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GC METHOD FOR QUANTITATIVE DETERMINATION OF RESIDUAL 2-(2-CHLOROETHOXY)ETHANOL (CEE) AND N-METHYL-2-PYRROLIDINONE (NMP) IN QUETIAPINE

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Quetiapine is an antipsychotic drug belonging to the group of the dibenzothiazepines and used for the treatment of schizophrenia and other psychotic syndromes (1, 2). Quetiapine is used in a form of tablets containing 25, 100, 150 and 200 mg of the active substance.

This active substance in the present study was synthesized with the use of N-methyl-2-pyrrolidone as a solvent and 2-(2-chloroethoxy)ethanol as starting material. N-methyl-2-pyrrolidone: NMP, structural formula C_5H_9NO; CAS number 872-50-4, boiling point 202°C at 101.3 kPa, 2-(2-chloroethoxy)-ethanol: CEE, structural formula $C_4H_9ClO_2$; CAS number 628-89-7 , boiling point 200°C at 101.3 kPa. The solvents and starting material are often not totally removed by practical manufacturing techniques, and consequently low levels are present in most pharmaceuticals.

Acceptable levels of many residual solvents are included in guideline Q3C issued by ICH (3). In this guideline, the ICH classified solvents in three categories and set limits depending on toxicity data for each solvent. The Expert Working Group (EWG) received new toxicity data for the solvent NMP late last year. The consensus was to remove NMP from Class 2 with a permissible daily exposure (PDE) of 48.4 mg/day (4840 ppm) and place it into Class 2 too but with a new PDE of 5.3 mg/day (530 ppm) (4). CEE is unclassified but it is known impurity so was specified with acceptance criterion of 0.10% (5). The European Pharmacopoeia (Eur. Ph.) included this guideline in the chapter "Residual Solvents" (6) and described a general procedure for identification and control of residual solvents in a drug substances. Some problems have been overcome, for instance quantitative determination of non-volatile solvents such as 2-(2-chloroethoxy)-ethanol (CEE) and N-methyl-2-pyrrolidinone (NMP). In the literature there are not information about the methods for simultaneous determination of CEE and NMP in the Quetiapine and other substances.

In the present study, a gas chromatographic method with direct injection for the determination of CEE and NMP in the active substance has been developed. This method can be also applied to quantitative determination of other residual solvents used in the synthesis of this active substance: ethanol, acetone, toluene, dichloromethane, benzene (which can be formed from acetone or toluene) as was shown in testing selectivity of the method.

The separation was obtained on a DB-624 column (60 m × 0.32 mm i.d. × 1.0 μm coating thickness). A dimethylformamide was used as sample diluent to obtain good selectivity and sensitivity.

EXPERIMENTAL

Reagents and chemicals

The active substance was synthesised by Ł. Kaczmarek (Pharmaceutical Research Institute, Warsaw, Poland). Ethanol (EtOH), acetone, toluene were provided by POCh (Poland), N,N-dimethylformamide (DMF), dichloromethane (DCM) were purchased from Merck (Germany), benzene was provided by Chempur, 1-methyl-2-pyrrolidone (NMP) was provided by Sigma-Aldrich and 2-(2-chloroethoxy)ethanol (CEE) was provided by Maruzen Chemical (Japan).

Analytical method

Quantitative standard solution of CEE and NMP

Standard solutions were prepared from standard stock solutions. Standard stock solutions were prepared in DMF. *Standard stock solution A:* containing 1000 ppm of CEE; *Standard stock solution B:* containing 1000 ppm of NMP; *Standard solution:* containing 50 ppm of CEE and 26.5 ppm of NMP which coressponds to 1000 ppm of CEE and 530 ppm of NMP in the tested substance.

Qualitative standard solution of CEE and NMP for system suitability

Selectivity solution was prepared to check Eur. Ph. system suitability requirements. A total of 7 solvents were included in this standard solution. *Selectivity solution* contained 250 ppm of EtOH, 250 ppm of acetone, 30 ppm of DCM, 30 ppm of benzene, 45 ppm of toluene, 50 ppm of CEE and 25 ppm of NMP.

Test solution

In this procedure the sample size was 50.0 mg. Test solution containing 5 % of active substance was prepared in DMF. In order to improve poor sample solubility ultrasonic bath was applied.

Blank solution

A blank was prepared using the diluent (DMF), but without sample or standard solution.

Chromatography

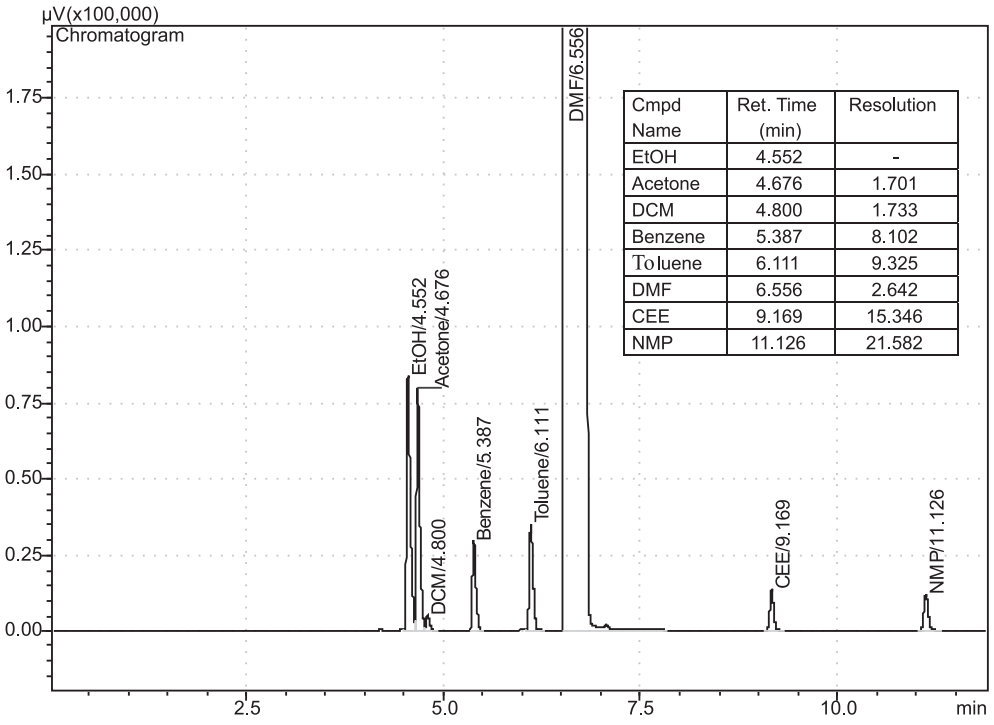
The experiments were performed on a Shimadzu GC-2010 gas chromatograph (GC) equipped with a Shimadzu AOC -20i autosampler and a flame ionization detector. A DB-624 column (phase composition: 6% cyanopropylphenyl – 94% dimethylpolysiloxane) film thickeness 1.8 µm, 60 m long, 0.32 mm ID was used. GC conditions: inlet heater 240°C, detector 260°C, oven initial temperature 150°C, then raised at a rate of 5°C/min to 230°C, then raised at a rate of 40°C/min to 240°C. Nitrogen was used as a carrier gas at 120 kPa (constant flow, approximately 1.56 mL/min) and a split flow of 5 mL/min. FID air flow was 400 mL/min and FID hydrogen flow was 47 mL/min. 1 µL was injected.

Procedure

Separately inject 1 µL of standard solution and test solution into gas chromatograph, each of them 2 or 3 times. Record chromatograms and compare peak areas of analytes from the test and standard solution. Under descibed conditions the retention time of CEE is ca. 9.2 minutes and that of NMP ca. 11.1 minutes.

The mean area of the peak of CEE in the chromatogram from the test solution must not be greater than the mean area of the peak from the standard solution (1000 ppm in the substance).

The mean area of the peak of NMP in the chromatogram from the test solution must not be greater than the mean area of the peak from the standard solution (530 ppm in the substance).



Cmpd Name	Ret. Time (min)	Resolution
EtOH	4.552	-
Acetone	4.676	1.701
DCM	4.800	1.733
Benzene	5.387	8.102
Toluene	6.111	9.325
DMF	6.556	2.642
CEE	9.169	15.346
NMP	11.126	21.582

Figure 1. Selectivity solution chromatogram. Inset: Selectivity results.

The concentration of these analytes may be calculated from the equation:

$$Residual\ solvent\ in\ ppm = \frac{c_{std} \cdot A_{test}}{A_{std} \cdot c_{test}} \cdot 10^6$$

where:
c_{std} – concentration of residual solvents in standard solution, % w/v,
c_{test} – concentration of tested substance in test solution, % w/v,
A_{std} – mean responses (peak area) of analytes in the chromatogram of the standard solution
A_{test} – mean responses (peak area) of analytes in the chromatogram of the test solution.

RESULTS

System suitability test (SST)

The selectivity of the method was evaluated by injecting the selectivity solution to ensure the separation of all analytes. The selectivity solution contained: ethanol, acetone, dichloromethane, toluene, benzene, NMP, CEE, DMF. Resolution was calculated directly by the software: Shimadzu GC solution ver. 2.10. Chromatogram of selectivity solution is shown in Figure 1, the results are presented in Figure 1 (inset) .

Good separation was obtained between all the solvents used in the synthetic route of the active substance.

This method is currently under investigation in our laboratory.

DISCUSSION AND CONCLUSION

In this study, a GC analytical method was developed for control of residual 1-methyl-2-pyrrolidone (NMP) and 2-(2-chloroethoxy)ethanol (CEE) in the active substance. Sample solvent DMF was selected to obtain good selectivity and sensitivity for CEE and NMP. The sample dilution factor was adapted to detect Class 2 solvent – NMP at ICH levels (530 ppm, ICH limit) and unclassified solvent – CEE at known impurity levels (1000 ppm) by FID. The method is selective for all solvents tested. This GC method is suitable for its intended purpose.

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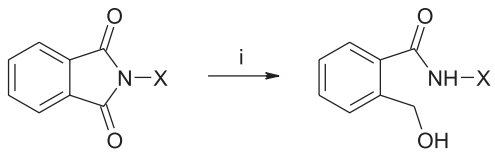
ERRATUM

Erratum to „Synthesis and pharmacological evaluation of 2-hydroxymethylbenzamides as anti-inflammatory and analgesis agents”
[Acta Pol. Pharm. Drug Res. Vol. 63, No. 1, p. 28]
The equation in scheme 3 should be:



i = $NaBH_4$, $MeOH/H_2O$

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