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VALIDATION OF AN ANALYTICAL PROCEDURE – CONTROL OF RESIDUAL SOLVENTS IN PHARMACEUTICAL SUBSTANCE

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In this study elements of validation of headspace GC method of determination of residual methanol, n-pentane, ethanol, *tert*-butylamine, 2-propanol, acetonitrile, dichloromethane and toluene in pharmaceutical substance are presented. Validation of the method included: selectivity, system precision, method precision, accuracy (recovery), limits of detection and quantitation (in substance), robustness and linearity.

Acceptable levels of these solvents are included in guideline Q3C issued by ICH (1) and must not exceed: methanol 3000 ppm, n-pentane, ethanol, 2-propanol 5000 ppm, acetonitrile 410 ppm, dichloromethane 600 ppm, and toluene 890 ppm. Specification limit has been established for *tert*-butylamine at the level of 1000 ppm.

EXPERIMENTAL

Analytical method

Apparatus: gas chromatograph (Shimadzu GC-2010) with flame-ionization detector, DB-624 column (60 m long, 0.32 mm ID, phase composition: 6% cyanopropylphenyl – 94% dimethylpolysiloxane) and headspace autosampler injector (PerkinElmer TurboMatrix 40).

Chromatographic conditions: column temperature: 40°C, 10 min at this temperature, ramp 40°C/min to 240°C, 8 min at final temperature, injecton port temperature: 200°C, detector temperature: 260°C, carrier gas: nitrogen, pressure: 100 kPa, split ratio: 5.

Headspace conditions: vial oven: 100°C, needle: 110°C, transfer line: 120°C, pressurize: 1 min, inject: 0.05 min, thermostat: 30 min, column: 140 kPa.

Solvent: N,N-Dimethylacetamide (DMA).

Test solution: accurately weighed ca. 100 mg of examined substance into headspace vial and added 5 mL of DMA. Separated vial was prepared for each injection.

RESULTS

Selectivity: The results are presented in Table 1 and Figure 1. The acceptance criterion was: resolution = 1.5 and it was satisfied.

System precision: The results are presented in Table 2. The acceptance criterion was: RSD = 10% and it was satisfied.

Method precision: The results are presented in Table 3. Methanol, ethanol, 2-propanol, acetonitrile, dichloromethane, toluene were not determined. The acceptance criterion was: RSD = 15% and it was satisfied.

Accuracy (recovery): The results are presented in Table 4. The accuracy of the method was examined with the use of 9 independent samples spiked with analytes at 50%, 100% and 120% of specification. The acceptance criteria were: recovery 80% ÷ 120%, RSD = 15% and were satisfied.

Quantitation and detection limits: The results are presented in Table 5. The acceptance criterion was: LOQ = 50% of the specification limit and it was satisfied.

Robustness: The results are presented in Table 6. The following parameters were changed: carrier gas pressure: A – 90 kPa; B – 110 kPa, column temperature: C – 35°C; D – 45°C, rate: E – 41°C/min; F –

Table 1. Selectivity

Compound	Retention time (min)	Resolution
Methanol	5.94	-
n-Pentane	7.67	15.495
Ethanol	7.96	2.188
tert-Butylamine	9.06	7.375
2-Propanol	9.80	4.554
Acetonitrile	10.28	3.101
Dichloromethane	10.70	3.481
Toluene	17.16	63.965
DMA	19.42	20.359

Table 2. System precision

Compound	The mean of 6 responses	SD	RSD %
Methanol	37314	979.85	2.63
n-Pentane	3741126	61136.86	1.63
Ethanol	69980	1902.30	2.72
tert-Butylamine	130912	2936.12	2.24
2-Propanol	69145	1485.94	2.15
Acetonitrile	6307	283.82	4.50
Dichloromethane	6117	185.84	3.04
Toluene	27700	443.20	1.60

Table 3. Method precision

Compound	Concentration (ppm) (the mean of 6 responses)	SD	RSD %
n-Pentane	65.8	2.02	3.07
tert-Butylamine	722.2	13.51	1.87

Table 4. Accuracy (recovery).

Compound	Recovery % (the mean of 9 responses)	SD	RSD %	Confidence interval %
Methanol	94.4	4.81	5.10	90.7 ÷ 98.1
n-Pentane	100.8	3.01	2.99	98.5 ÷ 103.1
Ethanol	96.2	4.42	4.60	92.8 ÷ 99.6
tert-Butylamine	116.2	4.44	3.82	112.8 ÷ 119.6
2-Propanol	97.8	3.61	3.69	95.0 ÷ 100.6
Acetonitrile	97.1	4.57	4.69	93.6 ÷ 100.6
Dichloromethane	86.9	3.92	4.51	83.9 ÷ 89.9
Toluene	96.5	5.54	5.74	92.2 ÷ 100.8

Table 5. Quantitation and detection limits

Compound	Acceptable levels (ppm)	Limit of quantitation LOQ (ppm)	Limit of detection LOD (ppm)
Methanol	3000	90	27
n-Pentane	5000	1.5	0.5
Ethanol	5000	200	70
tert-Butylamine	1000	38	12
2-Propanol	5000	120	40
Acetonitrile	410	100	50
Dichloromethane	600	100	60
Toluene	890	40	16

Table 6. Robustness

Compound	Resolution						
	Standard method	A	B	C	D	E	F
Methanol	-	-	-	-	-	-	-
n-Pentane	15.423	16.559	14.325	16.409	14.295	15.421	15.408
Ethanol	2.240	2.375	2.128	3.167	1.543	2.246	2.245
tert-Butylamine	7.492	8.338	7.025	7.595	7.536	7.473	7.500
2-Propanol	4.499	4.280	4.236	5.040	3.701	4.500	4.514
Acetonitrile	3.046	3.164	2.948	2.566	3.381	3.111	3.066
Dichloromethane	3.659	3.797	4.061	3.463	4.232	3.716	3.707
Toluene	69.504	72.251	58.591	68.477	63.065	68.864	69.222

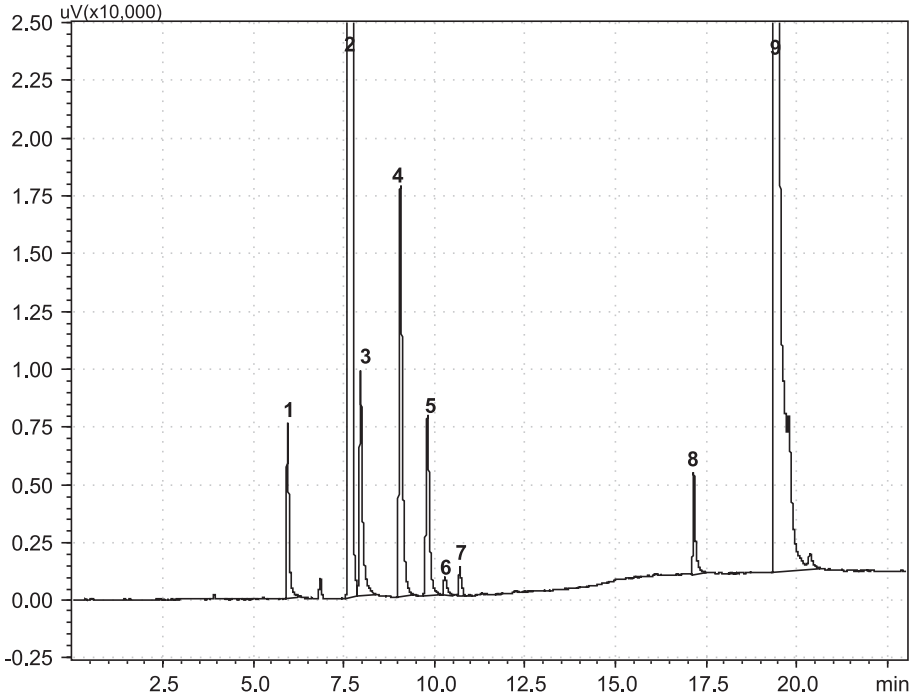

Figure 1. Selectivity solution chromatogram. 1 – methanol; 2 – n-pentane; 3 – ethanol; 4 – *tert*-butylamine; 5 – 2-propanol; 6 – acetonitrile; 7 – dichloromethane; 8 – toluene; 9 – DMA.

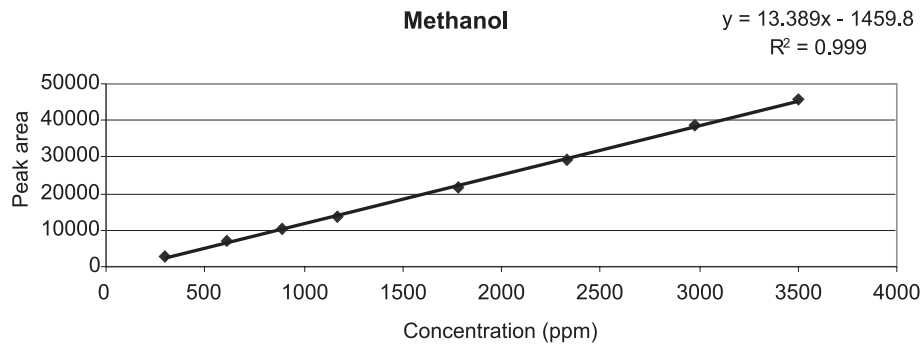

Figure 2. Linearity of methanol determination.

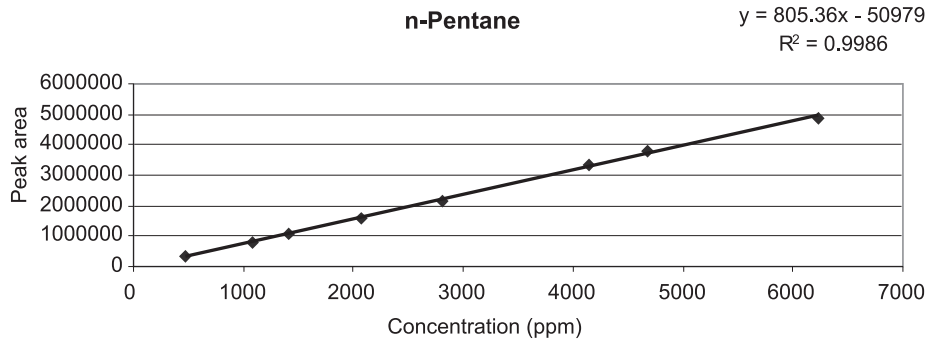

Figure 3. Linearity of n-pentane determination.

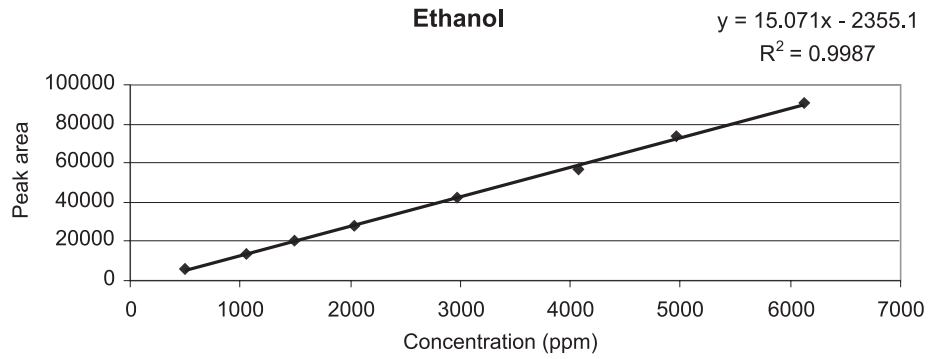

Figure 4. Linearity of ethanol determination.

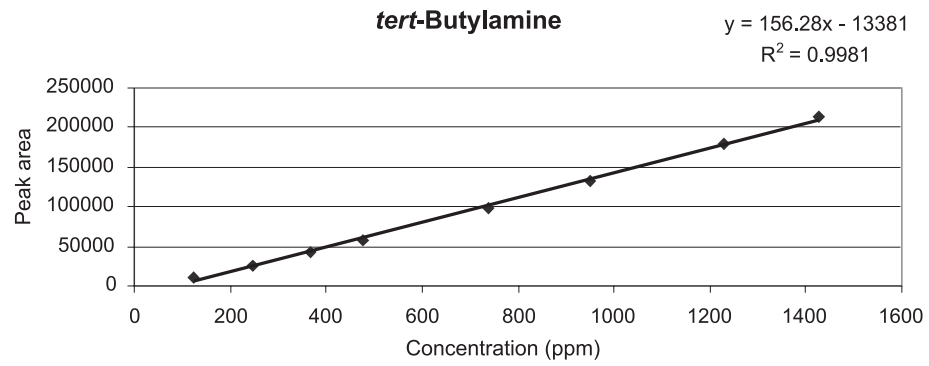

Figure 5. Linearity of *tert*-butylamine determination.

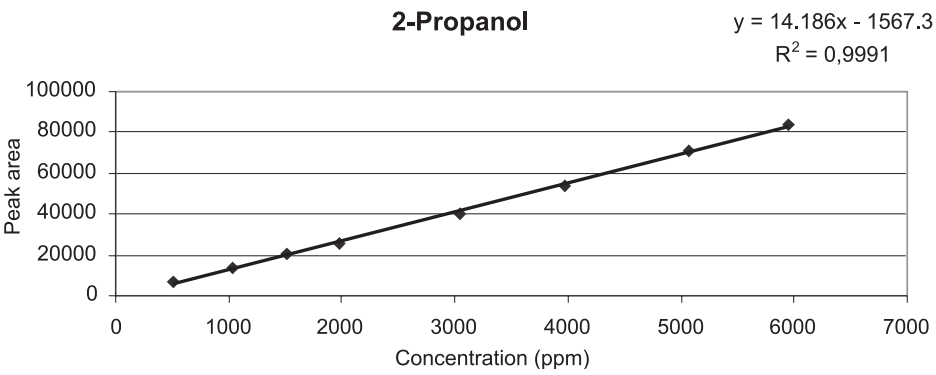

Figure 6. Linearity of 2-propanol determination.

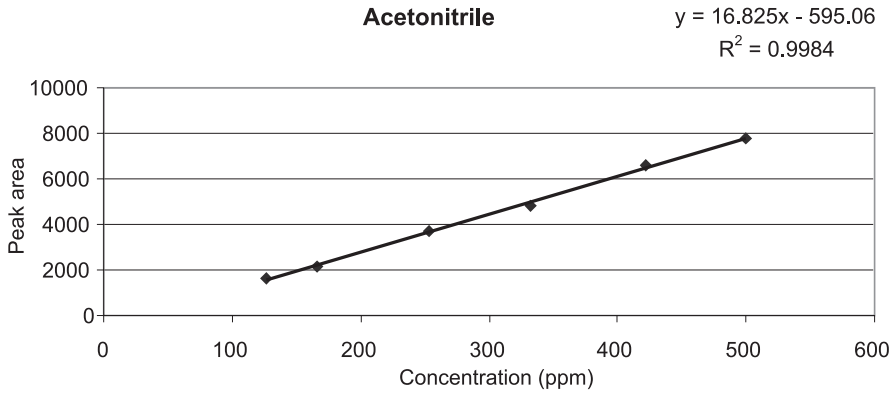

Figure 7. Linearity of acetonitrile determination.

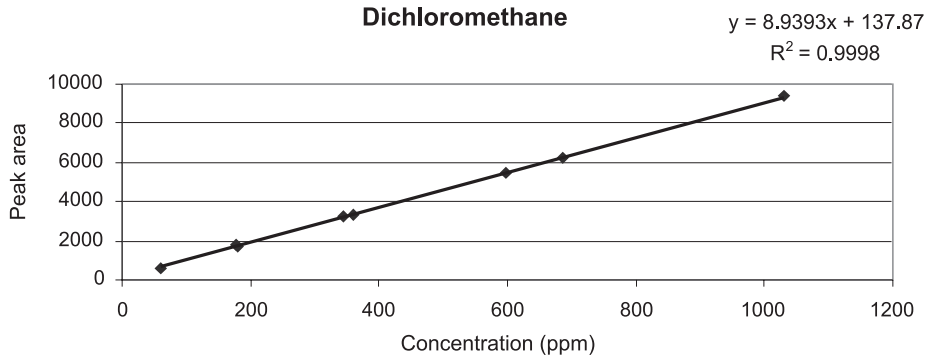

Figure 8. Linearity of dichloromethane determination.

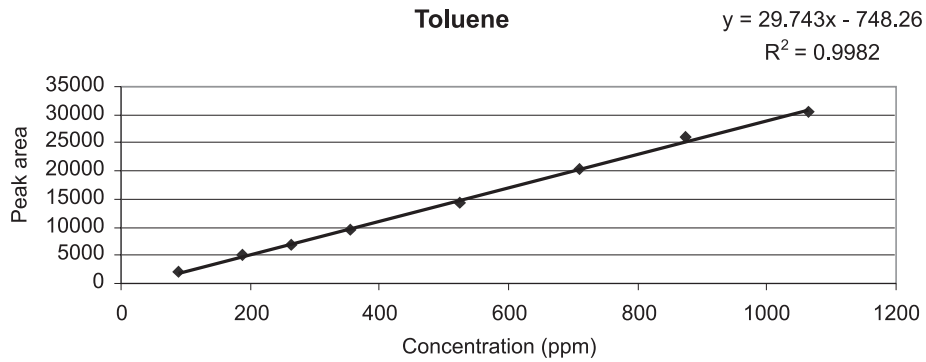

Figure 9. Linearity of toluene determination.

39°C/min. The acceptance criterion was: resolution = 1.5 and it was satisfied.

Linearity: The results are presented in Figures 2 – 9. The acceptance criterion was: $R^2 = 0.98$ and it was satisfied.

CONCLUSION

Validation results demonstrate that analytical procedure – Control of residual methanol, n-pentane, ethanol, *tert*-butylamine, 2-propanol, acetonitrile, dichloromethane and toluene in pharmaceutical substance by GC method – is suitable for its intended purpose. All the parameters fall within the limits desired for the method.

REFERENCES

1. Proceeding of International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Tripartite harmonised guideline Q3C „Impurities: Residual Solvents", 1997.