DETERMINATION OF ETHANOL CONTENT IN MEDICATED SYRUPS BY STATIC HEADSPACE GAS CHROMATOGRAPHY

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Abstract: Liquid drug preparations are the most convenient for pediatric patients. Unfortunately, these formulations very often contain ethanol, which may have an impact on children development. Moreover, medicines containing alcohol may cause undesirable interactions in conjunction with other drugs. This work reports complete validated method for the quantitation of ethanol in commercial medicated syrups. For determination of ethanol headspace gas chromatography and different methods of quantitative analysis were used. The analyzed samples of commercial medicated syrups available on the home marked contained from 3.37 to 8.65% (v/v) of ethanol. The estimated theoretical values of blood ethanol concentration for children after single recommended dose ingestion were at least twice lower than 0.125 g/mL. The process of validation showed that the applied GC method is selective, sensitive, linear and precise. The use of internal standard makes it accurate. The developed method could be considered as an analytical tool for the quality control of various liquid drug preparations.

Keywords: ethanol content, liquid drug preparations, medicated syrups, headspace sampling, quality control

Ethanol is a common substance which occurs in various formulations of pharmaceutics. It is very often used as a solvent. An addition of ethanol may be also applied to increase solubility of some ingredients which are less soluble in water. The other function of ethanol is a preservation against microbial attack (1).

Ethanol content in pharmaceutics depends on formulation and varies in the wide range – from fraction to tens of percent (2–4). The highest ethanol concentrations are characteristic for liquid formulations, including solutions, syrups, suspensions and emulsions. On the other hand, these preparations are most convenient for pediatric patients who are very often unable to swallow the solid preparations like capsules or tablets (5). Kulkarni et al. have reported that nearly 80% of pediatric medicines are produced as liquids and ethanol content in these products is in the range from 2.3 to 20% (6).

Administration of ethanol can cause hypoglycemia and central nervous system effects including decreased reaction time, muscular incoordination, behavioral changes etc. (3, 5, 7). It has been reported that even prenatal exposure to ethanol may have an influence on child development, including hyperactivity and attention problems, learning and memory deficits and problems with social and emotional development (8, 9). Moreover, medicines containing alcohol may cause undesirable interactions in conjunction with other drugs (e.g., psychiatric medicines or disulfiram) (3, 10, 11). Disulfiram-like reactions are also observed in some individuals after the simultaneous use of alcoholic beverages or medicinal elixirs and antibacterial drugs which are common pediatric medicines (maxolactam, metronidazole, sulfonamides, chloramphenicol, cefamandole) (3, 7, 12).

Due to the harmful effects associated with children exposure to ethanol, the American Academy of Pediatrics proposed the limit for the inclusion of ethanol in OTC pediatric formulations of 5% (v/v) (3). In consequence, a simple and accurate methods for the determination of ethanol are needed, but there is limited information in the literature about determining of ethanol content in this group of drugs. The most popular method is based on the density measurements of distillates by pycnometer or aerometer (13–18). This method is also recommended by the European Pharmacopoeia (19). The literature reports that for the quantitative analysis of

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ethanol gas chromatography method is also used (13–15). Gharate et al. determined ethanol content in Ayurvedic formulations. In their studies the samples were analyzed chromatographically after previous distillation (14). The other method of sample preparation has been reported by Pienta et al., who applied liquid-liquid extraction by 1-pentanol to extract of ethanol from cough syrups (15). The headspace method applied for the diluted samples of liquid herbal drugs by Apers et al. (13) seems to be the most interesting, however, requires very expensive instrumentation (HS-GC-MS).

The medicated syrups are the preparations with very high viscosity and density due to high sugar content. It makes determination of alcohol in this group of products significantly difficult. Tarko and Tuszyński have evaluated methods which may be used for determination of alcohol content in similar products – alcoholic emulsion creams (16). Their results indicated that methods based on the density measurements of distillates by both pycnometer and oscillation density meter are credible and characterized with relatively high precision (16), which strongly depends on the presence of other volatile compounds and technical aspects of a distillation process (condensation efficiency, tightness of apparatus) (18). Unluckily, these methods are the most time-consuming and not applicable for the samples with small amount of ethanol (16, 18). The less time-consuming are refractometric and chromatographic methods. The disadvantage of refractometric determination of ethanol is applying of benzene or toluene for extraction. Chromatographic determination of ethanol after solid-phase microextraction in a headspace system does not require any previous sample preparation and is distinguished with high precision (16).

In this investigation, for determination of ethanol content in medicated syrups two strategies were assumed. The first strategy is based on the method recommended by European Pharmacopoeia. According to this method, distillation of samples was preformed, but ethanol was determined by headspace gas chromatography method. The second strategy involves analyses of diluted samples without previous distillation.

EXPERIMENTAL

Equipment

The analyses were performed using a CHROM 5 gas chromatograph with FID detectors (Laboratorni Přístroje Praha, Czech Republic). The apparatus was provided with two steel chromatographic columns. Column I was 2 meter long of 3 mm inside diameter packed with 8% SE-30

(Supelco, Bellefonte, PA, USA) + 0.21% Carbowax 20M (Supelco, Bellefonte, PA, USA) on Chromosorb W NAW, 60–80 mesh (Johns Manville, Denver, CO, USA). Column II was 1 meter long of 3 mm inside diameter packed with Chromosorb 102, 80–100 mesh (Johns Manville, Denver, CO, USA). The following temperatures were applied: column I 50°C, column II 100°C, injectors 120°C, detectors 150°C. As a carrier gas the nitrogen (40 mL/min) was used. The qualitative analysis was performed using both columns, whereas the quantitative analyses were performed only using column II.

Ultrathermostat UL-1 with accuracy of temperature control ±0.05°C (WAT Horyzont, Kraków, Poland) was used to stabilize the samples at temperature 30°C.

Chemicals

Ethanol and methanol were analytical standard grade (≥99.9% GC) from Fluka (Buchs, Switzerland). n-Propanol and 2-propanol were for gas chromatography grade from Merck (Darmstadt, Germany). To prepare a simple syrup sugar available on the home market was used. Redistilled water was used as solvent.

Seven medicated syrups available on the home market were analyzed as the samples. There were cough, expectorant and sedative syrups. The packaged volume of all analyzed products was 125 mL.

Solutions

The simple syrup was prepared by dissolving 850 g of sugar in redistilled water in order to obtain 1000 mL of the solution. Redistilled water temperature was about 60°C.

Internal standard solution of methanol was prepared by diluting the appropriate amount of substance in order to obtain concentration of 100 mg/mL.

Water solutions of ethanol were prepared by dissolving the appropriate amount of substance in order to obtain following concentrations: 20 mg/mL, 25 mg/mL and 500 mg/mL.

Preparation of syrup samples

The samples of syrups were prepared in different ways, which depended on applied method. Determination of ethanol in syrups was carried out by standard addition, external and internal standard methods.

External standard method (ESM-syrup)

The volume of the analyzed syrups of 1 ml was pipetted into measuring flasks and diluted with

Table 1. Ethanol content in commercial syrups determined by different method.

Syrup	Content of ethanol[a] ± SD (mg/mL) coefficient of variation (%)					
	ESM-syrup	ESM-distillate	ISM-syrup	ISM-distillate	SAM-syrup	DSM-syrup
S1	66.55 ± 1.57[ac] 2.36	70.72 ± 1.84[b] 2.60	68.22 ± 0.95[ab] 1.39	67.39 ± 2.23[abc] 3.31	62.16 ± 2.54[c] 4.09	66.08 ± 2.60[abc] 3.93
S2	57.25 ± 0.83[ad] 1.45	66.22 ± 2.88[b] 4.35	59.06 ± 0.82[ac] 1.39	59.78 ± 1.08[c] 1.81	54.82 ± 2.03[d] 3.70	59.36 ± 1.31[ac] 2.21
S3	44.47 ± 0.48[ad] 1.08	49.91 ± 1.67[b] 3.35	46.22 ± 0.57[c] 1.23	46.60 ± 1.05[c] 2.25	43.04 ± 1.44[a] 3.35	46.25 ± 1.36[cd] 2.94
S4	30.10 ± 0.57[a] 1.89	34.47 ± 1.01[b] 2.93	33.66 ± 1.25[bc] 3.71	32.39 ± 0.69[c] 2.13	29.63 ± 1.36[a] 4.59	33.07 ± 0.81[bc] 2.45
S5	25.28 ± 0.47[a] 1.86	29.08 ± 0.89[b] 3.06	26.17 ± 0.56[ad] 2.14	26.12 ± 0.92[ad] 3.52	23.62 ± 0.53[c] 2.24	26.46 ± 0.48[d] 1.81
S6	43.78 ± 0.71[a] 1.62	50.29 ± 0.56[b] 1.11	47.75 ± 0.79[c] 1.65	47.41 ± 0.93[c] 1.96	42.69 ± 0.87[a] 2.04	48.10 ± 1.00[c] 2.08
S7	36.94 ± 0.25[a] 0.68	41.75 ± 0.88[b] 2.11	38.86 ± 0.36[c] 0.93	39.31 ± 0.66[c] 1.68	34.63 ± 0.59[d] 1.70	38.13 ± 0.79[ac] 2.07

[a] average of three determinations, ESM – external standard method; ISM – internal standard method; SAM – standard addition method; DSM – dual standard method (internal standard and standard addition), values marked with the same letter for particular syrups are not significantly different (t-Student's test, α = 0.05)

redistilled water to a total volume of 10 mL. Next 5 mL of diluted samples were placed into 65 mL headspace vials.

Internal standard method (ISM-syrup)

The samples were prepared in the similar way as for ESM-syrup analysis. In this case 0.25 mL of IS-solution of methanol was added to each sample before filling up to 10 mL.

Standard addition methods

After the analyses of ethanol content by the external and internal standard methods 40 µL of ethanol solution (500 mg/mL) was added into the each vial and after a stabilization, the samples were analyzed by standard addition method (SAM-syrup) and dual standard method (DSM-syrup). The latter method is based on two standards, i.e., internal standard (methanol) and ethanol standard.

Preparation of distillates for analysis

Twenty five mL of the analyzed sample was measured at room temperature, transferred into the distillation flask and diluted with 100 mL of redistilled water. A few pieces of pumice were added into the distillation flask and the distillation head and condenser were attached. The distillate was collected in a 100 mL volumetric flask which was cooled in an ice-water mixture to obtain about 90 mL. Then, the collected solution was adjusted to the room temperature and diluted with distilled water to 100 mL.

To determine the ethanol concentration in the distillate headspace technique was used. Two methods were applied and for both of them 5 mL of analyzed distillate was transferred into two head-space vials. The first was analyzed by the external standard method (ESM-distillate) and the second by the internal standard method (ISM-distillate). Using the internal standard method 100 µL of IS-solution of methanol was added into the headspace vial contained 5 mL of distillate.

Additionally, the ethanol concentration in distillates was also determined by pycnometer method according to European Pharmacopoeia (19).

Table 2. The average corrected values of ethanol content in commercial syrups determined by proposed methods and by the European Pharmacopoeia (EP) method.

Syrup	Average concentration[a] ± SD (mg/mL)	Coefficient of variation (%)	Confidence interval[b] (mg/mL)	Average ethanol content ± SD (% vol.)	
				Proposed methods[c]	EP method[d]
S1	68.25 ± 1.85	2.71	66.31–70.19	8.65 ± 0.23	8.46 ± 0.15
S2	60.60 ± 1.53	2.52	58.99–62.21	7.68 ± 0.19	7.65 ± 0.10
S3	47.02 ± 0.92	1.96	46.05–47.99	5.96 ± 0.12	5.92 ± 0.09
S4	32.86 ± 0.77	2.34	32.05–33.67	4.16 ± 0.10	4.11 ± 0.09
S5	26.63 ± 0.62	2.33	25.98–27.28	3.37 ± 0.08	3.41 ± 0.04
S6	47.59 ± 0.79	1.66	46.76–48.42	6.03 ± 0.10	5.97 ± 0.08
S7	39.02 ± 0.40	1.03	38.80–39.44	4.94 ± 0.05	4.90 ± 0.05

[a] average of six results obtained by proposed methods (ESM-syrup, ESM-distillate; ISM-syrup, ISM-distillate; SAM-syrup; DSM-syrup), [b] n = 6 (number of methods used to determine of ethanol content), α = 0.05, [c] calculated on the basis of average concentration expressed in mg/mL, [d] average of three determinations

Standard solutions for calibration

The ESM-syrup standard solutions were prepared by pipetting 1 mL of the simple syrup into five measuring flasks of 10 mL capacity and respectively 0.5, 1.0, 2.0, 4.0 and 5.0 mL of ethanol solution (20 mg/mL). Redistilled water was added up to a total volume of 10 mL. The ISM-syrup standard solutions were prepared in the similar way, but before filling up 0.25 mL of IS-solution was added to each flask. Next, 5 mL of ESM-syrup standard solution or ISM-syrup standard solution was pipetted into 65 mL headspace vials.

In order to prepare the ESM-distillate standard solutions 0.25, 0.5, 1.0, 2.0, 4.0 and 5.0 mL of ethanol solution (25 mg/mL) were placed into 65 mL headspace vials and redistilled water was added up to a total volume of 5 mL. The ISM-distillate standard solution was prepared in the same way, but 100 µl of methanol IS-solution was additionally added into each vial.

Headspace sampling

Before analyses, the headspace vials with the samples were stabilized in the UL-1 ultrathermostat at 30°C for 1 hour. Headspace sampling was performed by manual pressurization with a Hamilton gas-tight syringe. During the initial step, the syringe needle was inserted into the vial and the vial content was pressurized with 0.5 mL of clean air. The headspace samples of 0.5 mL volume were drawn with the syringe and analyzed using a CHROM 5 gas chromatograph.

RESULTS AND DISCUSSION

The samples of medicated syrups and their distillates were analyzed in triplicate. When diluted samples of syrups were analyzed, the ethanol content was estimated direct from linear equation of proper calibration curve. Results calculated from calibration curves for distillates were multiplied by four to obtain the ethanol content in the preparation. All results are summarized in Table 1. It was found that the ethanol concentration in the analyzed samples was in the range of 25–70 mg/mL but the results obtained by different methods were significantly different. Differences between standard deviations of determined ethanol content were insignificant (F-Snedecor test was applied) so to compare the results the Student's *t*-tests were performed (α = 0.05). Values which were not significantly different, shown in Table 1, are marked with the same letters. The biggest differences were observed when external standard method was applied. It can be a result

of sample matrix composition. In the ESM-distillate method matrixes of samples and standard solutions for calibration were very similar (distilled water). The standards for the ESM-syrup method contained only distilled water, sugar and ethanol, whereas matrixes of real samples were more complex. It could have an influence on equilibrium between ethanol concentrations in the liquid and the gas

Table 4. Data of applied methods linearity.

Parameter	Method			
	ESM-syrup	ESM-distillate	ISM-syrup	ISM-distillate
Concentration range (mg/mL)	10–100[a]	1.25–25[b]	10–100[a]	1.25–25[b]
Detector response	Ethanol peak area	Ethanol peak area	Ethanol/methanol peak area ratio	Ethanol/methanol peak area ratio
Number of standards (triplicate)	5	6	5	6
Slope ± SD	4.0795 ± 0.0265	36.7930 ± 0.1598	0.0797 ± 0.0003	1.1014 ± 0.0037
Intercept ± SD	-11.255 ± 1.4751	-9.7107 ± 2.2203	-0.1845 ± 0.0210	-0.2018 ± 0.0513
Intercept confidence interval ($\alpha = 0.05$)	-11.9921 to -10.5179	-10.8201 to -8.6013	-0.1962 to -0.1728	-0.2275 to -0.1761
Correlation coefficient	0.9997	0.9998	0.9998	0.9999

[a] values which correspond to ethanol content in syrup, [b] values which correspond to ethanol content in distillate

Table 3. Chromatographic separation parameters for alcohols (column II: Chromosorb 102, 80–100 mesh).

Parameter	Methanol	Ethanol	2-Propanol	1-Propanol
Retention time (min)	2.81	6.94	14.84	22.72
Column efficiency[a] (mm)	1.63	1.07	1.38	1.45
Resolution[b]	6.1	-	5.0	7.3
Selectivity[b]	2.7	-	2.2	3.4
Tailing factor	1.4	1.2	1.3	1.4
Asymmetry factor	1.0	1.4	1.5	1.5

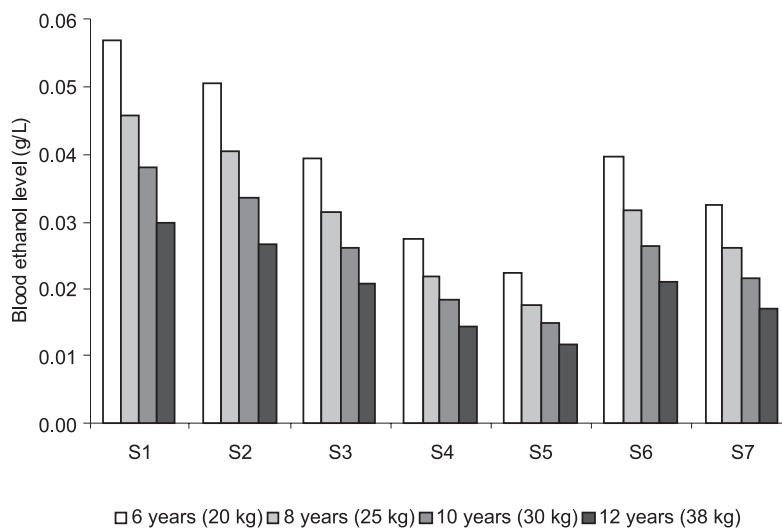[a] the height equivalent to a theoretical plate, [b] related to ethanol

Figure 1. Estimated blood ethanol level after ingestion of 10 mL of syrup for children between 6 and 12 years of age

Table 5. Results of recovery test.

Method	Recovery[a] (%)				Mean recovery[b] ± SD	Coefficient of variation (%)	Confidence interval[c] (%)	Student's t-test parameter[d]
	20 mg/mL	40 mg/mL	50 mg/mL	70 mg/mL				
ESM-syrup	91.0	92.4	97.6	95.0	94.0 ± 2.9	3.1	89.4–98.6	4.138
ESM-distillate	103.6	101.8	109.0	107.0	105.4 ± 3.3	3.1	100.1–110.6	3.242
ISM-syrup	97.2	101.1	98.6	102.0	99.7 ± 2.2	2.2	96.2–103.2	0.250
ISM-distillate	102.5	102.9	99.6	100.9	101.5 ± 1.5	1.5	99.1–103.9	1.967
SAM-syrup	88.9	84.8	90.7	90.3	88.7 ± 2.7	3.0	84.4–93.0	8.389
DSM-syrup	99.4	99.7	97.2	99.9	99.1 ± 1.3	1.3	97.0–101.1	1.462
According to EP	96.9	97.9	98.6	98.5	98.0 ± 0.8	0.8	96.7–99.2	5.063

[a] average of three determinations, [b] average value for different levels of concentration, [c] n = 4 (number of concentration levels), $\alpha = 0.05$, [d] expected value 100%, $t_{crit\,(n=4,\,\alpha=0.05)} = 3.182$

phase. The similar effect can be observed when diluted syrups are analyzed by SAM-syrup method. By both ESM-syrup and SAM-syrup methods the lowest values of ethanol concentrations were obtained. The mentioned differences in matrixes can be eliminated by using of internal standard, which has properties similar to ethanol (methanol, 1-propanol or 2-propanol). It was found that contents of ethanol determined by methods with the use of methanol as an internal standard were consistent. To verify above considerations recovery tests were performed.

On the basis of the determined values of recovery (section Accuracy and precision) corrected contents of ethanol in analyzed syrups for all six proposed methods were calculated. It was found that the obtained values of concentrations for particular syrups were not significantly different, so they were averaged. The mean concentrations, standard deviations, variation coefficients and confidence intervals were calculated and are collected in Table 2. The ethanol content expressed in % vol. obtained by proposed methods were compared with values determined by European Pharmacopoeia method. Differences between these values were insignificant (Student's t-test, $\alpha = 0.05$).

It was found that almost 60% of analyzed commercial syrups contain ethanol over recommended value of 5% (v/v) (3). To estimate a risk associated with taking of the analyzed syrups, potential blood ethanol level for children aged between 6 and 12 years after ingestion of 10 mL of syrup (typical target dose volume for pediatric liquid formulations for children of 5 years and older) was calculated. The blood ethanol concentration following a single dose of syrup should not exceed 0.125 g/L. Above this value the psychomotor dysfunctions can be observed. The blood ethanol concentration (*BEC*) was calculated as follows:

$$BEC = \frac{m}{V_D W_B} = \frac{CV}{V_D W_B}$$

where m is ingested ethanol amount, V_D is volume distribution, W_B is body weight, C is concentration of ethanol in syrup and V is volume of syrup. It was assumed that the entire dose is completely and instantaneously absorbed, the volume of distribution is constant (0.6 L/kg) and ethanol degradation is not observed (5). The calculated values of blood ethanol concentration for children are presented in Fig. 1. If the recommended volume of syrup is not exceeded (10 mL), *BEC* will be at least twice lower than 0.125 g/mL. Additionally, in a case of an accidental ingestion of the entire content of syrup bottle (125 mL)
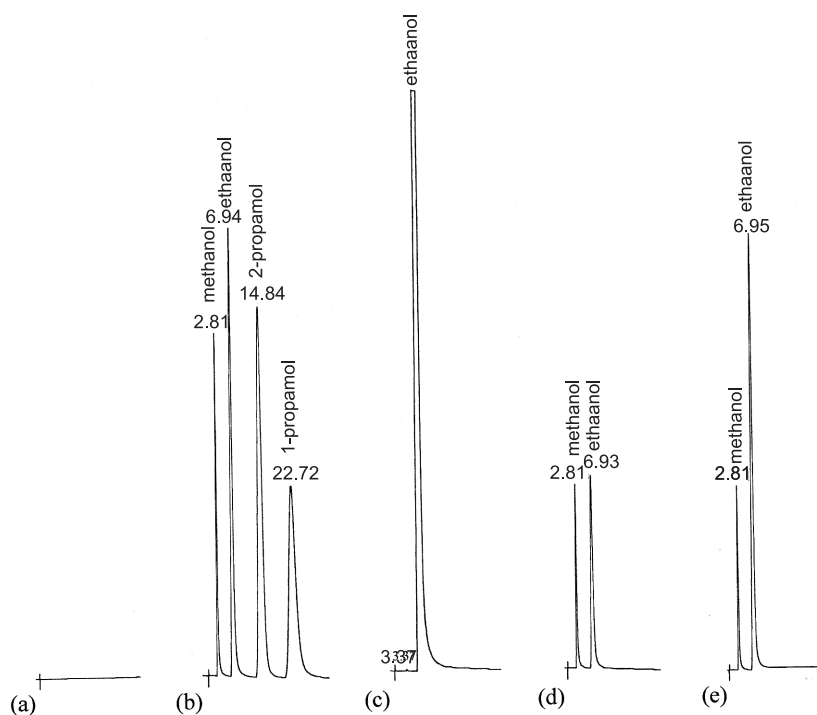
Figure 2. Headspace chromatograms of (a) blank sample, (b) alcohol standard mixture, (c) undiluted sample S7, (d) diluted sample S7 with internal standard (ISM-syrup method) and (e) diluted sample S7 with dual internal standard (DSM-syrup method)
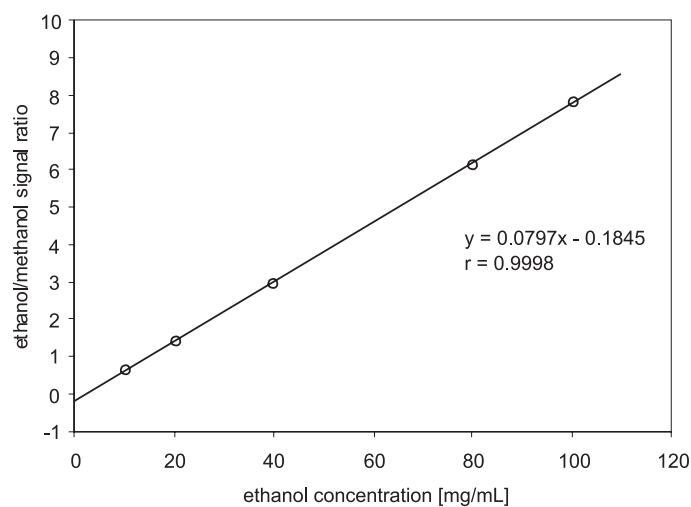

Figure 3. Calibration curve obtained for ISM-syrup method

the toxic ethanol blood concentration (1 g/L) would not be exceeded too.

Method validation
Selectivity and resolution
    The selectivity of the chromatographic method depends on the resolution of the targeted compounds

and on the absence of interference. In the present paper, the resolution was defined between ethanol and other potential sample components. The ethanol-containing liquid formulation can also include the other alcohols like methanol and 2-propanol. European Pharmacopoeia recommends test of these alcohols content in liquid drug prepara-

tions. The specificity of the gas chromatography method was checked by analysis of a blank sample (the simple syrup), a sample containing the simple syrup and alcohol standard mixture, and the real samples. The samples were analyzed according to the experimental methods. Obtained chromatograms are presented in Fig. 2. The presence of methanol and 2-propanol in the commercial syrups was not confirmed (Fig. 2c), so methanol was chosen to be used as an internal standard (Fig. 2d, e). If methanol or 2-propanol were present in the sample, 1-propanol would be used as the standard. Ethanol had chromatographic resolution more than 1.5 from the other peaks. The chromatographic separation parameters are summarized in Table 3.

Linearity and range

Linearity of methods was studied by analyses of standard solutions at different concentration levels, with triplicate determination at each level. Standard solutions were prepared and analyzed according to the above described methods. The calibration curves were constructed by plotting detector responses against corresponding concentrations using the least squares linear regression method. As the detector response, ethanol peak area or ethanol/methanol peaks area ratio were used and concentrations expressed ethanol content in a syrup or in a distillate. The calibration curves values of slopes (b), intercepts (a) and correlation coefficients are presented in Table 4. All parameters indicate good linearity of the applied methods. The concentrations of calibration standards correspond to the range from 20 to 150% or from 40 to 150% of ethanol concentration in commercial syrups samples. An example of the calibration curve is presented in Fig. 3.

Accuracy and precision

Recovery tests were performed for evaluation of applied methods accuracy. Syrups used for recovery tests contained 20, 40, 50 and 70 mg/mL of ethanol. They were prepared in a volumetric flasks of 100 mL and contained the simple syrup and appropriate amounts of ethanol. Ethanol content in these syrups was determined according to previously described methods. The analyses were replicated three times for each concentration level. The values obtained for particulate methods were averaged. Results are summarized in Table 5.

The mean recoveries calculated for the internal standard methods (ISM-syrup, ISM-distillate, DSM-syrup) were proven to be equal to 100%. The Student's t-test parameters determined for these methods were below critical value ($t_{crit (n=4, \alpha=0.05)}$ = 3.182). Values of recoveries for ESM-syrup and SAM-syrup methods were substantially lower than 100% and were found to be 94.0 ± 2.9 and 88.7 ± 2.7%, respectively. Recovery value determined for ESM-distillate method was also significantly different from 100% but it was higher and was found to be 105.4 ± 3.3%. The matrixes of samples and standard solutions in recovery tests were the same, so it was stated that besides the effects of matrix, the errors associated with manual sampling affected the results of determination. The use of the internal standard makes possible to eliminate both problems. The recovery test conducted for European Pharmacopoeia method indicate good accuracy 98.0%, however, by reason of low CV value (0.8%) the obtained recovery was not proven to be equal to 100%. Variation coefficients of results obtained by proposed methods were in the range from 1.3 to 3.1%. These values indicate very good precision of applied methods. Variation coefficients for the real samples were a bit higher, but did not exceed 5% (Table 1).

Detection and quantitation limits

For external and internal standard methods limit of detection (LOD) was determined based on the residual standard deviations ($S_{x,y}$) and a slope (b) of the calibration curves according to the formula:

Table 6. Limits of detection and quantitation of applied method.

Method	LOD		LOQ	
	(mg/mL)	(% vol.)	(mg/mL)	(% vol.)
ESM-syrup	1.88	0.24	5.65	0.70
ESM-distillate	0.31	0.04	0.94	0.12
ISM-syrup	1.11	0.14	3.32	0.42
ISM-distillate	0.24	0.03	0.73	0.09
SAM-syrup	1.09	0.14	3.27	0.41
DSM-syrup	1.11	0.14	3.32	0.42

$$LOD = \frac{3.3 S_{x,y}}{b}$$

For methods where ethanol was added as a standard (SAM-syrup, DSM-syrup) the limits were determined in a different way. Ten blank samples were prepared and ethanol content (*C*) was determined. It was near the expected value of *LOD* (1 mg/mL). Standard deviations of the results (*SD*) were calculated and the limits of detection were determined as follows:

$$LOD = C_{mean} + 3SD$$

The limits of quantitation (*LOQ*) were calculated by triplicate multiplying of *LOD* values. The limits of detection and quantitation for all methods are collected in Table 6. The concentration range for which the methods were validated was above values of *LOQ*. All calculated limits of quantitation were below 1% (v/v), therefore, the developed methods are suitable to control the ethanol content in medicated syrups.

Conclusion

A user-friendly static headspace gas chromatography method to quantify ethanol content in medicated syrups was developed. In described investigation a manual headspace technique was used. The obtained results indicate that the headspace technique can be used without an expensive instrumentation (headspace sampler, mass detector). The process of validation showed that the applied method is selective, sensitive, linear and precise. Trueness of the applied GC method depends on a way of analysis. The use of an internal standard makes it accurate. Described method of analysis of the samples diluted with water and an internal standard may be alternative to the method recommended by European Pharmacopoeia. Gas chromatography also makes possible to determine the ethanol content in distillates (instead of density measurements). The described procedure can be used for the quality control of medicated syrups.

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