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Validation of the analytical method for the determination of residual solvents in albuterol sulphate through the chromatography of the gas analyzer

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Abstract
In this paper validation of a GCHS method, for the determination of Residual solvents (Methanol, Isopropyl alcohol, Dichloromethane, Ethyl acetate, Tetrahydrofuran, Toluene) in Levalbuterol Sulphate using the BP-624, 30 m x 0.32mm ID, 1.8 µm columns as stationary phase, is described. The injection volume of samples taken is 1.2 ml with split less injection. The temperature maintained at the injector and detector was to be 200ºC and 220ºC respectively. Nitrogen gas with flow 2.0 ml/minute used as mobile phase and the detection was by FID. The flow of hydrogen and Air was maintained at 30ml/min and 300ml/min respectively. The method was validated as meets all the regulations of System suitability, Specificity, Method Precision, Linearity, LOD & LOQ, Precision of LOQ and Accuracy/Recovery under ICH specifications.

Keywords: residual solvents, GC, BP-624 stationary phase, levalbuterol sulphate etc.

Introduction

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

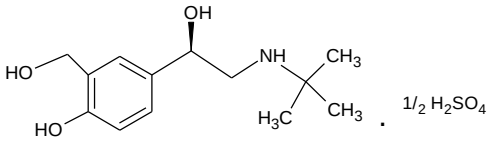

Fig 1: Structure of Leval buterol Sulphate

Salbutamol sulfate is sold in the United States. UU. Like Ventolin HFA, Pro Air HFA or Proventil HFA, and it are also available as prolonged-release tablets. It is usually administered by inhalation to obtain a direct effect on the bronchial muscles. This is usually achieved through a measured dose inhaler (MDI), nebulizer or other patented delivery devices (eg, Rotahaler or Autohaler). In these forms of administration, the maximum effect of salbutamol can occur within five to twenty minutes of administration.

Clinical studies have shown that levalbuterol sulphate offers the β2-agonist action necessary to solve the problem of bronchial constriction. Clinical studies show that the delayed effect of the relief of bronchial constriction in patients who have asthama when treated with S-Salbutamol. Therefore, compared to salbutamol S and racemic salbutamol, levalbuterol sulfate can provide rapid bronchodilation.

The albuterol is on the list of the most important medicines of the World Health Organization. This list covers the drugs that are essential in a vital health structure. There are several methods for the analysis of levalbuterol sulphate with UV methods [1, 2, 3] and HPLC methods [4].

Currently, in the pharmaceutical industries, particular emphasis is placed on the testing of residual solvents. Residual solvents are potentially undesirable substances, modify the properties of certain compounds and are also dangerous for the health of the individual. OVI (volatile organic impurities) also influence the physico-chemical properties such as crystallinity [5, 6] of the bulk drug, since a difference in the crystalline structure can cause changes in the dissolution properties and problems with the formulations of the finished product. Residual solvents can also create odor problems and color changes in the final products [7, 8]. The safety of the drug is determined by the pharmacological, toxicological and adverse effects [9, 10]. The residual solvent content in the API is analyzed by gas chromatography [11, 12].

Validation is an activity that demonstrates that the analytical method works as intended in a given set of conditions and also provides authentic results with precision, accuracy, sensitivity, robustness required, etc. The intention to validate the method is to ensure that the method works reproducibly. When it is carried out by identical or different people, in the same or different laboratories, using different reagents, different equipment, etc.

In this work, the validation of a new method for the determination of the residual solvent in levalbuterol sulfate has been described, using the technique of the head space for gas chromatography.

Materials and methods

The chromatographic separation was carried out in a Perkin Elmer chromatographic system (Model-Clarus 500) equipped with an FID detector. The mobile phase (carrier gas) used was gas nitrogen with detection at 260 ° C. Methanol, isopropyl

alcohol, dichloromethane, ethyl acetate, tetrahydrofuran, toluene and DM grade dimethylformamide (DMF) were used. DMF has been used as a diluent. The limits for solvents have been established according to the ICH guidelines.

Table 1: 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 1; Attenuation 4

Table 2: 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

Sample preparation

Preparation of the system suitability solution

1. Preparation of the solution 1: About 0.6 g of methanol, 1.0 g of isopropanol, 0.12 g of dichloromethane, 1.0 g of ethyl acetate, 0.144 g of tetrahydrofuran and 0.174 g of toluene in a 100 ml flask were carefully weighed and diluted by volume with diluent.
2. Preparation of the standard solution 2 (System Suitability Solution): 5 ml of solution 1 were diluted to 100 ml with diluent.

Preparation of vials

1. Preparation of an empty vial: 5 ml of diluent was pipetted into an ampoule and the vial was sealed.
2. Preparation of the system suitability vials: 5 ml of suitability system solution was pipetted into six different vials and sealed vials.
3. Preparation of the test vial: Weigh exactly 0.5 g of the sample into an ampoule. Precisely 5 ml of diluent is added and the vial sealed.
4. Preparation of test vials with the system suitability solution: Weigh exactly 0.5 g of the sample into an ampoule. It is added precision 5 ml of suitability system of the solution and sealed vial.

Procedure

The GC-HS system was established with the chromatographic conditions as mentioned in the analytical method. The solutions were injected as follows, First solution injected in white. After the injection of white, the system suitability solution was injected. After solution solution of system suitability and vacuum, the solution was injected.

Method Validation

The validation of the analytical method was performed according to the validation guidelines of the ICH method. Validation parameters addressed specificity, accuracy, and linearity, limit of detection (LOD), limits of quantification (LOQ), accuracy and suitability of the system.

Specificity

The specificity of the analytical method was determined by injecting individual solvent solutions and a DMF blank solution under the same experimental conditions. The individual retention times of residual solvents were observed (Table 3). No peak was observed to interfere with solvent peaks when the target was injected.

Suitability of the system (system accuracy)

Six injections were made from six separate standard solution vials to verify the accuracy of the system. % RSD of the six injections for all solvents was found to be less than 15% (Table 4).

LOD and LOQ

LODs were calculated as the concentrations that gave a ratio ≥ S / N 3. The LOQs were calculated as the concentrations that gave a S / N ratio ≥10 and LOQ values were confirmed to verify the accuracy of the LOQ level method (Table 5 and 6)

Accuracy

For the precision of the method, six preparations were made by increasing the limit concentration of all the solvents in the test. The recovery of each solvent in the six preparations was calculated and the relative standard deviation of the recovery was calculated for six preparations. Recoveries were obtained in the acceptance limit of 80% to 120% and the RSD% recoveries six solvents meet the acceptance criteria below 15%, so it is said that the method is in good condition. (Table 7)

Linearity

A series of solutions containing each solvent was prepared [LOQ i.e. Sali: 50%, 80%, 100%, 120% and 150% above the specification limit for each solvent]. The calibration curves for each solvent concentration tested waste range (ie LOQ 150% of the specification level of each solvent) and the correlation coefficient for solvents were tracked was within the limits, ie, no less than 0.99. (Table 8-9)

Precision study/recovery

Weigh accurately about 250 mg of levalbuterol sulphate

sample into different vials and add the mixture solution with LOQ solvent concentration, 50%, 100% and 150% of the threshold concentration and then add diluents according to the procedure. The% recovery of each residual solvent must be between 80 and 120% for the four recovery levels studied (LOQ, 50, 100 and 150) of the target concentration. (Table 10)

Results and discussion

All validated parameters were found within the limits. The linearity is performed by the LOQ at 150% and the graph obtained is linear and shows the correlation coefficient R2 ≥0.99%. Recoveries were found for all solvents between 80-120%. The suitability of the system for 6% RSD injections was 15% NMT.

Table 3: Specificity (Individual RT's of Residual solvents and Diluent)

Solvents	Retention time (min)
Methanol	3.59
Isopropanol	5.87
Dichloromethane	6.43
Ethyl acetate	9.24
Tetrahydrofuran	9.58
Toluene	12.82
DMF	14.40

Table 4: % RSD of area's for standard solution

Sr. No	Methanol	IPA	DCM	Ethyl Acetate	THF	Toluene
1	2824985	4637640	360835	8198902	2325115	1686816
2	2805560	4616295	359046	8163013	2317567	1686517
3	2805131	4579113	355180	8050545	2291964	1667296
4	2627353	4102821	325020	7276714	2092741	1460919
5	3186209	5316877	389021	8929025	2503563	1923986
6	2812147	4640527	354900	8115708	2299636	1688509
Avg	2843564	4648879	357334	8122318	2305098	1685674
Std. Dev	183524.6	387434.1	20366.7	525078.8	130569.8	146734.6
%RSD	6.45	8.33	5.70	6.46	5.66	8.70

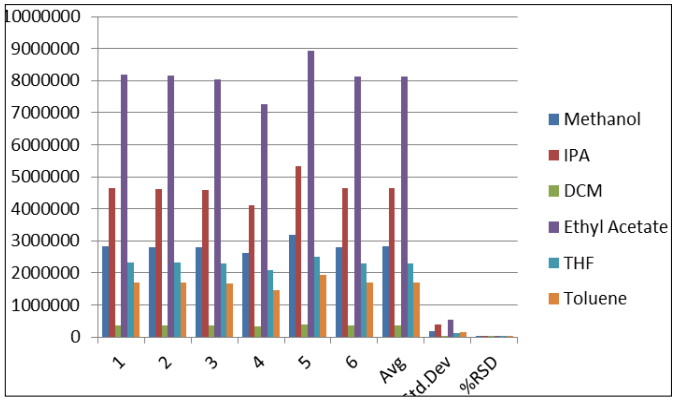

Fig 2

Table 5: LOD & LOQ values

Component	Limit of Detection in ppm of the test concentration	Limit of Quantitation in ppm of the test concentration
Methanol	70	212
Isopropanol	146	442
Dichloromethane	26	79
Ethyl acetate	72	219
Tetrahydrofuran	13	38
Toluene	24	73

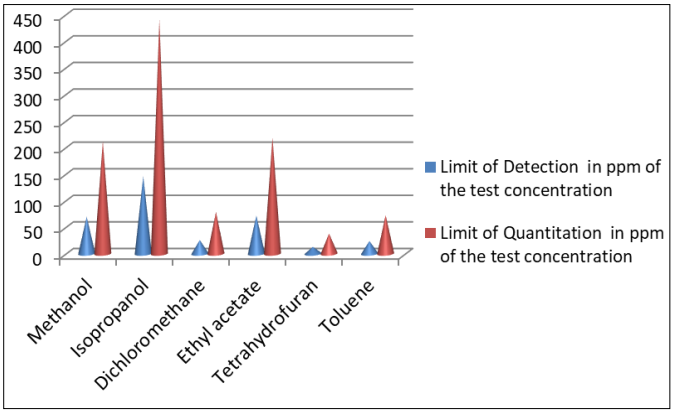

Fig 3

Table 6: % RSD of areas of RS for Precision at LOQ solution

Sr. No	Methanol	IPA	DCM	Ethyl Acetate	THF	Toluene
1	418981	808369	95867	690333	259587	286711
2	448420	816001	97127	695899	265036	288941
3	443277	851559	98157	707887	264427	304077
4	432957	835971	97407	695242	263965	295924
5	455555	880107	100061	723949	272354	314210
6	425105	812228	95510	696592	264695	289851
Avg	437383	834039	97355	701650	265011	296619
Std. Dev	14112.0	27903.3	1651.6	12360.7	4120.1	10662.8
%RSD	3.23	3.35	1.70	1.76	1.55	3.59

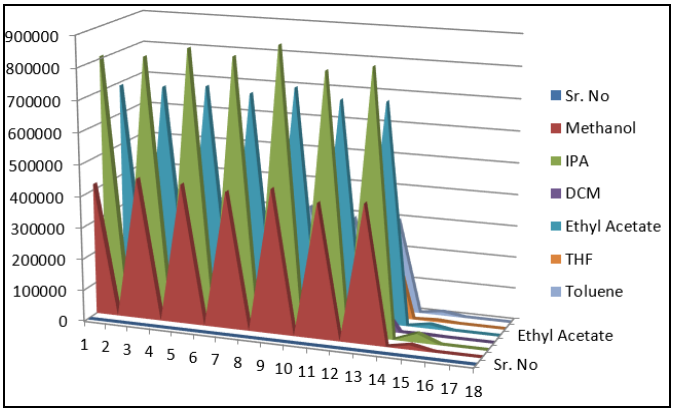

Fig 4

Table 7: %recovery and %RSD for six injections at 100% spiking for precision study

Sr. No	Methanol	IPA	DCM	Ethyl Acetate	THF	Toluene
1	109.4	113.8	109.9	109.4	104.2	111.0
2	107.9	112.5	107.8	107.0	102.4	109.9
3	116.8	122.4	114.6	114.2	108.3	119.6
4	101.5	103.6	103.0	101.7	98.3	101.3
5	104.8	106.6	105.9	104.3	100.8	104.4
6	109.9	114.2	111.0	109.4	104.9	111.2
Avg	108.38	112.17	108.7	107.7	103.2	109.6
Std. Dev	4.95	5.96	4.1	4.4	3.5	6.3
%RSD	4.56	5.31	3.7	4.1	3.4	5.8

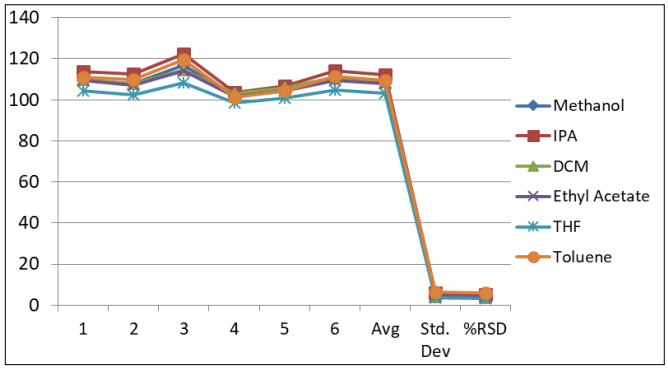

Fig 5

Table 8: Average Area of Methanol, IPA and DCM in Linearity Solution

Level	Methanol	IPA	DCM
Level I (LOQ)	436893	825310	97050
Level II (50%)	1480146	2454933	183132
Level III (80%)	2366249	3972151	298665
Level IV (100%)	2995379	5003200	379328
Level V (120%)	3502544	5929045	450382
Level VI (150%)	4399484	7394787	575332
Slope	1937.9	1967.8	1273.4
Y-Intercept	31495.6	-20717.0	-7223.5
Corr. Coeff.	0.9998	0.9999	0.9998

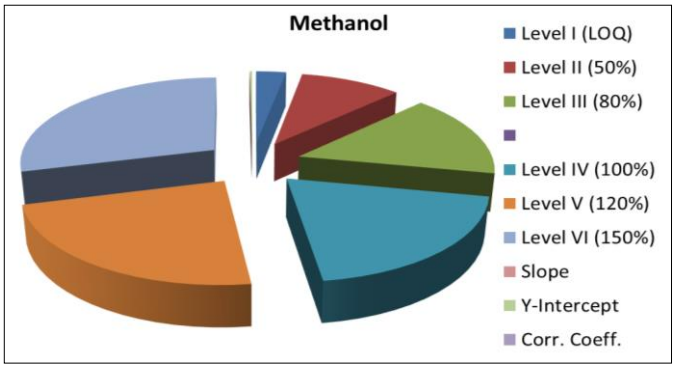

Fig 6

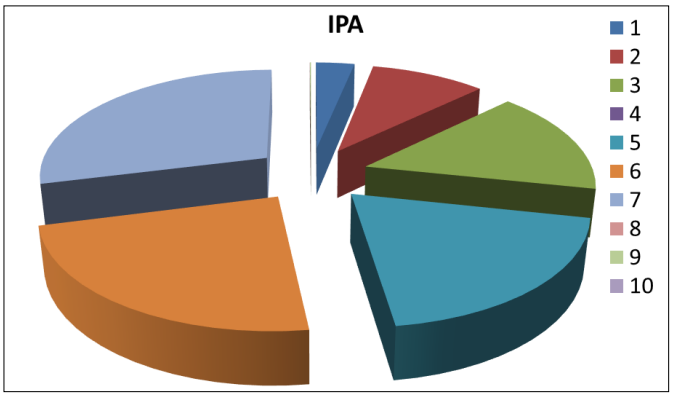

Fig 7

Table 9: Average Area of Ethyl Acetate, THF and Toluene in Linearity Solution

Level	Ethyl acetate	THF	Toluene
Level I (LOQ)	698040	263017	293243
Level II (50%)	4210072	1184102	893023
Level III (80%)	6827469	1917295	1451841
Level IV (100%)	8538575	2391998	1816815
Level V (120%)	10194350	2866062	2164562
Level VI (150%)	12858094	3619667	2707634
Slope	3429.8	6435.9	4161.2
Y-Intercept	-66746.5	1240.8	-8008.2
Corr. Coeff.	0.9999	0.9999	0.9999

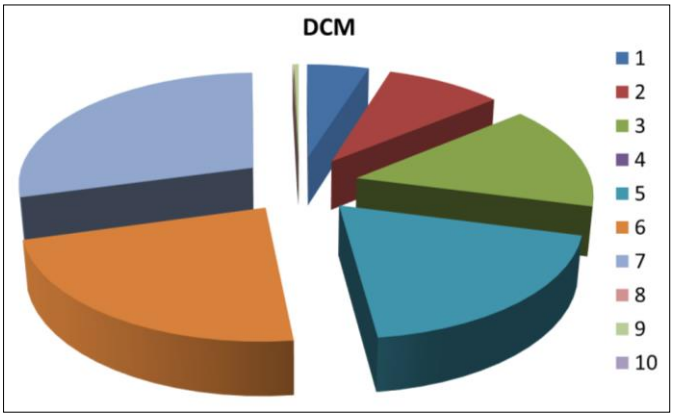

Fig 8

Table 10: %Recovery of solvents for LOQ to 150% levels

Component	Recovery at LOQ level	Recovery at 50% level	Recovery at 100% level	Recovery at 150% level
Methanol	101.4	105.7	104.2	105.7
Isopropanol	106.3	111.7	110.2	110.6
DCM	108.2	108.0	106.3	107.9
Ethyl acetate	103.9	108.2	106.3	106.8
THF	104.3	103.7	101.6	102.1
Toluene	111.4	109.6	107.2	107.8

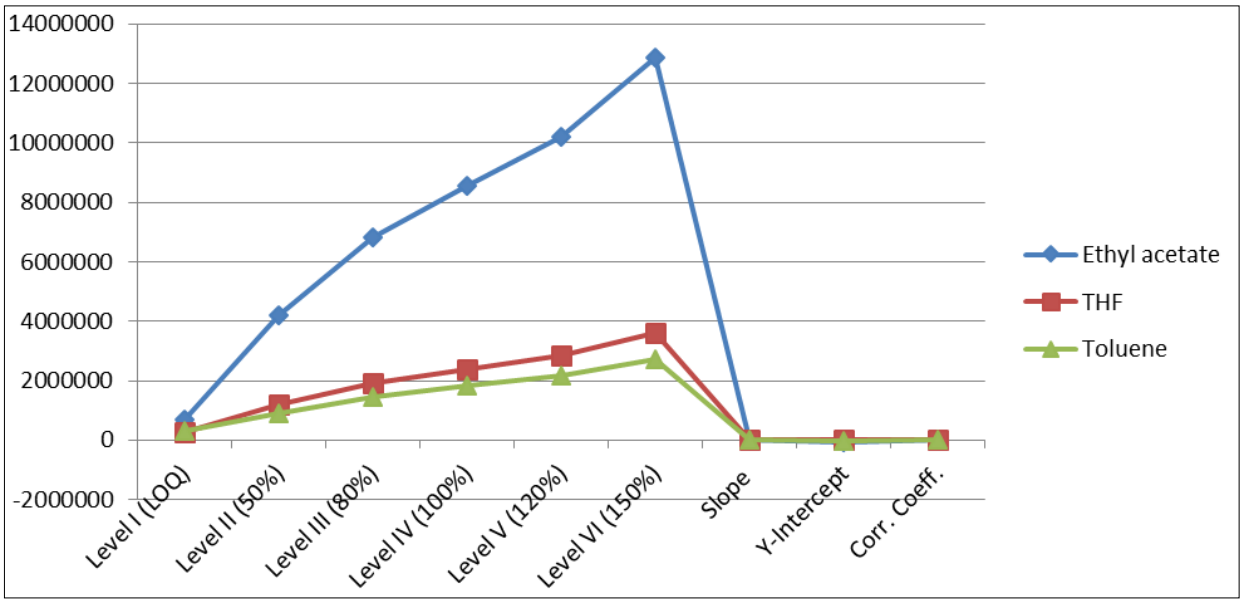

Fig 9

Summary and conclusion

This study presents a validation approach of the gas chromatography head space method for the determination of the residual solvent in the levalbuterol sulfate. The validation study shows that the method is specific, linear, precise and precise. Therefore, this method can be used in industry for routine quality control purposes.

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