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Analytical Study of Residual Solvents in Levalbuterol Sulphate by Gas Chromatography

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ABSTRACT: The purpose of this research study was to develop and optimize an accurate and precise GC method for the determination of Residual solvents (Methanol, Isopropyl alcohol, Dichloromethane, Ethyl acetate, Tetrahydrofuran, Toluene) in Levalbuterol Sulphate. The method optimized on BP-624, 30 m x 0.32mm ID, 1.8 µm column as stationary phase. The injection volume of samples taken was 1.2 ml with split less injection. The temperature maintained at the injector and detector was to be 220°C and 260°C respectively. Nitrogen gas was used as mobile phase and the detection was done by FID. The flow of hydrogen and Air was maintained at 30ml/min and 300ml/min respectively. The diluents used was N, N-Diethyl Formamide (DMF). All solvents were well resolved each other with diluents' peak. Total run time was 33 minutes.

Keywords: GC; Residual solvents; Levalbuterol Sulphate; BP-624 stationary phase.

INTRODUCTION: Levosalbutamol or Levalbuterol is a short-acting β2-adrenergic receptor agonist treatment of asthma and chronic obstructive pulmonary disease (COPD). It is an R-Isomer of Salbutamol or Albuterol. It is marketed under the brand name X opened, by Sunovion Pharmaceuticals Inc. The drug is the R-enantiomer of its prototype drug salbutamol or albuterol.

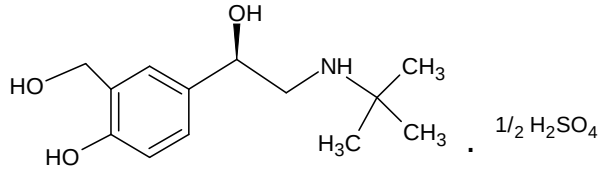


Figure 1: Structure of Levalbuterol Sulphate.

Salbutamol sulfate is sold in the USA as Ventolin HFA, Pro Air HFA, or Prudential HFA, and is also available in extended release tablets. It is usually given by the inhaled route for direct effect on bronchial smooth muscle. This is usually achieved through a metered dose inhaler (MDI), nebulizer or other proprietary delivery devices (e.g. Rotahaler or Autohaler). In these forms of delivery, the maximal effect of salbutamol can take place within five to twenty minutes of dosing,

Clinical studies proved that Levalbuterol Sulphate offers the β2-agonist action which requires for the relief from the problem of bronco constriction. Clinical studies prove that, late effect from relief from broncho constriction in patients having asthma when treated with S-Salbutamol. Thus, compared to S-Salbutamol and raceme salbutamol, Levalbuterol Sulphate can give fast bronchodilator.

Albuterol is listed in the most important medicine list of the World Health Organization. This list is of the medicines which are essential in a vital health structure.

There are different methods are reported for the analysis of Levalbuterol Sulphate by UV methods[1,2,3] and HPLC methods.[4] In this research work a new method for residual solvent determination in Levalbuterol sulphate, using Gas chromatography head space technique, has been developed. This new developed method can be applied in the industry for quality control purpose.

Chromatography is defined as a procedure by which solutes are separated by a dynamic differential migration process in a system consisting of two or more phases. One of which moves continuously in a given direction and in which the individual substances exhibit different motilities by reason of differences in adsorption, partition, solubility, vapor pressure, molecular size, or ionic charge density. The individual substances thus obtained can be identified or determined by analytical methods.

Presently, in the pharmaceutical industries, special importance being given for the residual solvent testing. The residual solvents are potentially undesirable substances, they modify the properties of certain compounds and also hazardous to the health of the individual. OVI's (Organic Volatile Impurities) also affect physicochemical properties like crystallinity[5, 6] of the bulk drug, as a difference in the crystal structure may lead to change in dissolution properties and problems with formulations of the finished product. Also residual solvents may create odor problem and color change in the finished products.[7, 8] The safety of the drug is determined by its pharmacological, toxicological profile and adverse effects.[9, 10] The content of residual solvents in APIs are analyzed by using gas chromatography.[11, 12]

The objective of this work is to report a simple, precise, accurate and cost effective method for the estimation of residual solvents impurities present in Levalbuterol Sulphate.

MATERIAL AND METHOD:

Method Development: Chromatographic separation was performed on a Perkin Elmer chromatographic system (Model- Claus 500) equipped with FID detector. Mobile phase (carrier gas) used was Nitrogen gas with detection at 260ºc. Methanol, Isopropyl Alcohol, Dichloromethane, Ethyl acetate, Tetrahydrofuran, Toluene and Diethyl Form amide (DMF) were used of AR grade. DMF was used as diluents. The limits for solvents were decided based on ICH guidelines.

Limits of solvents:

Solvent	Methanol	IPA	DCM	EA	THF	Toluene
Limit (ppm)	3000	5000	600	5000	720	890

Sample Preparation:

Preparation of System suitability solution:

i) Preparation of Solution 1: Weighed accurately about 0.6g of Methanol, 1.0g of Isopropanol, 0.12g of Dichloromethane, 1.0g of Ethyl acetate, 0.144g of Tetrahydrofuran and 0.178g of Toluene in a 100 ml flask and diluted to volume with Diluents.

ii) Preparation of Solution 2(System suitability solution): Diluted 5ml of Solution 1 to 100ml with Diluents.

Preparation of Vials:

*i) Preparation of a Blank vial***:** Pipette 5ml of diluents in a vial and sealed the vial.

ii) Preparation of System suitability vials: Pipetted 5ml of System suitability solution in six different vials and sealed the vials.

iii) Preparation of Test Vial: Weighed accurately about 0.5g of the test sample into a vial. Added accurately 5ml of diluents and sealed the vial.

iv) Preparation of Test Vials spiked System suitability solution: Weighed accurately about 0.5g of the test sample into a vial. Added accurately 5ml of System suitability solution and sealed the vial.

Procedure: The GC-HS system was set with the chromatographic conditions as mentioned in analytical method. The solutions were injected as below,
Injected blank solution first. After blank injection, system suitability solution was injected.

After blank and system suitability solution test solution was injected and then injection of test spiked with system suitability solutions was done.

Trial 1:

Injector temperature: 220ºC

Column: BP 624, 30m, 0.32mm ID, 3µ

Initial Column Oven temperature: 40ºC (Temperature 35ºC also tried but not practical as difficult to attain after every run)

Hold time: 5 minutes (varied from 3 minutes to 12 minutes to check the resolution of highly volatile solvents)

Ramp rate: 15ºC (varied from 8ºC to 15ºC for to achieve fast analysis)

Final Column Oven temperature: 240ºC (varied from 200ºC to 280ºC to check the elution of high boiling impurities)

Hold time: 5 minutes (Initially tried with 40 minutes to ensure elution of diluents and high boiling components)

Carrier gas: Nitrogen

Detector: FID

Detector Temperature: 260ºC (varied from 200ºC to 300ºC to check the impact on detection)

Detector sensitivity: Range 1 & Attenuation 4

Head Space Parameters:

Vial Oven temperature: 90ºC (Varied from 70ºC to 110ºC to ensure maximum extraction of the traces)

Vial conditioning time: 30 minutes (Varied from 10 minutes to 40 minutes to optimize the extraction of solvent impurities in the head space)

Needle temperature: 95ºC (Varied based on the vial oven temperature to avoid condensation in the needle)

Transfer line temperature: 100ºC (Varied based on the needle temperature to avoid condensation in the transfer line)

Vial pressurizing time: 2 minutes (Varied from 1 minute to 2.5 minutes to get the optimum response)

Programmable pneumatic control pressure: 20 psi

Injection volume: 1 ml (Varied from 1ml to 1.5ml to get the optimum response)

Injection time: In 0.1 minutes (Varied from 0.1minute to 0.15 minute to get the optimum response)

Diluents: N, N-Dimethyl Formamide.

Also tried DMSO as a solvent but ghost peaks were observed interfering with solvent peaks. These ghost peaks were formed because of reaction between the sulphate and DMSO causing DMSO to degrade.

Trial 2:

Injector temperature: 220ºC (Higher temperature up to 250ºC tried but no impact was observed)

Column: BP 624, 30m, 0.32mm ID, 1.8µ

Initial Column Oven temperature: 40ºC (Temperature 30ºC also tried but not practical)

Hold time: 7 minutes (varied from 3 minutes to 15 minutes to check the resolution of highly volatile solvents)

Ramp rate: 15ºC (varied from 5ºC to 15ºC for to achieve fast analysis)

Final Column Oven temperature: 240ºC (varied from 200ºC to 280ºC to check the elution of high boiling impurities)

Hold time: 5 minutes (Initially tried with 30 minutes to ensure elution of diluents and high boiling components)

Carrier gas: Nitrogen

Detector: FID

Detector Temperature: 260ºC (varied from 200ºC to 300ºC to check the impact on detection)

Detector sensitivity: Range 1 & Attenuation 4

Head Space Parameters:

Vial Oven temperature: 90ºC (Varied from 70ºC to 110ºC to ensure maximum extraction of the traces)

Vial conditioning time: 30 minutes (Varied from 5 minutes to 40 minutes to optimize the extraction of solvent impurities in the head space)

Needle temperature: 95ºC (Varied based on the vial oven temperature to avoid condensation in the needle)

Transfer line temperature: 100ºC (Varied based on the needle temperature to avoid condensation in the transfer line)

Vial pressurizing time: 2 minutes (Varied from 1 minute to 2.5 minutes to get the optimum response)

Programmable pneumatic control pressure: 20 psi

Injection volume: 1.2ml (Varied from 1ml to 1.5ml to get the optimum response)

Injection time: In 0.12 minutes (Varied from 0.1minute to 0.15 minute to get the optimum response)

Diluents: N, N-Dimethyl Formamide

Trial 3:

Injector temperature: 220ºC

Column: BP 5, 30m, 0.53mm ID, 5.0µ

Initial Column Oven temperature: 50ºC (Lower temperature also tried but as the film thickness is high retention expected more hence higher initial temperature was proffered)

Hold time: 5 minutes (varied from 2 minutes to 10 minutes to check the resolution of highly volatile solvents)

Ramp rate: 12ºC (varied from 7ºC to 15ºC for to achieve fast analysis)

Final Column Oven temperature: 260ºC (varied from 200ºC to 280ºC to check the elution of high boiling impurities)

Hold time: 10 minutes (Initially tried with 40 minutes to ensure elution of diluents and high boiling components)

Carrier gas: Nitrogen

Detector: FID

Detector Temperature: 280ºC (varied from 240ºC to 300ºC to check the impact on detection)

Detector sensitivity: Range 1 & Attenuation 4

Head Space Parameters:

Vial Oven temperature: 90ºC (Varied from 70ºC to 100ºC to ensure maximum extraction of the traces)

Vial conditioning time: 30 minutes (Varied from 10 minutes to 40 minutes to optimize the extraction of solvent impurities in the head space)

Needle temperature: 95ºC (Varied based on the vial oven temperature to avoid condensation in the needle)

Transfer line temperature: 100ºC (Varied based on the needle temperature to avoid condensation in the transfer line)

Vial pressurizing time: 2 minutes (Varied from 1 minute to 2.5 minutes to get the optimum response)

Programmable pneumatic control pressure: 20 psi

Injection volume: 1.5ml (Varied from 1ml to 1.5ml to get the optimum response)

Injection time: In 0.15 minutes (Varied from 0.1minute to 0.15 minute to get the optimum response)

Diluents: N,N-Dimethyl Formamide

Trial 4:

Injector temperature: 220ºC

Column: BP 1, 30m, 0.53mm ID, 1.0µ

Initial Column Oven temperature: 35ºC (Temperature 30ºC also tried but not practical. 35ºC also difficult to achieve after every run and takes long time)

Hold time: 15 minutes (varied from 3 minutes to 15 minutes to check the resolution of highly volatile solvents)

Ramp rate: 10ºC (varied from 5ºC to 10ºC for to achieve fast analysis)

Final Column Oven temperature: 200ºC (varied from 200ºC to 240ºC to check the elution of high boiling impurities)

Hold time: 15 minutes (Initially tried with 30 minutes to ensure elution of diluents and high boiling components)

Carrier gas: Nitrogen

Detector: FID

Detector Temperature: 260ºC (varied from 200ºC to 300ºC to check the impact on detection)

Detector sensitivity: Range 1 & Attenuation 4

Head Space Parameters:

Vial Oven temperature: 90ºC (Varied from 80ºC to 100ºC to ensure maximum extraction of the traces)

Vial conditioning time: 30 minutes (Varied from 20 minutes to 40 minutes to optimize the extraction of solvent impurities in the head space)

Needle temperature: 95ºC (Varied based on the vial oven temperature to avoid condensation in the needle)

Transfer line temperature: 100ºC (Varied based on the needle temperature to avoid condensation in the transfer line)

Vial pressurizing time: 2 minutes (Varied from 2 minutes to 2.5 minutes to get the optimum response)

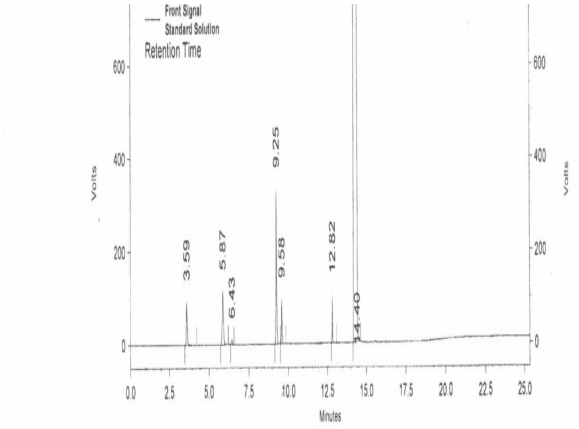
Programmable pneumatic control pressure: 20 psi

Injection volume: 0.8 ml (Varied from 0.8 ml to 1 ml to get the optimum response)

Injection time: In 0.1 minutes (Varied from 0.1minute to 0.15 minute to get the optimum response)

Diluents: N,N-Dimethyl Formamide

After altering various components like column, GC parameters and headspace parameter the optimized method which gave best resolution between closely eluting peaks was selected.



Front Signal Results

Peak Number	Name	Retention Time	Area	Area %
1	Methanol	3.59	2959315	0.403
2	Isopropyl alcohol	5.87	4946999	0.674
3	Dichloromethane	6.43	367142	0.050
4	Ethyl acetate	9.25	8458111	1.153
5	Tetrahydrofuran	9.58	2375351	0.324
6	Toluene	12.82	1759301	0.240
7	N,N-DMF	14.40	712583764	97.155
Totals			733449983	100.000

Figure 2: A Representative chromatogram for optimized method.

RESULTS AND DISCUSSION: Here a novel residual solvent estimation method has been developed using gas chromatography head space technique.

Firstly various components of method like column, flow, temperature gradient and head space parameters were varied to optimize method conditions. The database obtained was reviewed for best resolution between closely eluting peaks and tailing factor. The optimized chromatographic condition which gives the best resolution and tailing factors was selected as below.

Table 1: Optimized Chromatographic conditions.

Instrument	Claus 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	7.0minutes
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 1; Attenuation 4

Table 2: Head space parameters.

Instrument	Turbo matrix 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

CONCLUSION: This study presents a development approach to develop Gas chromatographic method for estimation of residual solvents in Levalbuterol Sulphate. The developed method can be applied in the routine quality control purpose in the pharmaceutical industry for the analysis of Levalbuterol Sulphate.

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