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HEADSPACE GAS CHROMATOGRAPHY FOR THE DETERMINATION OF RESIDUAL SOLVENTS IN METFORMIN HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE

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ABSTRACT

An accurate analytical method was developed using headspace gas chromatography for the determination of residual solvents in metformin hydrochloride and hydrochlorothiazide. The residual solvent was studied with the help of gas chromatography (Shimadzu 2014 model) combined with Teledyne Tekmar headspace and GC solution software. The residual solvents were separated using DB-WAX column 30-meter-long, 0.32mm internal diameter for metformin hydrochloride and BP624 column 30-meter-long, 0.53 mm internal diameter for hydrochlorothiazide. The limit of detection and limit of quantitation of dimethylacetamide, methanol and benzene were 17.00, 10.93, 0.18 and 51.92, 33.13, 0.57 ppm respectively for metformin hydrochloride and in case of hydrochlorothiazide, the values were 3.40& 1.30 ppm and 10.15 & 4.00 ppm for methanol and methyl isobutyl ketone respectively. The method was validated according to international conference on harmonization guideline in terms of specificity, linearity, precision, accuracy and robustness.

Keywords: *Metformin hydrochloride, Hydrochlorothiazide, Residual Solvents, Dimethylacetamide,Methanol, Benzene, MIBK, HSGC,Validation.*

1. INTRODUCTION

Metformin hydrochloride (MH) in Figure 1 belongs to the biguanide class, it is chemically known as 1,1-dimethyl biguanide monohydrochloride and is specific for the treatment of diabetes [1–2]. MH controls gluconeogenesis process in the liver during the production of glucose, it also reduces absorption of glucose in the intestines and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Hydrochlorothiazide (HCTZ) in Figure 1 is an antihypertensive drug and a thiazide type diuretic prescribed for the last 5 decades as a medicine to treat high blood pressure [3]. There are many other drugs available in the market but HCTZ have the ability to minimize cardiovascular attack, and efficacy due to its pharmacokinetic property. 2H-1,2,4-Benzothiadiazine-7-sulfonamide,6-chloro3,4-dihydro-,1,1-dioxide is the chemical name of HCTZ, and is mainly used for the treatment of hypertension, diabetes and kidney stones. The mechanism of drug synthesis consists of many routes and each one requires an intermediate as well as a different solvent. It is very important to remove all impurities from the drug, but the results show that some are still present as volatile

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organic impurities (residual solvent), this is because the traces of solvent is not possible to remove completely. These solvents are toxic in nature, so pharmaceutical industries have concern over the presence of residual solvent in the final product. The international conference on harmonization (ICH) has limited the amount of residual solvent in their guidelines and has classified it as I, II and III according to the toxicity level and environmental hazard [4]. In our opinion the best technique to determine the residual solvent in bulk as well as in formulation is gas chromatography combined with static headspace (HSGC), as it has the ability to separate solvents with great accuracy and with very low detection limit [5–11]. The supplier claims dimethylacetamide, methanol, benzene for metformin hydrochloride and methanol, methyl isobutyl ketone for hydrochlorothiazide are present in the final product. To the best of our knowledge there is no validated HSGC method available for the analysis of residual solvents in MH and HCTZ. Therefore, a precise HSGC method is essential for the determination of residual solvent present in the above mentioned drugs. In the present study, static headspace gas chromatography methods with flame ionization detector are developed for the determination of residual solvent. The methods are then validated according to ICH guidelines. The developed method is quiet simple and precise for the determination of residual solvent in bulk and it can be used to quantify the same in the pharmaceutical formulations.

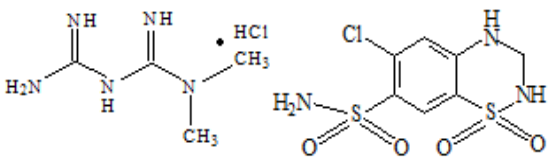

Fig. 1. Structure of metformin hydrochloride and hydrochlorothiazide.

2. EXPERIMENTAL

2.1 CHROMATOGRAPHIC CONDITIONS

The analytical methods were developed with the help of Shimadzu 2014 gas chromatography (Japan) in combination with headspace auto sampler (USA). Flame ionization detector (FID) is suitable for the analysis and nitrogen was used as carrier gas for the study. GC was connected with computer and controlled by Total Chrome Navigator software. All experiments were performed using a DB-WAX column with 30-meter-length and 0.32mm internal diameter for metformin hydrochloride (MH) and a BP624 column with 30-meter-length and 0.53mm internal diameter for hydrochlorothiazide (HCTZ). Below are the parameters (Table 1) that were followed throughout the analysis for the quantification of residual solvents in MH and HCTZ.

2.2 DRUGS AND CHEMICALS

Dimethylacetamide (GC Headspace grade), methanol (HPLC grade), methyl isobutyl ketone (HPLC grade) from Thermo Fisher Scientific Private Limited, India and benzene (HPLC grade), dimethyl sulphoxide (HPLC grade) and drugs metformin, hydrochlorothiazide were purchased from Sigma Aldrich, India. Drug formulations, Formin 500mg (Alembic) Glumet 500mg (Cipla) contain MH and Aquazide 12.5mg (Sun Pharma), Klorzide 25mg (Zydas Cadila) were obtained from local market, India.

2.3 STANDARD SOLUTIONS AND CALIBRATION CURVE

In order to construct standard calibration curve, stock solution of benzene (1000 ppm), dimethylacetamide (1000ppm), methanol (3000ppm) for metformin and methyl isobutyl ketone (5000ppm), methanol (3000ppm) for hydrochlorothiazide was first made. 0.1g benzene, 0.1g dimethylacetamide, 0.3g methanol were transferred into 100ml

volumetric flask and diluted up to the mark with DMSO. Another 100ml volumetric flask was taken with 0.3g methanol and 0.5g MIBK as contents and was diluted with DMSO up to the mark. The concentration of each solvent was in the range of 50–1000ppm after diluting with DMSO. A linear calibration plot was made between concentration (ppm) of the solvent vs peak area and a linear equation was established after calculating slope and intercept using the straight line that depends on correlation coefficient (R^2) value.

TABLE 1: PARAMETERS FOR HSGC ANALYSIS.

GC	Headspace auto sampler
Gas Flow	GC Cycle-31 min
N_2–1 ml/min	Valve Oven-110°C
H_2 – 40 ml/min	Transfer line-150°C
Air – 450 ml/min	Sample-40°C
Column Temp	Equilibrium-0.5 min
Initial-60°C	Sample Equil. Time-3.0 min
60°C hold for 10 minutes; Raised to 240°C at ramp 15°/minute and hold for 2 minutes; Run Time 24 minutes	Pressurize time-2.00 min
FID	Pressurize Equil. Time-0.25 min
240°C	
Injector	
240°C	

2.4 BULK DRUG AND PHARMACEUTICAL DOSAGE FORM

Metformin hydrochloride (MH) (500mg) and hydrochlorothiazide (HCTZ) (250mg) were dissolved with 50 ml DMSO and made up to the mark to obtain 5000 ppm and 2500ppm respectively. The commercial products of metformin (Formin, Glumet) and hydrochlorothiazide (Aquazide, Klorzide) were accurately weighed and finely powdered separately. 500mg metformin and 250mg hydrochlorothiazide was dissolved with DMSO and filtered with 0.45µm Millipore filter, the solution was then diluted with DMSO to get 5000ppm and 2500ppm respectively.

2.5 PROCEDURE

The HS vials were of 10 ml capacity and 2 ml of each solvent with different concentration are transferred in to the 10 ml HS vials and kept at 40°C after tightening with the septum. The sample was collected by turbometrix and heated to produce vapor at injector temperature in the injector. The vapor of the sample was then passes through a transfer line to the gas chromatography and moved towards the column by carrier gas for separation and detection.

3. RESULTS AND DISCUSSIONS

A headspace gas chromatographic method was developed for the determination of residual solvent in metformin hydrochloride (dimethylacetamide, benzene, methanol) and hydrochlorothiazide (methyl isobutyl ketone, methanol). The methods were validated according ICH guidelines with respect to specificity, linearity, accuracy, precision, limit of detection, limit of quantitation, ruggedness and robustness.

3.1 SPECIFICITY

Stock solution is diluted to get dimethylacetamide (1000 ppm), methanol (3000 ppm), benzene (2 ppm) and methyl isobutyl ketone (5000 ppm) separately and each standard is prepared with same concentration as well. The standard sample of each solvent are injected separately to compare the retention time with composite sample in Figures 2 and 3. To avoid overlap and ensure better separation of peaks, two columns were used and the specificity results are provide in Table 2.

3.2 LINEARITY AND RANGE

The standard stock solution of benzene (2 ppm), dimethyl acetamide (2000ppm), methanol (1000ppm) and methyl isobutyl

ketone (2500ppm) were prepared. All reference standard solution was prepared in triplicate by diluting stock solution with DMSO. The results were recorded and a graph was constructed between concentration (ppm) and peak area to obtain calibration curves of all residual solvents present in metformin and hydrochlorothiazide**.** Correlation coefficient **(**R^2) was calculated for all the regression equations. The linearity ranges were 0.3–1.5ppm for benzene, 40–250 ppm for dimethyl acetamide, 50–500ppm for methanol and 80–950ppm for methyl isobutyl ketone in Table 3.

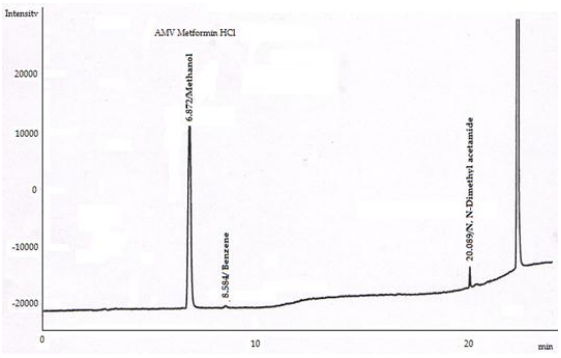

Fig. 2. Chromatogram for Metformin hydrochloride.

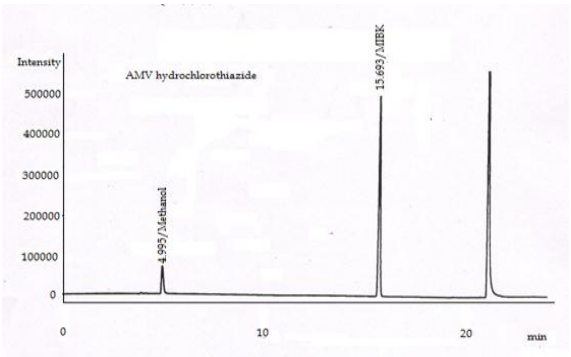

Fig. 3. Chromatogram for Hydrochlorothiazide.

3.3 PRECISION

The instrumentation precision was determined by applying benzene (1.5ppm), DMA (250ppm), methanol (500ppm) and MIBK (950ppm) with independent six replicate injections from the same vial. The percent relative standard deviation (% RSD) for benzene, DMA, methanol and MIBK were 1.99, 1.87, 1.03 and 0.76 respectively in Table 4 within the limit (15%, ICH guidelines).

3.4 LIMIT OF DETECTION (LOD) AND LIMIT OF QUANTITATION (LOQ)

The LOD and LOQ were calculated using the following equations:

$$\text{Limit of detection (Conc.ppm)} = \frac{3.3 \times SD}{b}$$

$$\text{Limit of quantification (Conc.ppm)} = \frac{10 \times SD}{b}$$

where, 3.3 and 10 are factor SD=Standard deviation of linear regression; b= Slope of linear regression. The LODs and LOQs for benzene, DMA, methanol and MIBK are provided in Table 3.

3.5 ACCURACY

The accuracy of standard solution of all solvents was calculated in terms of % recovery for triplet injections of individual solvent in Table 5. The percentage recovery was calculated using the standard calibration curve or linear plot. The percentage values are within the limit (80–120%).

3.6 ROBUSTNESS

The robustness studies were conducted by changing the oven temperature to 5°C below and above the normal oven temperature. The % RSD values for benzene, DMA, methanol and MIBK are injected triplicate separately and presented in Table 6.

3.7 APPLICATION OF THE PROPOSED METHOD WITH PHARMACEUTICAL FORMULATIONS

The proposed method was developed and applied to quantify the residual solvents present in pharmaceutical formulations of metformin hydrochloride (Formin, Glumet) and hydrochlorothiazide (Aquazide, Klorzide). All samples were injected three times individually but no peak of residual solvent was detected. So the results indicated solvents are not present in the pharmaceutical formulations.

TABLE 2: SPECIFICITY RESULTS.

Drug	Retention time (Minute) Individual Standard	Retention time (Minute) Composite Sample
Metformin HCl	Methanol – 6.87 Dimethylacetamide – 20.09 Benzene – 8.60	Methanol – 6.87 Dimethylacetamide – 20.09 Benzene – 8.59
Hydrochlorothiazide	Methanol – 4.99 Methyl isobutyl ketone –15.70	Methanol – 5.00 Methyl isobutyl ketone – 15.69

TABLE 3: PARAMETERS OF LINEAR REGRESSIONS OF RESIDUAL SOLVENTS.

Parameters	Benzene-MH	DMA-MH	Methanol -MH	MIBK-HCTZ	Methanol -HCTZ
Linearity Range (ppm)	0.3-1.5	40-250	50-500	80-950	50-500
Slope	1665.7	10.9	124.0	1144.6	100.2
Intercept	-4.5	6.1	326.9	32.3	332.1
Correlation coefficient (r^2)	0.9999	0.9991	0.9991	0.9999	0.9994
LOD (ppm)	0.18	17.00	10.93	1.30	3.40
LOQ (ppm)	0.57	51.92	33.13	4.00	10.15

TABLE 4: INSTRUMENT PRECISION OF THE PROPOSED METHOD FOR THE DETERMINATION OF RESIDUAL SOLVENT.

Parameters	Peak area of benzene	Peak area of DMA	Peak area of methanol	Peak area of MIBK
Mean	2471.67	2758.17	63660.67	109442.50
SD	49.09	51.51	658.38	832.15
% RSD	1.99	1.87	1.03	0.76

TABLE 5: ACCURACY RESULTS OF RESIDUAL SOLVENTS FOR BENZENE, DMA, METHANOL AND MIBK.

Solvent	Concentration (ppm)	Avg. peak area	Concentration by graph	% Recovery
Benzene	1.80	2472.50	1.49	99.33
DMA	250	2742.8	252.09	100.84
Methanol	500	63101	506.20	101.24
MIBK	950	1100225	961.20	101.18

TABLE 6: ROBUSTNESS OF THE PROPOSED METHOD.

Condition	Avg. peak area Benzene	Avg. peak area DMA	Avg. peak area methanol	Avg. peak area MIBK
Oven temperature decrease 5°	2534	2842	63395	1117007
	%RSD = 1.92	%RSD = 2.71	%RSD = 1.44	%RSD = 1.91
Oven temperature increase 5°	2649	2768	64580	1151902
	%RSD =2.93	%RSD = 2.45	%RSD = 1.52	%RSD =1.51

4. CONCLUSION

The proposed investigation was done for the determination of residual solvents in MH and HCTZ using headspace gas chromatography equipped with flame ionization detector. The repeatability and accuracy results of the method were quite satisfactory, and the obtained %RSD is within the limit of ICH guidelines. This method is sensitive for the quantification of residual solvents present in bulk and dosage forms. We recommend that the proposed method can be applied for routine analysis in academic institutions and research laboratories for its simplicity and low cost.

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