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Research Article

APPLICATION OF TWO GC ANALYTICAL SYSTEMS [GC/DB-17/ N_2 / FID /DMSO] AND [GC/RTX-5MS/HE/MS/DMF] FOR THE DETECTION AND ESTIMATION OF RESIDUAL DICHLOROMETHANE IN OMEPRAZOLE DRUG SUBSTANCE

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ABSTRACT

The determination of residual solvents in drugs and pharmaceuticals is one of the most important quality parameter and also considered to be a challenge to the recent gas chromatography (GC) applications in quality control laboratories in the pharmaceutical industry. The main objective of this research investigation is to detect and estimate the levels of dichloromethane residues in Omeprazole drug substance. Two different analytical procedures, namely: GC/DB-17/N_2/FID/DMSO and GC/Rtx-5MS/He/MS/DMF were adopted to achieve the objective. The specification of the column in the former system is DB-17 capillary column (30m length X 0.25 mm ID X 0.25µm film thickness (Methyl 50% Phenyl polysiloxane) with DMSO sample diluent. In the latter system was equipped with Rtx-5MS capillary column length 30 m, diameter 0.25 mm and thickness 0.25µm (5% diphenyl / 95% Dimethyl poly siloxane) with DMF as sample diluents. Direct injection method was adopted in both techniques. The analytical methods verification was carried out as per International Conference on Harmonization (ICH) method validation guideline Q2B. Selectivity of the two procedures was established via securing good resolutions of the two pure diluents and DMSO was resolved at 18.00 min and in DMF which was resolved at 6.5 min. Similarly, pure standard dichloromethane in DMSO and DMF diluents was resolved, excellently, at 3.56 min and 1.99 min, respectively. A linear calibration plot was obtained for five concentration levels of dichloromethane standard for the range (30.0-480.0 ppm) in DMSO and in the range (0.200-1.0 ppm) for DMF affording a correlation coefficient R^2 of 0.9995, (0.9970), respectively. The percentage RSD for dichloromethane was found to be low for techniques 1.79%, 3.20% for the former and the latter systems, respectively, indicating high precision and extremely low coefficient of variation**.** The LOD and LOQ of dichloromethane were calculated by statistical method to be 12.7 and 38.5 ppm, for DMSO; and $0.324x10^{-3}$, $0.107x10^{-3}$ ppm for DMF. The residual concentration level of dichloromethane in Omeprazole drug substance was found to be 485.66 ppm (0.831ppm) in system: GC/DB 17/N_2/FID/DMSO and the system GC/Rtx-5MS/He / MS/DMF, respectively. It is concluded that both levels are well, below the ICH permissible limits of 600 ppm. The analytical reliability and sensitivity of the MS detector is remarkably higher than the FID detector.

Keywords: Omeprazole, Dichloromethane, Gas Chromatography (GC), Flame Ionization Detector.

INTRODUCTION

Residual solvents in manufactured drugs and pharmaceutical products are defined as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The solvents are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis and recrystallization of drug substance may enhance the yield, or determine characteristics such as crystal form, purity and solubility[1]. The residual solvents are divided into three classes: Those solvents with unacceptable toxicities, which should be avoided (Class I), solvents with less severe toxicities, use of which should be limited (Class II) and those with less toxic solvents (Class III)[2].

In manufacturing drug substances, residual solvents arising from the final purification by recrystallization, and also from one or more steps of the whole synthetic process, can be retained in the end products. Very often these solvents, referred to as organic volatile impurities (OVIs), are transferred to the pharmaceutical preparation concerned, making their determination mandatory. In fact, as the major part of OVIs are recognized to be toxic to various degrees[3, 4].

The determination of residual solvents in pharmaceuticals is very important because of the potential risk to human health from the toxicity. Organic solvents play a key role in the production of pharmaceuticals, and traces of these solvents will remain in the final product. The presence of these unwanted chemicals even in small amounts may influence the efficacy, safety and stability of the pharmaceutical products[5, 6].

The most commonly used technique for the analysis of residual solvents is conventional gas chromatography (GC)[7, 8]. The traditional technique of sample preparation for residual solvent determination is direct injection in which the drug substance or the formulation is dissolved in or extracted with a high boiling point solvent[9]. This technique is simple but its disadvantage is that non-volatile components are also injected leading to injector contamination, column contamination and deterioration with unavoidable matrix effects[10]

Thus, headspace analysis (HS) is thought to be the most suitable and convenient technique for residual solvent testing which avoids many of the drawbacks of direct injection[11, 12]. Headspace injection is an alternative technique, but is rather limited in terms of optimization possibilities with respect to its selectivity , Multiple head space extraction (MHE), presented in 1977[13], is a stepwise technique based on extrapolation to an exhaustive extraction of the compounds through three or four cycles of consecutive extractions from the same sample; thus, in theory, the extraction could continue until all the analytes were removed from the sample, resulting in complete recovery. MHE technique was developed to remove the influence of matrix effect for direct quantitative determination of analytes from solid matrices by combination with different headspace extraction techniques such as solid-phase micro extraction (SPME) and SDME[14].

To avoid the unwanted effects of non-volatile material a number of analytical techniques had been attempted and developed such as solid phase micro extraction (SPME) or bar sorptive extraction (SBSE), headspace sorptive extraction(HSSE), static (HSS) and dynamic head space sampling (DHS). All these techniques have many well documented applications in the literature[15-20].

The determination of polar residual solvents in pharmaceutical preparations continues to present an analytical challenge mainly because these compounds are quite difficult to remove from water or polar solvents[21-23].

The quantitative determination of residual ethanol static headspace gas chromatography (HS-GC) was used to seal the hard gelatin capsules by liquid encapsulated and microspray sealing (LEMS; cfs 1200, Greenwood, SC, USA). The effects of decane, dodecane, heptane, 0.1 M HCl, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidinone and dimethyl sulfoxide on the method sensitivity are compared. It is observed that the ethanol headspace concentrations can be increased by four folds when aliphatic hydrocarbon solvents are added into the aqueous sample solutions in a HS vial[24].

The matrix medium used is influence the determination of residual solvents in pharmaceuticals by static headspace gas chromatography, the peak shape of each analyte was not affected by the matrix medium, whereas the peak intensities for all solvents were strongly affected by the matrix medium[25].

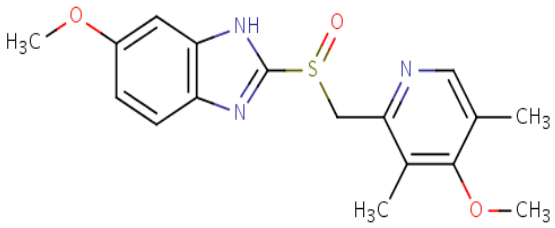
Cyclohexane and toluene were gas chromatographically determined via headspace solid-phase micro extraction both in ketoprofen drug substance and ketoprofen capsules by a procedure relying on isotopic dilution (ID), an analytical tool derived from mass spectrometry (MS). This approach, using an internal standard method, gave mean precision and accuracy (RSD 2.56%, 2.97% and bias 0.21%, 20.99% for cyclohexane and toluene, respectively) not obtainable by the

more commonly used external standard ones in the presence of real sample matrices[26].

The relationship between residual solvent (methylene chloride) concentration and the stability ampicillin trihydrate crystals stability. The amounts of residual solvents determined by GC, X-ray powder diffraction (XRPD) and Fourier transform infrared spectroscopy (FT-IR) were used for characterization of solid state. As with the increasing methylene chloride concentration in the sample the degree of crystallinity decreased after stability test[27].

Omeprazole is a potent reversible inhibitor of the gastric proton pump H+/K+-ATPase used for treatment of peptic ulcer. It is composed of a substituted pyridine ring linked to a benzimidazole by a sulfoxide chain. Chemically designed as 5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole. Omeprazole is a white powder, slightly soluble in water, but is highly soluble in alkaline solutions, soluble in methylene chloride and sparingly soluble in Ethanol 96% and Methanol. It was reported that the determination of dichloromethane and chloroform residues is performed using Head space GC and the BP limits of dichloromethane and chloroform in 0.5g Omeprazole drug substance are 100 ppm and 50 ppm respectively[28].

The molecular formula of Omeprazole is $C_{17}H_{19}N_3O_3S$ (M.wt. 345.4), and the chemical structure is shown below [28]



The main aim of the present research investigation is to establish a laboratory analytical procedure of high degree of specificity, accuracy and precision for the detection and quantification of residual solvents in general with emphasis of dichloromethane residue in Omeprazole drug substance. The research laboratory protocol and the methodology associated with it consist of: choosing two Gas-Chromatographic GC procedures, namely; [GC/DB-17/ N_2 / FID /DMSO] and [GC/Rtx-5MS/He/MS/DMF].

MATERIALS AND METHODS

MATERIALS

Omeprazole raw material (99.7% purity) was obtained from Amipharma industry, Dimethyl Formamide (DMF) HPLC Grade (SCHARLAU) European Union, Dimethyl sulphoxide (DMSO) HPLC Grade (SCHARLAU)European Union and Dichloromethane (Methylene chloride) standard with 98% minimum assay GC, density of 1.323-1.327 gm/ml, and molecular weight 84.93 gm/mol, from the market.

METHODS

Optimization of the gas chromatographic conditions: (GC/FID)

In the present study a GC-2010 (SHIMADZU) with Flame ionization detector (FID) was optimized. Instead of BP 624 column (30m X 0.53mm ID X 0.25µm coating thickness (4% cyanopropyl phenyl and 96% dimethyl polysiloxane stationary phase) which used by Puranik and Sanjay in the direct injection GC method mentioned previously[29], the separation was carried out on DB-17 capillary column (30m X 0.25mm ID X 0.25 µm film thickness with serial number US5287884H (Methyl 50% Phenyl polysiloxane), with nitrogen as carrier gas in the split mode by direct injection method. The temperature of injection port was maintained at 250°C. The pressure of 85.6 kPa with flow of 1.2 mL/min was maintained with linear velocity of 29.3 cm/sec and total flow of 50 mL/min.The temperature of the detector was set at 300°C. Temperature was maintained at 40°C for five minutes and then increased at a rate of 5°C /min to 80°C, finally increased at the rate of 10°C/min to reach the final temperature of 200°C for 2 minutes. Analysis time was 27 minutes. And total run time for each injection was 40 minutes.

Optimization of gas chromatographic conditions(GC/MS)

In the present study a GC.MS-QP 2010 Ultra (SHIMADZU) Japan with Mass spectroscopy detector (MS) was optimized. The separation was carried out on Rtx-5MS, Length (30 m), Diameter (0.25 mm), and thickness (0.25µl), with Helium as carrier gas in the splitless mode. The temperature of injection port was maintained at 300°C. The pressure of 47.6 KPa with flow of 1.00 mL/min was maintained with linear velocity of 36.0 cm/sec and total flow of 50.0 mL/min. The temperature of the detector was set at 200°C. Temperature was maintained at 35.0°C for five minutes and then increased at a rate of 3.0°C/min to 200°C. Analysis time was 5 minutes for each injection.

Determination of the retention times of dichloromethane (GC/FID)
(1µL) was injected into GC injection port and the retention time was recorded.

Determination of the retention time of dichloromethane standard (GC/MS)
1µL of Dichloromethane standard was injected into GC.MS injection port and the retention time was recorded. The determination of the retention time was carried out in triplicate at the same GC/MS conditions.

Preparation of Omeprazole drug substance sample (GC/FID)
Omeprazole raw material (1g) was accurately weighed by sensitive balance. It was dissolved and sonicated for 30 minutes with DMSO in 10 mL volumetric flask, filtered through whatman filter paper No 1 and the volume made up to 10mL with DMSO, in separate 10 mL volumetric flask. The solution was filtered again through PTFE 0.45µm filter. The sample solution (1µL) was injected into GC injection port, three replicates were done and chromatograms were recorded [13].

Preparation of Omeprazole drug substance (GC/MS)
Omeprazole (1.0gm) raw material was accurately weighed by sensitive balance. It was dissolved and sonicated for 15 min with DMF in 10 mL volumetric flask, filtered through 70 mm Whatman filter paper and the volume made up to 10 mL with DMF, in separate 10 mL volumetric flask. The solution was filtered again through PTFE 0.45µm filter. The sample solution (1µL) was injected into GC injection port, and chromatograms were recorded.

Preparation of dichloromethane stock solut ion (GC/FID)
Dichloromethane (0.25ml) was measured and placed in 25ml volumetric flask and completed with DMSO solvent, to get stock solution with concentration of 13.25mg/ml (13250 ppm).

Preparation of dichloromethane serial dilution solutions
A measured volume of standard stock solution 22.64µL, 45.28µL, 90.566µL, 181.13µL and 0.3623 ml were taken in separate 10 ml volumetric flasks, and the volume was adjusted to the mark with DMSO to obtain concentration of 30, 60, 120, 240 and 480 ppm respectively. From each solution 1µL was injected into GC injection port separately, three replicates were done and chromatograms were recorded.

Preparation of dichloromethane stock solut ion (GC/MS)
Dichloromethane (0.25 ml) was measured and placed in 25 ml volumetric flask and completed with DMF solvent, to get stock solution with concentration of 13034 mg/ml (13034 ppm).

Preparation of dichloromethane working solution
The stock solution (0.023 ml, 3.00 µl) was measured and placed in 10 ml volumetric flask and completed the volume with DMF solvent, to get solution with concentration of 30 ppm (30000 ppb), 1.666 ml (1666 µl) of this solution was measured and placed in 50 ml volumetric flask and completed the volume with DMF solvent, to get working solution with concentration of 1.00 ppm (1000 ppb).

Preparation of dichloromethane serial dilution solutions
A measured volume of standard working solution 2.00 µL, 4.00 µL, 6.00 µL, 8.00 µL and 10.00 ml were taken in separate 10 ml volumetric flasks, and the volume was adjusted to the mark with DMF to obtain concentration of 200, 400, 600, 800 and 1000 ppm respectively. The solutions were filtered through 70 mm Whatman filter paper and PTFE 0.45 µm filter. From each solution 1µL was injected into GC/MS injection port separately, and chromatograms were recorded.

RESULTS AND DISCUSSION
The hazard, toxicity and carcinogenicity of volatile organic solvents (VOC) are well documented in the literature. Concentration limits of these solvents and their permissible levels in drugs and pharmaceutical products are governed by International Specifications which are rules and laws set by International Organizations and agencies such as WHO, ICH, US-FDA, US-EPA, EU, ASDRA etc. quite a good number of countries realized the importance of this health issue and accordingly governmental agencies had also set and published permissible levels of residual solvents parallel and similar to those of the International Organizations. Based on the portrayed literature in the introduction and this preface the main aim of the present research investigation is to establish a laboratory analytical procedure of high degree of specificity, accuracy and precision for the detection and quantification of residual solvents in general with emphasis of dichloromethane residue in Omeprazole drug substance. The research laboratory protocol and the methodology associated with it consists of: choosing two Gas-

Chromatographic GC procedures, namely; GC instrument equipped with Flame Ionization Detector FID and another GC instrument equipped with Mass Spectrometric MS detectors. Analytical trials in both instruments were carried out also on different types of capillary columns DB-17 capillary column (30m length X 0.25 µm) film thickness with serial number US5287884H [Methyl 50% Phenyl polysiloxane] for the GC/FID instrument and Rtx-5MS, capillary column (Length (30 m), Diameter 0.25 mm), and thickness (0.25µl) [5% diphenyl / 95% Dimethyl poly siloxane] for the GC/MS instrument Moreover, Dimethyl sulfoxide (DMSO) was used in the former technique; while in the latter technique Dimethyl Formamide (DMF) was attempted as diluents for the tested or analyzed samples and drug standards. The carrier gases were also different: nitrogen N_2 gas was used for GC/FID instrument, while helium He gas was used as a carrier gas for GC/MS instrument. The laboratory protocol and methodology consisted of several phases: the excellent resolution that occurred when a suitable column and appropriate optimization instrumental conditions were being set up. For both columns this was achieved as it can be noticed from the chromatograms shown in Figure 1 and Figure 2.

At the optimum GC-conditions described in the Material and Methods Section the standard dichloromethane was resolved at an optimum retention times of 1.99 min and 3.57 min, respectively, in the GC/MS/ and GC/FID instruments, see also Table 1.

Selectivity

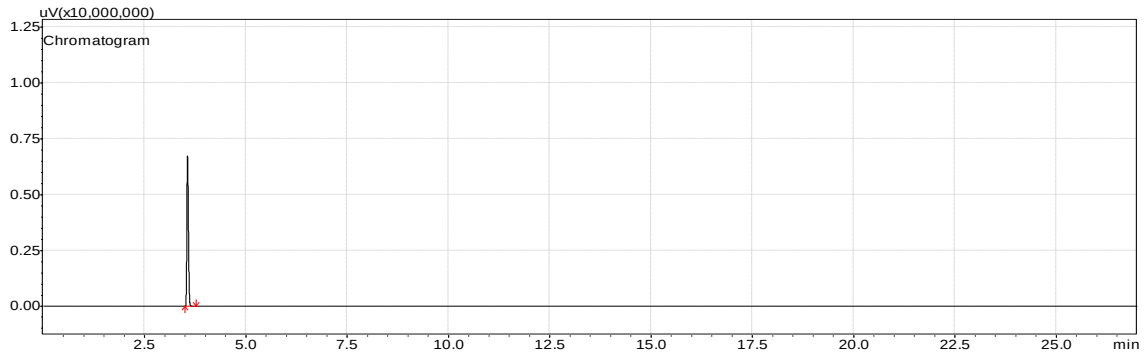


Fig. 1: GC/FID Resolution of dichloromethane standard on DB-17 capillary column

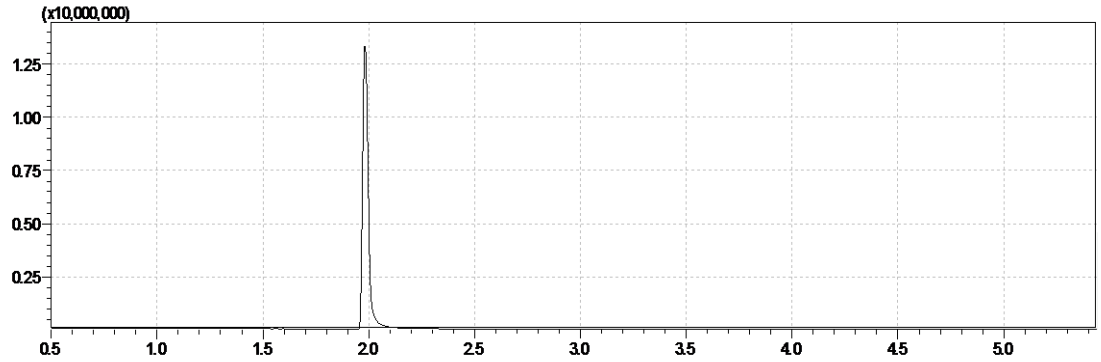


Fig. 2: GC/MS resolution of dichloromethane standard on Rtx-5 MS column capillary column

It could be observed that a narrow peak width (sharp) was achieved verifying an excellent column efficiency. It could also be noticed that the resolution is perfect without the appearance of any baseline noise. The retention times for both standards occurred at retention times far from the retention times of diluents solvents. This could be observed in the chromatograms of the diluents solvents shown in Fig.3 and Fig.4, below.

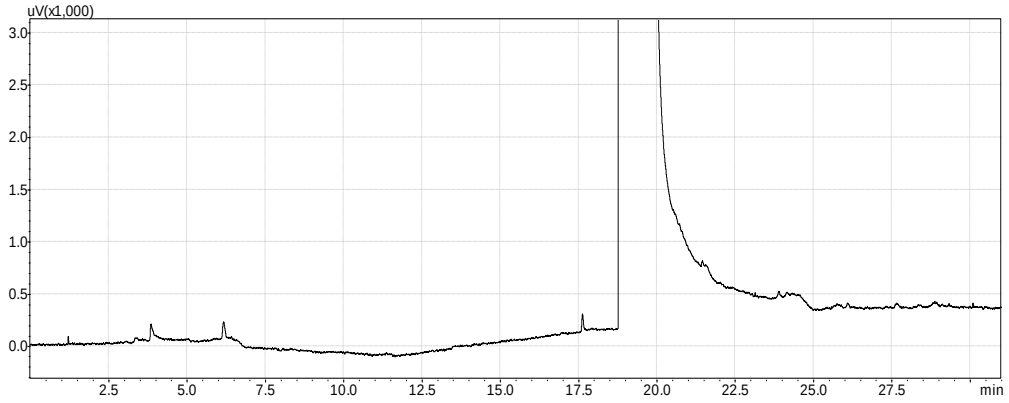


Fig. 3: Resolution of Dimethyl sulfoxide DMSO diluent solvent GC/FID-DB-17

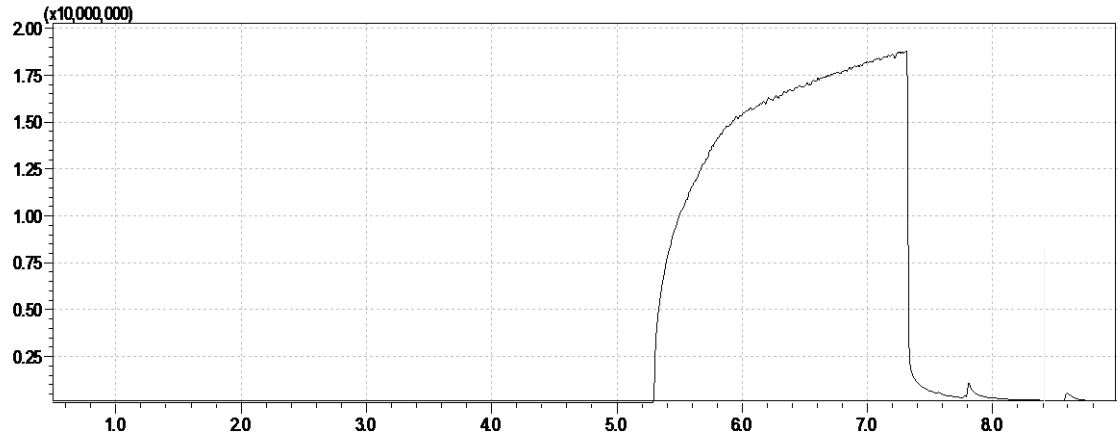


Fig. 4: Resolution of Dimethyl formamide DMF diluent solvent GC/MS/Rtx-5MS

Several GC-runs were performed to improve the resolution and to remove the tailing observed in the signal of the diluent solvent DMF, which occurred in the chromatogram shown in Fig. 4. These attempts included changes of flow rate, temperature, pressure, dilutions etc. But all these improvement efforts and attempts failed. It was then concluded that the tailing was inevitable. It is fortunate that the retention time of signal of the DMF diluent appears at the retention time 6.50 min, which is, comfortably, far from that of dichloromethane, 1.99 min. Table 1, below.

Table 1: Retention Times of Diluent Solvent and Standard Dichloromethane on DB-17 and Rtx-5MS

	Diluent solvents	Standard Dichloromethane
GC/FID-DB-17	18.00 min (DMSO)	3.56 min
GC/MS- Rtx-5MS	6.50 min (DMF)	1.99 min

The methodology adopted in the present investigation was based on one chromatographic technique (GC) but with two different laboratory analytical tools GC/MS/Rtx-5MS and GC/FID/DB-17. Moreover, the former analytical technique utilized nitrogen as a carrier gas and the latter technique utilized helium as a carrier gas. Furthermore, it is important to mention that both techniques are targeting the same objective: the detection and estimation of the concentration levels of dichloromethane residual solvent in Omeprazole drug substance. Both techniques were validated in the same general customary manner via the determination of the validation parameters: linearity, correlation coefficient R^2, relative standard deviation RSD, coefficient of variation CV, reproducibility, lowest limit of detection LOD and lowest quantification detection LQD.

Linearity of Results

The linearity parameter was determined by injecting two different Batches of 5 series of concentration levels (one in the range of 30.00-480 ppm and the other within the range of 200.00-1000.00ppm). The former batch was injected into GC/FID/DMSO/ Rtx-5MS and the latter into the GC/FID/DB-17. The response for each of the two batches of serial dilutions was found to be linear for the two methods, as it can be noticed in the plots shown in Fig. 5 and Fig. 6, below. The two methods have shown linear plot within a wide range of concentration levels.

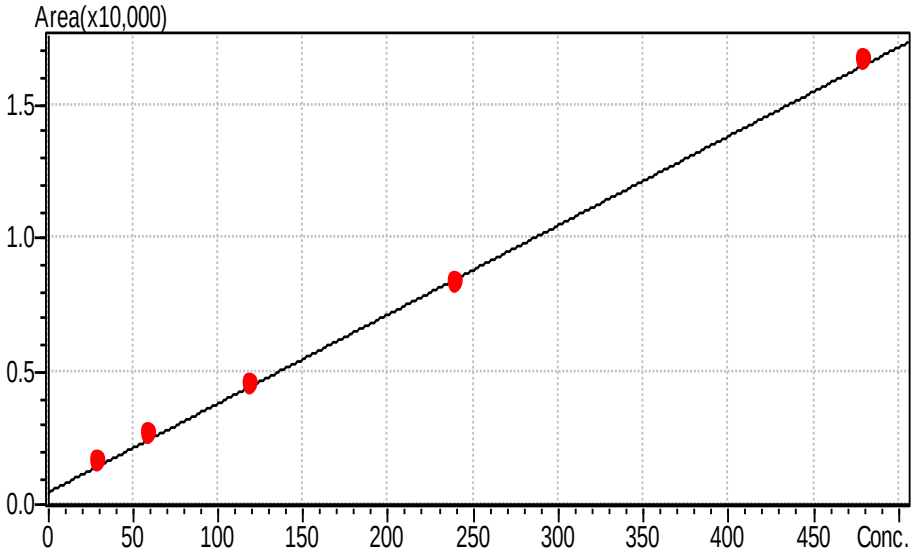


Fig. 5: Linearity plot of dichloromethane response versus concentration using GC/FID

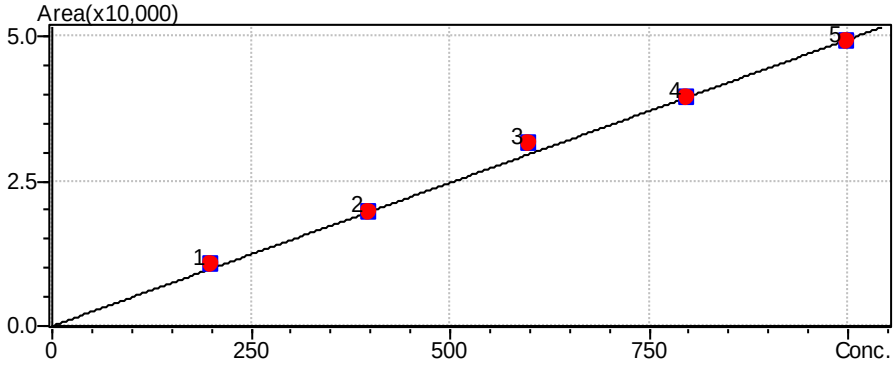


Fig 6: Linearity plot of dichloromethane response versus concentration using GC/MS

Table 2: Validation Parameters of the Standard Dichloromethane Residual Solvent within the GC/FID/DB-17 and GC/MS- Rtx-5MS Methods

Methods / parameters	linearity (µg/ml)	Detection limit (µg/ml)	Quantification limit (µg/ml)	Method Precision (RSD%)	correlation coefficient (R)
Dichloromehane GC/FID/DB-17	30 - 480	12.7	38.5	1.79	0.99953
Dichloromethane GC/MS- Rtx-5 MS	0.2-1 × 1.0	0.324×10^{-3}	0.107×10^{-3}	3.2	0.99707

The correlation coefficients R^2 were 0.99953 and 0.99707 GC/FID//DB-17 and GC/FID/Rtx-5MS, respectively. The linear regression showed a positive response throughout the range of concentrations. The results obtained from both methods have shown an excellent coefficient of variation and very good reproducibility, which are reflected by the low relative standard deviation values 1.79 and 3.20, Table 2.

Precision

The precision of an analytical procedure as defined by ICH is the closeness of agreement between a series of measurements obtained from multiple sampling of the same homogenous sample under the prescribed conditions. For the precision of the method the RSD% for dichloromethane complies with the acceptance criteria of less than 2%. The RSD% of dichloromethane was calculated as shown in Table (2)

Detection (LODs) and LOQs) quantification limits

LOD is the lowest amount of the analyte that can be detected and LOQ is the lowest amount of analyte that can be quantified by the method. LODs were calculated as those concentrations that gave an 3.3standard deviation/slope of approximately. LOQs were calculated as those concentrations that gave an LOQ = 10 standard deviation/slope ratio and low residual linearity values. The sensitivity of the method was demonstrated by the low-LOD values obtained for the solvents analyzed (Table 2).

CONCLUSION

It could be concluded that the present study has achieved its objectives: firstly the conditions for optimization of the two systems was established and the validation parameters being determined. Secondly, the validation parameters emphasized that the two GC-systems were found to be sensitive, selective, precise and of high degree of accuracy and specificity. Thirdly, the two methods were found to be ideal for the detection and quantification of residual dichloromethane in Omeprazole drug substance. Fourthly, the level of the residual dichloromethane was found to be in the permissible range set by the International Specification Organizations e.g. ICH and USP-limits. The value of residual Dichloromethane level in Omeprazole sample analyzed by the system of [GC/DB-17/ N_2 / FID /DMSO] was found to be 485.66 ppm which is below ICH limits and above BP limits of 200 ppm for 1 g of Omeprazole substance. Moreover, the two methods could be recommended for the detection and quantification of other residual solvents such as chloroform, for which work has already being started; and acetone in Omeprazole or in other drugs substrates. It could, confidently, also be recommended that the quality control laboratories in the pharmaceutical industry be advised to adopt the two methods.

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