Review Article

A Review on Recent Developments in the Determination of Residual Solvents by Gas Chromatography

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ABSTRACT

Residual solvents are the unwanted substances (solvents) used or created throughout the manufacture of a excipients, drug or pharmaceutical formulation and don't seem to be utterly removed by sensible ways within the final finished product. These solvents may be harmful in nature. Therefore, analysis of residual solvents becomes a necessary tool for the standard management of prescribed drugs. The appropriate limits for these substances are given in ICH (Guideline for Residual solvents, Q3C). The connotation of this paper is to review harmful limit of residual solvents and to debate varied GC techniques to investigate concerning all the residual solvents mentioned in ICH guideline, Q3C. GC is including varied alternative techniques to extend the sensitivity of the tactic. varied techniques enclosed during this study are; gas chromatography, direct injection method, headspace gas chromatography(HSGC), static headspace sampling, dynamic headspace sampling, fast gas chromatography, headspace gas chromatography coupled flame ionisation detector (HSGC-FID), head space gas chromatography- mass spectrometry (HSGC-MS), flow- modulation technique for gas chromatography, thermal desorption- headspace gas chromatography (TD-HSGC), headspace gas chromatography- solid phase microextraction (HSGC-SPME), dual column gas chromatography, multiple headspace- single drop microextraction (MHS-SDME) and headspace gas chromatography- solid phase microextraction- mass spectroscopic analysis (HSGC-SPME-MS). Implementation of various gas chromatographic techniques to some drugs or pharmaceutical preparations are also placed under the paper.

Keywords: Carrier gas, gas chromatography, headspace, residual solvents.

INTRODUCTION

Residual solvents in pharmaceutical products are elucidated as organic volatile chemicals which are employed or may be formed during the manufacture process of drug substances or excipients, or during the process of preparation of drug products. The residual solvents don't seem to been utterly removed by practical manufacturing techniques. Appropriate choosing of the solvent for the synthesis of a drug substance or an excipient could help in the enhancement of the yield, or to determine the characteristics like crystal form, purity, and solubility. Therefore, the solvent could generally sometimes be an essential component in the synthetic process. This general chapter doesn't address solvents deliberately used as excipients, nor does it address solvates. However, the content of solvents in such products ought to be evaluated and justified. Considering, that the residual solvents don't provide any therapeutic profit, they ought to be removed, to the extent possible, to meet up with the ingredient and product specifications, good manufacturing practices, or other quality-based requirements. Drug products ought to contain no higher levels of residual solvents than is supported by safety data. Solvents that are illustrious to cause unacceptable toxicities (Class 1) ought to be avoided with in the production of drug substances, excipients, or drug products unless their use can be strongly justified in a risk-benefit assessment. Solvents related with less severe toxicity (Class 2) ought to be restricted so as to guard patients from potential adverse effects. Ideally, less toxic solvents (Class 3) ought to be used where possible.

It is solely necessary to check for residual solvents that are used or produced in the manufacture or purification of drug substances, excipients, or products. Although makers could favour to take a look at the drug product, a cumulative procedure may be used to calculate the residual solvent levels in the drug product from the levels in the ingredients used in producing the drug product. If the calculation leads to a level equal to or below, no testing of the drug product for residual solvents need be considered. If, however, the calculated level is higher than the counselled level, the drug product should be tested to ascertain whether the formulation process has reduced the relevant solvent level to within the acceptable amount. A drug product may ought to even be tested if a residual solvent is employed throughout its manufacture. Different makers turnout an equivalent pharmaceutical product using completely different organic solvents. Thus, the analysis of residual solvents becomes a difficult analytical task in pharmaceutical analysis and management. Unknown residual solvents are often detected throughout routine quality control testing. An error could occur whereas existing official methods are used in their determination. Hence, there is a need to develop a fast, sensitive methodology that identify, and quantitate all residual solvents in pharmaceuticals.

Methods accepted by pharmacopoeias and ICH guidelines

The first analytical technique for RS, which was published in pharmacopoeias.

Loss of weight

This method could be carried out at normal pressure and/or under vacuum. The loss of weight is a simple and not demanding method, but apart from that it has many disadvantages, including lack of specificity, high limit of detection (about 0.1%), and additionally a relatively huge quantity of sample needed to perform the tests. Moreover, atmospherical humidness will considerably modify the results obtained by the loss of weight technique. Nowadays, for this kind of determination, more sophisticated techniques like thermogravimetric analysis (TGA), differential thermal analysis (DTA) or differential scanning calorimetry (DSC) are used.

Infrared spectroscopy (IR) and Fourier Transform Infrared Spectrometry (FTIR)

These techniques are used to determine residual Tetrahydrofuran, Dichloroethane and Methylene Chloride in polymer samples by measuring the characteristic solvent bands in the spectra. The most common limiting factors is that the high detection limit (above hundred ppm) and an absence of accuracy at low concentrations. Thermogravimetric Analysis (TGA) is employed to estimate the concentration below 100ppm using only a few milligrams of substance. Differential Thermal Analysis (DTA) or Differential Scanning Colorimetry (DSC), are more sophisticated techniques that can be used for the determination of residual solvents. Nowadays all of above methods are replaced by Gas Chromatography (GC) as it has excellent separation ability, and can detect and quantify residual solvent up to a very low detection limits (up to ppb).

Gas chromatography (GC), because of its volatility of organic solvents and the excellent separating capability of capillary columns, it has governed the other analytical methods for RS determinations. It is no wonderment, that the pharmacopoeias have also adopted this excellent technique for RS determination. Gas Chromatography is very oftenly used in the detection of Residual Solvents. Gas Chromatography is an excellent option for residual solvents which have relatively low boiling points and are generally thermostable. The choosing of injection system is determined by the sample type, the types of analytes, their quantity levels and available lab equipment.

1) Direct Injection: The direct injection technique can be utilized when the sample which is tested is soluble in organic solvents (dissolution media) that has low boiling and all other components of sample and also evaporate at relatively low temperature. This method was found to be more time consuming method than headspace chromatography.

2) Headspace: The headspace analysis, is an extraction technique for semi volatile and volatile compounds, and generally can be split up into two forms: static and dynamic.

Static headspace sampling: The liquid or solid sample is placed in a vial and heated. Then a single aliquot of gas is taken from the sample and transferred to gas chromatography. A gas sample is collected after the equilibration between gas and liquid (or solid) phase is reached. It is the major tool for analysis of volatile organic compounds in environment, flavors and fragrance analysis for many years.

Dynamic headspace sampling: In dynamic headspace sampling carrier gas is passed by a liquid sample, and then volatile analytes gets trapped on a sorbent and then desorbs onto a gas chromatography. This is a well- known and validated technique. It is the method of choice for analysis of extremely low (ppb and ppt) concentrations of volatile organic compounds in aqueous matrices. Headspace gas chromatography (HSGC) is a very helpful technique required for the analysis of trace compounds that cannot be injected with syringe or have many difficulties It is an automated instrument which is useful for routine work and also removes the problems related to contamination and sample carry over. Even the non-volatile organic solvents can be detected using HSGC method. under this method organic acids are methylated and converted to volatile methyl esters or dimethyl ester in a headspace vial and then injection is done by means of an auto sampler. The choice of carrier gas can influence the analysis speed. An optimal temperature program rate gives the excellent separation in the less time and it also influence analysis speed. Isothermal analyses provides the rapid overall analysis times for simple mixtures of solutes with similar volatilities in hyphenated techniques.

Evaluations of Residual Solvents

Determination of Residual Solvents in Docetaxel by Headspace Gas Chromatography[1]

Using DB-WAXETR Polyethylene column in gas chromatographic method simultaneous analysis of nine residual solvents can be done. The selection of the columns is proposed through matching of polarities of solutes with stationary phases. The developed gas chromatographic method offers symmetric peak shape, good resolution and reasonable retention time for all the solvents. The limit of detection of methanol, acetone, iso-propanol, ethyl acetate, toluene, dichloromethane, tetrahydrofuran, pyridine and heptane were found to be 0.027, 0.50, 0.12, 0.070, 0.070, 0.180, 0.040, 0.170 and 0.040, respectively. Dimethylformamide was used as blank. The developed GC method with FID detector offers simplicity, selectivity, precision and accuracy. It produces symmetric peak shape and reasonable retention time for various solvents. All the solvents were eluted before fifteen minutes of injection of sample.

Experimental condition of the determination of residual solvents of docetaxel

Head space condition

Injector temperature-250°C, Vial temperature-100°C, Carrier gas (N2)-1.5 ml/min, Loop temperature-110°C, Run time-30 min, Transfer line temperature-120°C, Split ratio-20, Vial equilibration time-20 min, Vial pressurize time-2.0 min.

Detector -(FID) condition

Loop fill time-1.0 min, Detector temperature-270°C, Loop equilibration time-0.5 min, Hydrogen flow-40 ml/min, Injection time-0.2 min, Air flow-400 ml/min, GC cycling time-45 min, Make up flow (N2).

Method development and validation for the determination of residual solvents in methocarbamol pure drug by HS-GC[2]

Using DB-624 in gas chromatographic method simultaneous analysis of four residual solvents can be done. A simple HS-GC method for the determination of residual solvents in methocarbamol using nitrogen as the carrier gas at 3.5mL/min with DB-624 (30 meters X 0.53 mm ID) as column using FID as detector was developed. The retention time for residual solvents singly and in spiked standard solution was determined. The %RSD for six injections should be NMT15%. The percentage recovery ranges from 85-115%. The correlation coefficient R2 ≥ 0.999. The LOD and LOQ was found to be specific. Dimethylsulfoxide was used as blank.

Analytical method for residual solvents determination in Glibenclamide by gas chromatography (GC/FID) with head space[3]

Analysis was performed by headspace GC/FID method on Shimadzu 2014 system with auto sampler HT 200H. Nitrogen was used as carrier gas with constant flow rate of 4.2 mL/min and the separation of residual solvents were achieved on DB-624 column. An analytical method for the quantification of residual solvents in Glibenclamide was established by employing a static headspace gas chromatography (HSGC) coupled with a flame ionization detector (FID). Methanol, acetone and ethylene dichloride as residual solvents determined in Glbenclamide. The analysis was performed on Shimadzu Gas Chromatograph GC-2014 with Headspace Auto sampler HT 200H with flame ionization detector. The injection temperature was 190 ^{0}C and detector temperature was 290°C. Column used was DB- 624 m (30 m long, 0.53 mm internal Diameter coated with 3.0 um film of 6 % Cyanopropylphenyl 94 % Dimethyl polysiloxane). Split ratio of injection 1: 4, Oven temperature was maintain at 40 ^{0}C for 5 min, and then raised at rate of 10 ^{0}C/min to 170 ^{0}C, maintain for 7 min. Total run time was 25min. Nitrogen was used as a carrier gas at a constant flow rate of 4.2 mL/ min Oven temperature was maintain at 40 ^{0}C for 5 min, and then raised at rate of 10 ^{0}C/min to 170 ^{0}C, maintain for 7 min. Total run time was 25 min. Nitrogen was used as a carrier gas at a constant flow rate of 4.2 mL/ min

Headspace gas chromatographic method for determination of residual solvent in five drug substances[4]

The analysis for the simultaneous determination of ethanol, ethyl acetate, tetrahydrofuran, 2-propanol, hexane, dichloromethane and methanol by headspace techniques by employing a flame ionization detector in five drug substances.

Chromatographic Condition

All gas chromatography experiments were carried out by employing a Shimadzu 17A Version. 3 gas chromatograph which was then interfaced with a Shimadzu HSS-4a headspace auto-sampler. The oven temperature program initial temperature was 35 °C for 10 min it was then ramped up at a rate of 15 °C/min to 40 °C and the temperature was maintained for 10 min; it was then ramped up again at a rate of 18 ^{0}C/min to 235 ºC and, after holding for 8 min at 235 °C, the temperature was returned to its initial value. Total run time was 40 minutes.

Headspace conditions

Oven temperature was 80 ◦C for 60 min. The transfer line and loop temperatures were 85 ◦C. The pressurization time was 0.5 min, the loop fill and loop equilibration times were 0.1 min and 0.05 min, respectively, and the injection time was 1.5 min. Vial pressure was 18 p.s.i. and the carrier gas was regulated at 25 mL min^{-1}.

The proposed method utilizes the standard addition technique with an internal standard quantification of seven solvents. This method was validated as per the ICH guidelines Q2A and Q2B. Selectivity, limits of detection and quantitation, linearity, range, precision, recovery and robustness were determined. Excellent results were obtained, within global validation reference values, particularly taken into account the low concentration levels found. The test method was validated and has good reproducibility and linearity for the solvents used in the manufacturing process. The recovery was found to be good and it justified the preparation of the standard in DMSO without the product as matrix.

Development and validation of a headspace gas chromatographic method for the determination of residual solvents in levetiracetam (API). [5]

The analysis for the determination of residual solvents and its validation was performed on Agilent's gas chromatograph equipped with headspace sampler and a flame ionization detector (FID). SPB^{TM}- 624, Supelco, 60 m in length, with an internal diameter of 0.32 mm, and a film thickness of 1.8µm. The validated HSGC method for the separation of residual solvents utilized a flow rate of 1.5ml/min. Oven temperature was set at 40°C for 22 min, and then a linear thermal gradient of 30°C/min to 220°C was used with a final hold of 8 min. Total run time was 36.0

min. The carrier gas used was Nitrogen at a constant flow rate of 1.5ml/min.

Residual Solvents Determination by HS-GC with Flame Ionization Detector in Omeprazole Pharmaceutical formulations. [6]

The Residual solvents in omeprazole was determined by employing a Shimadzu Gas Chromatography; Japan which was equipped with model no Shimadzu-GC-2010 head-space AOC 5000 autosampler and a flame-ionization detector. The injector temperature was 100 C and detector temperature was 250 ^{0}C. Column was DB-624 .Split ratio of injection 1:10. Oven temperature was maintained at 40 ^{0}C for 5 min, and then raised at rate of 7^0 C/min to 220 ^{0}C, maintained for 10 min. Total run time was 40 min. Nitrogen was used as a carrier gas at a constant flow rate of 2.10 mL/min.

Determination of Residual Solvents in Linezolid by Static Headspace GC[7]

A headspace gas chromatographic method was developed for the determination of residual solvents in linezolid active substances. The solvents are petroleum ether (60–90°C), acetone, tetrahydrofuran, ethyl acetate, methanol, dichloromethane (DCM) and pyridine. The correlation coefficient (*r*) was greater than 0.9995 except for petroleum ether (0.9980). The LOD ranged between 0.12 µg/mL (petroleum ether) and 3.56 µg/mL (DCM), and LOQ ranged between 0.41 µg/mL (petroleum ether) and 11.86 µg/mL (DCM). The method achieved good accuracy (recoveries ranging from 92.8 to 102.5%) and precision for both run-to-run and day-to-day assay (relative standard deviation ranging from 0.4 to 1.3%) for all 7 solvents concerned, which was applied in the QC of 3 batches of linezolid successfully.

GC was conducted using the Agilent 7890A gas chromatograph equipped with an FID. The ZB-WAX capillary column (30 m length × 0.53 mm i.d., and 1.0 µm film thickness; Phenomenex Co., USA) and the DB-FFAP capillary column (30 m length × 0.53 mm i.d., and 1.0 µm film thickness; Agilent Co., USA) were used for the quantification of residual solvents. Analysis was performed using an oven programming at an initial temperature of 30°C for 15 min followed by a ramp rate of 10°C/min, 35°C for 10 min followed by 10°C/min ramp rate, 30°C for 5 min followed by 30°C/min ramp rate and finally, a temperature of 220°C with a hold time of 30 min and the total run time is 37 min. The temperature of the injector was set at 90°C with a split ratio of 5 : 1. The detector temperature was maintained at 280°C. Nitrogen (N_2, 99.999% purity) was used as carrier gas with a flow rate of 1 mL/min. The injection volume was 1 ml.

Development and validation of a headspace gas chromatographic method for the determination of residual solvents in Arterolane maleate bulk drug[8]

The primary goal of column selection was to resolve a total of 10 residual solvents (i.e., pentane, ethanol, 2-methylpentane, dichloromethane, 3-methylpentane, *n*-hexane, methylcyclopentane, cyclohexane, benzene and *n*-heptane) which were used during the process of synthesis and manufacturing of arterolane maleate. This proposed method development and the validation was performed on Perkin Elmer's gas chromatographic system equipped with Flame Ionization detector and head space analyzer. It involved a thermal gradient elution of 10 residual solvents present in arterolane maleate salt. The analysis was carried out on a RTx-624, 30 m × 0.32 mm, 1.8 µ column. Nitrogen gas was used as a carrier. The flow rate was 0.5 ml/min and flame ionization detector (FID) was employed. Oven temperature was maintained at 40°C for 20 min, and then a linear thermal gradient of 15°C/min to 200°C was used with a final hold of 5 min. Total run time was 35.0 min. Nitrogen was used as a carrier gas at a constant flow rate of 0.5 ml/min.

Development and validation of an analytical method for the determination of residual solvents in oxacillin sodium by headspace gas chromatography[9]

A headspace gas chromatographic (HSGC) method has been developed for simultaneous estimation of methanol, ethyl acetate and toluene in oxacillin sodium. The separation was achieved using a 30 m long Elite fused silica capillary column with an internal diameter of 0.32 mm.

A Perkin Elmer (Model Clarus 400) HSGC equipped with flame ionization detector was employed. HSGC carries a microprocessor controlled gas chromatograph with an optional built–in auto sampling system. The GC system is supported with the additional equipment Turbo Matrix 40 Sampler. All gas conduits that deliver carrier gas or any detector gas to the Clarus 400 GC must be formed from copper or stainless steel tubing that is free of grease, oil, or other organic materials. The data processing system was run with the Total Chrome Navigator software connected with a PC. The GC column was elite-5 fused silica capillary column, 30 m long and 0.32 mm in internal diameter. The column temperature was maintained at 50°C for 2 min, then raised at a rate of 20°C per min to 220°C and maintained at 220°C for 2 min. The injection port and detector temperature were maintained at 250°C. The carrier nitrogen gas passed with a velocity of 37.3 cm per second at 10 Kpa pressure and a split ratio of 1: 1. The GC cycle time was only 35 min.

The developed gas chromatographic method offers a symmetric peak shape, good resolution and reasonable retention time for all the solvents. Beer's law was obeyed in the following concentration ranges of 100 – 1500ppm for methanol, 100 – 800ppm for ethyl acetate and 100 – 500 ppm for toluene for oxacillin sodium. The method was validated under the ICH guidelines. The linearity of the calibration curves, the percent recoveries, relative standard deviation for the method were also determined. The correlation coefficient for methanol, ethyl acetate and toluene were found to be 0.9997, 0.9998 and 0.9996, respectively for oxacillin sodium.

Determination of residual solvents in pharmaceuticals by thermal desorption-GC/MS. [10]

The determination of residual solvents in pharmaceuticals was developed by thermal desorption (TD)-GC/MS. A programmed temperature pyrolyzer is applied for the TD. This method does not require any sample pretreatment and it allows a very small quantity of the sample. Directly desorbed solvents from intact pharmaceuticals (ca. 1 mg) in the desorption cup (5 mm x 3.8 mm i.d.) were cryofocused at the head of a capillary column prior to a GC/MS analysis. The desorption temperature was set at a point about 20 degrees C higher than the melting point of each sample individually, and held for 3 min. The analytical results using seven completely different pharmaceuticals were found to be in agreement with those obtained by direct injection (DI) of the solution, followed by USP XXIII. This proposed TD-GC/MS method was found to be demonstrated to be very useful for the identification and quantification of residual solvents. Hence, this method was simple, allowed rapid analysis and gave good repeatability.

Method development and validation for the determination of residual solvents in Oxfendazole API by using head space gas chromatography. [11]

The residual organic solvents (methanol, acetone and toluene) in Oxfendazole was determined using the DB WAX column (30 m length, 0.32 mm internal diameter, and 0.5 µm film thickness) Nitrogen was used as carrier gas. Split ratio was 1:30, detector temperature was 230 °C, Oven temperature was initially kept 50 °C, held for 2 minutes, raised to 100°C by 10°C/min, raised to 220°C by 20°C/min, 2 minutes hold. Headspace injector oven equilibrium was at 85 °C. Needle temperature was 90 °C. Transfer line temperature was 95 °C. Oven/vial equilibration time was 20 min and pressurization time was 3 min. N, N-dimethyl formamide was selected as a diluent.

The proposed method is found to be specific for the Residual solvent determination in Oxfendazole by HS-GC method. The method is found to be linear in the range of interest. Hence, this method stands validated can be used for routine analysis in the Quality Control Laboratory.

The method was validated according to ICH guidelines and found to be specific, linear i.e., correlation coefficient is 0.999, precise and % RSD of each analyte is less than 15%, sensitive, rugged and showed excellent recovery. The Present developed & validated method are run successfully for Oxfendazole residual solvents determination by Gas chromatography with head space in active pharmaceutical ingredient manufacturing.

Optimization of HS-GC–FID–MS Method for Residual Solvent Profiling in Active Pharmaceutical Ingredients Using DoE. [12]

The HS-GC–FID–MS analyses were performed on Agilent Technologies GC System 7890A (Agilent), equipped with electronic flow technology, MSD ChemStation software, NIST/EPA/NIH Mass Spectral Library 2005 and CTC CombiPAL Head Space injection system. The separation of Organic solvents was carried out on a capillary column with the standard mid-polar stationary phase (ZB-624, Phenomenex, 30 mm × 0.53 mm, i.d., 3 µm film thickness). The temperatures of the injection port, FID, MS ion source and GC–MS interface were 220, 280, 230 and 280°C, respectively. Helium was used as a carrier gas at a flow rate of 6.4 mL/min. The elution was performed with an oven temperature program as follows: an initial column temperature of 40°C (hold time, 8 min) was increased to a temperature of 45°C at a rate of 2°C/min and then to a final temperature of 240°C at a rate of 20°C/min. The split ratio was 1 : 5. The mass spectrometer was operated in an electron impact ionization/selective ion monitoring (EI/SIM) mode (70 eV).

MS scan parameters: 34-450 Daltons in approximately 1 second. The HS equilibration temperature was set at 90°C, syringe temperature at 95°C, equilibration time at 20 min and agitation at 500 rpm. An exact amount of 1 mL of the HS volume was injected into the system.

The HS equilibration temperature was set at 90°C, syringe temperature at 95°C, equilibration time at 20 min and agitation at 500 rpm. An exact amount of 1 mL of the HS volume was injected into the system.

In this present work, the convenient HS-GC–FID–MS method was optimized for the purpose of profiling Residual solvents in APIs. DoE was employed which helps in defining the influence of sample preparation on the chromatographic response. It was shown that the HS equilibration temperature and dilution medium have greater impact on the sensitivity compared with the time used for equilibration of the samples. It was also found that regardless of the sample solubility in the dilution media, the use of water in the sample preparation was crucial for better sensitivity. Validation data showed satisfactory linearity, sensitivity, accuracy and precision of the method for the tested RSs. DoE experiments for the assessment of the method robustness demonstrated that the method was robust for all variations. The method was applied in the analysis of different Active pharmaceutical ingredients and showed good overall performance. The data obtained proved that the proposed method was suited for the intended purpose and can be used for profiling of RSs in APIs.

Simultaneous Estimation of Residual Solvents (Isopropyl Alcohol and Dichloromethane) in Dosage Form by GC-HS-FID. [13]

A simple and sensitive method has been developed and validated for the determination of isopropyl alcohol and dichloromethane as residual solvent. The separation was achieved on a gas liquid chromatography with headspace sampler and a flame ionization detector was employed. (GC-HS-FID). The carrier gas which was used was helium and separation was carried out on Elite-624 (30 meter, 0.53 mm ID, 3µm df). The retention time for isopropyl

alcohol were 10.8 mins and dichloromethane were 11.4 mins.

Chromatographic condition: carrier gas: helium; flow rate: 1.0 mL/min; injector temperature: 190 ºC; split ratio: 1:10; oven program: initial 45 ºC hold for 5 min, Increase @ 15 ºC/min up to 200 ºC, hold for 5 min; detector temperature: 260 ºC; air gas flow - 450 mL/min; hydrogen gas flow - 45 mL/min; run time: 20 min.

Headspace sampler condition: Oven temperature: 85 ºC; needle temperature: 110 ºC; transfer line temperature: 90 ºC; thermostat period: 30 min; pressurize time: 2.0 min; inject time: 0.05 min; withdraw time: 0.02 min; GC cycle time: 30 min; capillary pressure: 15 psi.

The developed method was found to be accurate, precise and specific for the estimation of isopropyl alcohol and dichloromethane. The preparation procedure for samples is rapid and very simple. In conclusion, the proposed method is adequate for the purpose of confirmatory analysis of isopropyl alcohol and dichloromethane in the dosage form.

Determination of Organic Volatile Impurities in Twenty-Three Different Coated Tablet Formulations Using Headspace Gas Chromatography with Flame Ionization Detection Technique. [14]

An Agilent 7890B Gas Chromatograph (GC) with 7697A Headspace auto-sampler was used in method development and validation. Headspace auto-sampler was set to multiple extraction mode with 80°C, 90°C and 105°C temperature for oven, loop and transfer line respectively. GC was equipped with standard oven for temperature programming, split/splitless injection port and flame ionization detector. Separation was achieved on HP-Innowax polyethylene glycol gas chromatographic column (30 m × 250 µm × 0.25 µm) using nitrogen as a carrier gas. GC inlet temperature was set at 140°C with split ratio 10:1 and 250°C flame ionization detector temperature. e, a simple and sensitive method for simultaneous determination of methanol, acetonitrile, methylene chloride, n-hexane, cyclohexane, xylene, chloroform, nitromethane, toluene and pyridine were developed and validated. 23 marketed coated tablet formulations were tested for the presence of volatile organic impurities by using this method. Excellent results were obtained, particularly taking into account the low concentration levels were examined in 23 coated tablet formulations.

Simultaneous determination of class 1 residual solvents in organic diluents by chromatographic methods. [15]

A simple chromatographic method has been developed for the determination of tested Class 1 residual solvents (1, 1-dichloroethene, 1, 2- dichloroethane, 1, 1, 1-trichloroethane, carbon tetrachloride and benzene) in typical organic diluents like DMSO, DMF, DMA. The analytes separation was obtained on DB-624 and DB-WAX columns. The developed gas chromatographic method offers peak shape, good resolution and reasonable retention times for all the solvents.

Method A: 30m long DB-624 column, 0.530mm in inner diameter and 3.0µm in film thickness (manufactured by J&W Scientific, USA) was used. Injection port was heated at 140 ^{0}C while the temperature of detector was 250 ^{0}C. Helium was allowed to flow at a rate of 4.9 mL/min. Hydrogen gas and air supply to the detector was 30 mL/min and 300 mL/min, respectively. The sample was introduced in the column in a split mode with split ratio, 5.0:1. The column temperature was kept 40 ^{0}C for 20 min followed by an increase in the temperature at a rate of 10 ^{0}C/min to 240 ^{0}C. The 240 ^{0}C temperature was held up to 20 min.

Method B: 30 m long DB-WAX column, 0.320mm in inner diameter and 0.25µm in film thickness (manufactured by J&W Scientific, USA) was used. Injection port was heated at 140 ^{0}C while the temperature of detector was 250 ^{0}C. Helium gas was allowed to flow at a rate of 2.1 mL/min. Hydrogen gas and air supply to the detector was 30 mL/min and 300 mL/min, respectively. The sample was introduced in the column in a split mode with split ratio, 5.0:1. The column temperature was kept 50 C for 20 min followed by an increase in the temperature at a rate of 6 ^{0}C/min to 165^0 C. The 165 C temperature was held up to 20 min.

Headspace conditions

Vial temperature 80^0 C, Loop temperature 80^0 C, Transfer line temperature 85 ^{0}C, Vial equilibration time 60 min, Vial 6 Loop fill time 0.20 min, Loop equilibration time 0.1 min, Injection time 0.1 min, GC cycling time 75 min, inject volume 1.0 mL, pressurize time 0.50 min.

This procedure simplifies the test solution preparation in advance and allows to achieve good peaks response for these tested residual solvents in any of the most popular organic diluents (DMSO, DMF and DMA) used in routine quality control of drug substances, excipients or drug products.

Determination and Quantitation of Residual Solvents in Natural Food Ingredients Using a Static Headspace Gas Chromatography with Flame Ionization Detection and Mass Spectrometric Detection Method. [16]

The determination of residual solvents is critical for quality control in food production and manufacturing processes. A gas chromatographic and mass spectrometric detection (MSD) method was developed and validated to complement the static headspace flame ionization detection (FID) technique for identification, confirmation, and quantitation of solvent residues in botanicals, using Coffee berry extract and pomegranate powder was used as the samples under test. Relative standard deviations (RSDs) of less than 12% were obtained for residual solvents in water and dimethyl sulfoxide. Coffee berry extract are supplemented with10 µg/g of Residual Solvents Class 3 Mix showed MSD and FID recoveries mainly of 91 to 121% and

77 to 110%, respectively, while those samples which are supplemented with 100 µg/g of Residual Solvents Class 3 Mix displayed MSD and FID recoveries of 105 to 123% and 87 to 112%, respectively. For pomegranate samples supplemented with 10 µg/g of Residual Solvents Class 3 Mix, MSD and FID recoveries of 95 to 124% and 72 to 151% were observed, respectively. Those samples which are supplemented with 100 µg/g of Residual Solvents Class 3 Mix exhibited MSD and FID and the recoveries was found to be 109 to 135% and 97 to 127%, respectively. Hence, the developed method was demonstrated to be suitable for the analysis of residual solvents in natural food ingredients and is expected to find numerous industrial applications

Determination of Residual Solvents in Dapagliflozin Amorphous by Gas Chromatography with Static Head Space Method. [17]

A novel, sensitive and accurate analytical method for quantification of 12 residual solvents in Dapagliflozin Amorphous by using a static headspace gas chromatography (HSGC) by employing flame ionization detector (FID). Methanol, Ethanol, Diethyl ether, Methyl acetate, Dichloromethane, Ethyl acetate, Tetrahydrofuran, Cyclohexane, Isopropyl acetate, Methyl isobutyl ketone, Toluene, Chlorobenzene as residual solvents were determined in Dapagliflozin Amorphous. The separation of twelve residual solvents were achieved on DB-624 (60 meters ×0.53 mm I.D, 3.0µm) column. The carrier gas used was Nitrogen with a constant pressure of 7.0 psi. N-methyl-2-pyrrolidone was selected as a sample diluent owing to its high capacity for dissolving Dapagliflozin Amorphous sample. Excellent correlation coefficient between peak responses and concentrations were > 0.9936. The recoveries of all 12 solvents spiked in Dapagliflozin Amorphous were in the range from 97.1% to 103.0%. Limit of quantitation for all 12 solvents were sufficiently lower than limits specified by ICH. In the proposed method, USP resolutions between all the 12 solvents was found to be more than 1.6. A precise, accurate, linear and robust Headspace Gas Chromatography method was developed and validated for the quantification of twelve residual solvents in Dapagliflozin Amorphous.

Optimized chromatographic conditions

Column DB-624 60 meters ×0.53 mm I.D, 3.0µm, Flow rate 7.0 psi (Constant pressure), Carrier gas Nitrogen, Inlet Temperature 140°C, Injection mode Split (1:5), Detector Flame Ionization Detector, Detector Temperature 250°C, Hydrogen flow 40 mL/min, Air flow 400 mL/min, Make up flow 25 mL/min, Injection volume 1 µl, Run time 45 minutes .

Optimized Headspace conditions

Oven temperature 90°C, Loop temperature 95°C, Transfer line temperature 100°C, GC cycle time 55 min, Vial equilibration time 10 min, Vial pressurization time 0.5 min, Loop fill time 0.5 min, Loop equilibrium time 0.5 min, Injection time 1.0 min, Vial shake-High.

All the 12 residual solvents were well separated from each other, indicating that the developed GC method was specific. The method validation data showed satisfactory results for all tested method parameters. This simple GC method is precise, accurate, linear and rugged. Hence, it is proved that developed method can be used for routine testing in quality control laboratories for estimation of 12 residual solvents in Dapagliflozin Amorphous. The method is user-friendly and robust to operate.

Validation of the analytical method for the determination of residual solvents in Albuterol sulphate through the chromatography of the gas analyser. [18]

A HSGC method for the determination of Residual solvents (Methanol, Isopropyl alcohol, Dichloromethane, Ethyl acetate, Tetrahydrofuran, Toluene) in Levalbuterol Sulphate was carried out the BP-624, 30 m x 0.32mm ID, 1.8 µm columns. The injection volume was 1.2 ml with split less injection mode. The temperature maintained at the injector was 200ºC and detector was to be 220ºC. Nitrogen gas was used as a carrier gas with flow 2.0 ml/minute and the detector was FID. The hydrogen flow and Air flow was maintained at 30ml/min and 300ml/min respectively. The method was validated under ICH specifications.

Optimized Chromatographic conditions

Instrument Clarus 500, Instrument Make Perkin Elmer, Injector Temperature 220°C, Column 30m x 0.32 mm-ID, 1.8µm, BP-624 column, Initial Column Oven Temperature 40°C, Hold time 7.0 minutes, Ramp rate 15°C/min, Final Column Oven temperature 240°C, Hold time 5.0 minutes, GC Run time 25.33 minutes, Carrier gas Nitrogen, Carrier gas flow rate 1.2 ml/min, Detector type FID, Detector temperature 260°C, Detector Sensitivity Range.

Head space parameters

Instrument Turbomatrix 40 HS, Instrument Make Perkin Elmer, Vial oven temperature 90°C, Vial conditioning time for 30 minutes, Needle temperature 95°C, Transfer Line temperature 100°C, Vial Pressurization time for 2.0 minutes, Programmable Pneumatic Control pressure 20psi, Injection Volume 1.2 ml, Injection time in 0.12 minutes, Cycle time 33 minutes.

Analytical Method Development and Validation for Determination of Residual Solvent in Zopiclone Tablets by Headspace Gas Chromatography. [19]

A headspace gas chromatographic method has been developed and validated for simultaneous determination of isopropyl alcohol and methylene chloride in zopiclone tablets. The separation was achieved on 75 m long DB-624 column, 0.53 mm inner diameter and 3 µ film thickness Nitrogen was used as a carrier gas with a flow rate of 6 ml/min flow and FID as a detector. The developed method offers symmetric peak shape, good resolution and reasonable retention time for all the solvents. The LOD of isopropyl alcohol and methylene chloride was found to be 250 µg/tablet and 90 µg/tablet, respectively.

Method Development and Validation of Residual Solvents in Sumatriptan Succinate by using Headspace Gas Chromatography. [20]

A HSGC method was developed and validated for the quantification of residual solvents present in Sumatriptan succinate through an understanding of the synthetic process, nature of solvents and nature of stationary phases of columns. The residual solvents methanol, acetone and toluene, were determined. The developed method is specific, accurate, precise and robust as per ICH guidelines. The Head space gas chromatography (HSGC) method described utilized a DB-624 Capillary (30.0 m × 0.53 mm ID, 3.0 µm) column with total run time 25 min. using DMSO as sample diluents. Nitrogen at a constant flow rate of 3.0 mL/min was used as a carrier gas. The method was validated to be specific, linear, precise, sensitive and showed excellent recovery. The gas chromatographic system consisted of Shimadzu GC headspace HT15468 auto sampler with flame-ionization detector and EZ CHROME ELITE software was used. The chromatographic separation was made by using DB 624 Capillary (30.0 m × 0.53 mm ID, 3.0 µm particle size).

Chromatographic Conditions: The separations were carried out using nitrogen as carrier gas, oven temperature was initially set to 40 C and later increased to 200^0 C at a rate of 200 ^{0}C. The flow rate was set to 2.8mL/min. The run time was set to 25 min. Injector temperatures and detector temperature was maintained at 250^0 C and 25^0 C respectively. Head space conditions were the equilibration temperature, loop temperature was maintained at 80 ^{0}C and 100 ^{0}C respectively. Injection volume was 1.0ml and vial equilibration time and pressurization time was set to 30min and 2.0 min respectively.

Analytical Method Development to Determine Residual Solvents in Esomeprazole by Gas Chromatography (GC/FID) with Head Space. [21]

A HSGC method for the quantification of residual solvents in Esomeprazole was developed by employing it with a flame ionization detector (FID). Methanol, Acetone, Isopropyl alcohol, Methylene dichloride, Toluene as residual solvents were determined in Esomeprazole. The analysis was performed on Agilent GC 7820A FID detector and Chem station software. The injection temperature was 190 ^{0}C and detector temperature was 290 ^{0}C. Column employed for the separation was DB624m (30m long, 0.53mm internal Diameter). Split ratio of injection 1:4, Oven temperature was maintained at 40°C for 5 min, and then raised at rate of 10°C/min to 170°C, maintained for 7min. Total run time was 25 min. Nitrogen was used as a carrier gas at a constant flow rate of 4.2 mL/min

The % Relative standard deviation for six injections was obtained in acceptance criteria. The percentage recovery ranges obtained from 92.49 and 106.69%. The correlation coefficient R2 obtained greater than 0.99. The method parameters were validated included specificity, limit of detection and quantification, accuracy, linearity, precision, and robustness. A new, simple, specific, accurate and precise method was validated according to the International Conference on Harmonization (ICH) guidelines.

CONCLUSION

In the analysis of residual solvents various techniques are employed like loss on drying, infrared spectroscopy, FTIR, Thermogravimetric analysis (TGA), differential thermal analysis (DTA), differential scanning calorimetry (DSC) and gas chromatography. The sensitive and effective result is obtained using Gas Chromatography. Furthermore, Gas Chromatography is made more sensitive by combining this technique to various other techniques such as Head Space Gas Chromatography (HSGC), Fast Gas Chromatography, Head Space Gas Chromatography coupled Flame-Ionisation Detector (HSGC-FID), Head Space Gas Chromatography-Mass Spectrometry (HSGC-MS). All the residual solvents were analyzed by using various Gas Chromatographic techniques. Gas chromatography is an effective and sensitive tool in the determination of residual solvents in excipients, drugs or Pharmaceutical preparations. The purpose of this review is to describe and discuss some of the current analytic procedures including gas chromatographic and alternative techniques for residual solvents testing.

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