.00 g of the substance to be examined (m g) in a 250 ml conical flask fitted with a ground-glass stopper. Add 30 ml of a mixture of 2 volumes of chloroform and 3 volumes of glacial acetic acid (99.0 to 100.5 m/m of $C_2H_4O_2$). Shake and add 0.5 ml of saturated potassium iodide solution. Shake for exactly 1 min then add 30 ml of water. Titrate with 0.01 M sodium thiosulphate, adding the titrant slowly with continuous vigorous shaking, until the yellow colour is almost discharged. Add 5 ml of starch solution and continue the titration, shaking vigorously, until the colour is discharged (n1 ml of 0.01 M sodium thiosulphate). Carry out a blank test under the same conditions (n2 ml of 0.01 M sodium thiosulphate). The volume of 0.01 M sodium thiosulphate used in the blank titration must not exceed 0.1 ml.

$$\mathrm{Ip} = \frac{10\ (n_1 - n_2)}{m}$$

Residue on evaporation : maximum 0.05 per cent. *After ensuring that the substance to be examined complies with the test for peroxide value,* evaporate 10.0 g to dryness in a tared

quartz or porcelain crucible or platinum dish on a hot plate at a temperature not exceeding 200 °C. Ensure that the substance to be examined does not boil during evaporation. Dry the residue on the hot plate for 1h and allow to cool in a desiccator. The residue weighs not more than 5 mg.

ASSAY

To 0.900 g (*m* g) add 15.0 ml of a freshly prepared mixture of 1 volume of *acetic anhydride R* and 7 volumes of *anhydrous pyridine R* and heat under a reflux condenser on a water-bath for 30 min. Cool and add 25 ml of water. Using 0.25 ml of *phenolphthalein solution R* as indicator, titrate with *1 M sodium hydroxide* (n_1 ml). Carry out a blank titration (n_2 ml).

Calculate the percentage content of C_7H_8O from the expression:

$$\frac{10.81\ (n_2 - n_1)}{m}$$

REAGENTS

Cyclohexylmethanol. — $C_7H_{14}O$ (M_r 114.2). [100-49-2].

Cyclohexylcarbinol. Liquid. Slight odour of camphor. Soluble in alcohol, ether.

n_D^{25}: about 1.464.

bp: about 185 °C.

Bi(cyclohexyl). — $C_{12}H_{22}$ (M_r 166.3). [92-51-3].

mp: about 4 °C.

bp: about 227 °C.

d_{20}^{20}: about 0.864.

Hydrazine sulphate solution. Dissolve 1.0 g of hydrazine sulphate in water and dilute to 100.0 ml with the same solvent. Allow to stand for 4-6 h.

Hexamethylenetetramine solution. In a 100 ml ground-glass-stoppered flask, dissolve 2.5 g of hexamethylenetetramine in 25.0 ml of water.

Primary opalescent suspension (formazin suspension). To the hexamethylenetetramine solution in the flask add 25.0 ml of the hydrazine sulphate solution. Mix and allow to stand for 24 h. This suspension is stable for 2 months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use.

Standard of opalescence. Dilute 15.0 ml of the primary opalescent suspension to 1000.0 ml with water. This suspension is freshly prepared and may be stored for up to 24 h.

Reference suspension I. To 5.0 ml of standard of opalescence add 95.0 ml of water. Mix and shake before use.

Yellow primary solution. Dissolve 46 g of ferric chloride ($FeCl_3,6H_2O$) in about 900 ml of a mixture of 25 ml of concentrated hydrochloric acid (35.0 to 39.0 per cent *m/m* of HCl) and 975 ml of water and dilute to 1000.0 ml with the same mixture. Titrate and adjust the solution to contain 45.0 mg of $FeCl_3,6H_2O$ per millilitre by adding the same acidic mixture. Protect the solution from light.

Titration. Place in a 250 ml conical flask fitted with a ground-glass stopper, 10.0 ml of the solution, 15 ml of water, 5 ml of concentrated hydrochloric acid (35.0 to 39.0 per cent *m/m* of HCl) and 4 g of potassium iodide, close the flask, allow to stand in the dark for 15 min and add 100 ml of water. Titrate the liberated iodine with 0.1 M sodium thiosulphate, using 0.5 ml of starch solution, added towards the end of the titration, as indicator.

1 ml of 0.1 M sodium thiosulphate is equivalent to 27.03 mg of $FeCl_3,6H_2O$.

H.O.

Red primary solution. Dissolve 60 g of cobalt chloride ($CoCl_2,6H_2O$) in about 900 ml of a mixture of 25 ml of concentrated hydrochloric acid (35.0 to 39.0 per cent *m/m* of HCl) and 975 ml of water and dilute to 1000.0 ml with the same mixture. Titrate and adjust the solution to contain 59.5 mg of $CoCl_2,6H_2O$ per millilitre by adding the same acidic mixture.

Titration. Place in a 250 ml conical flask fitted with a ground-glass stopper, 5.0 ml of the solution, 5 ml of hydrogen peroxide solution (3 per cent) and 10 ml of a 300 g/l solution of sodium hydroxide. Boil gently for 10 min, allow to cool and add 60 ml of dilute sulphuric acid (98 g/l of H_2SO_4) and 2 g of potassium iodide. Close the flask and dissolve the precipitate by shaking gently. Titrate the liberated iodine with 0.1 M sodium thiosulphate, using 0.5 ml of starch solution, added towards the end of the titration, as indicator. The end-point is reached when the solution turns pink.

1 ml of 0.1 M sodium thiosulphate is equivalent to 23.79 mg of $CoCl_2,6H_2O$.

Blue primary solution. Dissolve 63 g of copper sulphate ($CuSO_4,5H_2O$) in about 900 ml of a mixture of 25 ml of concentrated hydrochloric acid (35.0 to 39.0 per cent *m/m* of HCl) and 975 ml of water and dilute to 1000.0 ml with the same mixture. Titrate and adjust the solution to contain 62.4 mg of $CuSO_4,5H_2O$ per millilitre by adding the same acidic mixture.

Titration. Place in a 250 ml conical flask fitted with a ground-glass stopper, 10.0 ml of the solution, 50 ml of water, 12 ml of dilute acetic acid (115 g/l to 125 g/l of $C_2H_4O_2$) and 3 g of potassium iodide. Titrate the liberated iodine with 0.1 M sodium thiosulphate, using 0.5 ml of starch solution, added towards the end of the titration, as indicator. The end-point is reached when the solution shows a slight pale brown colour.

1 ml of 0.1 M sodium thiosulphate is equivalent to 24.97 mg of $CuSO_4,5H_2O$.

Starch solution.

Triturate 1.0 g of soluble starch with 5 ml of water and whilst stirring pour the mixture into 100 ml of boiling water containing 10 mg of mercuric iodide.

Carry out the test for sensitivity each time the reagent is used.

Test for sensitivity. To a mixture of 1 ml of the starch solution and 20 ml of water, add about 50 mg of potassium iodide and 0.05 ml of iodine solution. The solution is blue.

B (brown) standard solution. Mix 3.0 ml of yellow primary solution, 3.0 ml of red primary solution, 2.4 ml of blue primary solution and 1.6 ml of hydrochloric acid (10 g/l HCl).

B9 reference solution. Mix 1.0 ml of B standard solution and 99.0 ml of hydrochloric acid (10 g/l HCl).

Phenolphtalein solution. Dissolve 0.1 g of phenolphthalein in 80 ml of ethanol (96 per cent) and dilute to 100.0 ml with water.

Test for sensitivity. To 0.1 ml of the phenolphtalein solution add 100 ml of carbon dioxide-free water. The solution is colourless. Not more than 0.2 ml of 0.02 M sodium hydroxide is required to change the colour to pink.

Colour change: pH 8.2 (colourless) to pH 10.0 (red).

Acetic anhydride. $C_4H_6O_3$. (M*r* 102.1) [108-24-7]

Content: minimum 97.0 per cent m/m of $C_4H_6O_3$.

A clear, colourless liquid.

bp: 136 °C to 142 °C.

Assay. Dissolve 2.00 g in 50.0 ml of 1 M sodium hydroxide in a ground-glass-stoppered flask and boil under a reflux condenser for 1 h. Titrate with 1 M hydrochloric acid, using 0.5 ml of phenolphthalein solution as indicator. Calculate the number of millilitres of 1 M sodium hydroxide required for 1 g (n1). Dissolve 2.00 g in 20 ml of cyclohexane in a ground-glass-

stoppered flask, cool in ice and add a cold mixture of 10 ml of aniline and 20 ml of cyclohexane. Boil the mixture under a reflux condenser for 1 h, add 50.0 ml of 1 M sodium hydroxide and shake vigorously. Titrate with 1 M hydrochloric acid, using 0.5 ml of phenolphthalein solution as indicator. Calculate the number of millilitres of 1 M sodium hydroxide required for 1 g (n2). Calculate the percentage of $C_4H_6O_3$ from the expression:

$$10.2(n_1 - n_2)$$

Potassium iodide solution, saturated.

A saturated solution of potassium iodide in carbon dioxide-free water. Make sure the solution remains saturated as indicated by the presence of undissolved crystals.

Test by adding to 0.5 ml of the saturated potassium iodide solution 30 ml of a mixture of 2 volumes of chloroform and 3 volumes of glacial acetic acid (99.0 to 100.5 m/m of $C_2H_4O_2$), as well as 0.1 ml of starch solution. Any blue colour formed should be discharged by the addition of 0.05 ml of 0.1 M sodium thiosulphate.

Storage: protected from light.

CN H.O. KTm