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Research Article

# A STABILITY INDICATING GC-FID METHOD FOR CAMYLOFIN DIHYDROCHLORIDE AND DICLOFENAC POTASSIUM IN PHARMACEUTICAL PREPARATION

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**ABSTRACT**

A simple Gas Chromatography (GC) method has been developed for the simultaneous estimation of Camylofin dihydrochloride and Diclofenac Potassium in presence of Benzoic acid used as an internal standard. Validation was carried out in compliance with the International Conference on Harmonization guidelines. The method utilized GC (Agilent Technologies 6890N Network GC system with FID detector), and RTX-5 capillary column (Crossbond 50% diphenyl-95% dimethyl polysiloxane), 30m x 0.53mm, 1.5µm as stationary phase. Helium was used as the carrier gas. The proposed method was validated for linearity, LOD, LOQ, accuracy, precision, ruggedness and solution stability. It can be conveniently adopted for routine quality control analysis.

**Keywords:** Gas chromatography, Pharmaceutical preparations, Camylofin dihydrochloride, Diclofenac Potassium

## INTRODUCTION

Camylofin dihydrochloride is 3-methylbutyl 2-(2-diethylaminoethylamino)-2-phenyl-acetate hydrochloride is a drug used an antispasmodic [1]. Diclofenac potassium is potassium-[(2, 6-dichlorophenyl) amino]-phenyl acetate [2]. It is a potassium salt of an aryl acetic acid derivative. It possesses analgesic, anti-inflammatory, and antipyretic activity. The structure of the drug is shown in Figure 1 and 2. One such combination contains 25 mg of Camylofin dihydrochloride and 25 mg of Diclofenac potassium. A literature survey indicated few methods for the determination of Camylofin dihydrochloride and Diclofenac Potassium individually or in combination with other drug preparations by HPLC.A simple uv spectrophotometric method for the estimation of Diclofenac Potassium in a formulation was reported [3]. An HPTLC method was reported for estimation of Diclofenac potassium in presence of another drug substance in a pharmaceutical preparation [4]. Other analytical method mentioned for assay of Diclofenac Potassium were HPLC method [5-7], uv-spectroscopy method [8-9]. An HPLC method was developed for the estimation of Diclofenac in complex matrix like gels and injections [10]. An HPTLC method was reported for the estimation Camylofin dihydrochloride in pharmaceutical preparation [11].An HPLC method was also reported for the estimation of Camylofin dihydrochloride in pharmaceutical preparation [12]. HPLC method of Camylofin dihydrochloride in combination with other drug preparation were reported [13-14]. An HPLC method was reported for the determination of Camylofin dihydrochloride in drug substance [15].

The literature revealed that an HPLC method was available for simultaneous determination of this drug in such pharmaceutical preparation [16]. The HPLC method has scope for some improvement. The resolution between the internal standard (Methylparaben is used as the internal standard) and Camylofin dihydrochloride is less i.e. about 2.9. The tailing factor of Camylofin dihydrochloride is more i.e. about 1.7. Since the tailing factor is on the higher side the correlation coefficient of Camylofin dihydrochloride is 0.9993, which can be improved. The limit of correlation coefficient for assay as per the ICH guidelines [17] is not less than 0.999. The recovery studies were not done on actual placebo, it was done on the drug product. Hence there can be an error during the estimation of percent recovery. The solution stability of the sample was established only until 48 hours. The aim of the present work was to develop an accurate, precise, rugged and stability indicating GC method for the simultaneous determination of Camylofin dihydrochloride in the presence of its degradation products. The proposed method was validated according to ICH guidelines. All the required improvements have been incorporated in the current method. In the current method the tailing factor of all the analyte was around 1.1. The correlation coefficient of both the components are more that 0.9999.The tailing factor of Camylofin dihydrochloride is less than 1.2. Solution stability was established for 120 hours when kept in tightly capped volumetric flask at room temperature. The method described is simple, fast, precise and accurate for simultaneous determination of Camylofin dihydrochloride and Diclofenac potassium from pharmaceutical preparation. The method is very cost and time effective since it does not require any mobile phase preparation and can be easily adapted to Quality control testing laboratory.

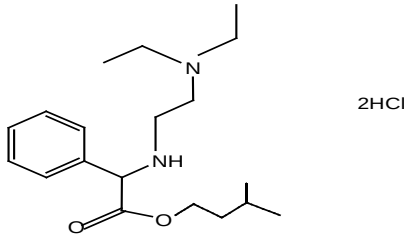


**Fig. 1: Structure of Camylofin dihydrochloride**

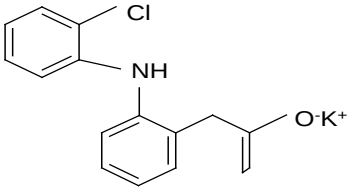


**Fig. 2: Structure of Diclofenac Potassium**

## MATERIALS AND METHODS

### Chemicals and reagents

Active pharmaceutical ingredient of Camylofin dihydrochloride was procured from Sigma Aldrich and Diclofenac Potassium was procured from USP. Benzoic acid was procured from EMD chemicals, USA. Tablet dosage form developed by Khandelwal Laboratories, India. High purity methanol was purchased from EMD chemicals, USA.

### Instrumentation and chromatographic conditions

The GC used is of Agilent Technologies 6890N Network GC system with FID detector. Column used in GC is a capillary column RTX-5, 30m x 0.53mm, 1.5µm. Photo stability studies were carried out in a photo stability chamber (Sanyo, Leicestershire, UK). Thermal

stability studies were carried out in a dry air oven (Lindberg- Blue, USA).

The system was run at a flow rate of 1.5mL $min^{-1}$, 1 µL of sample was injected in the chromatographic system and flame ionization detector was used for simultaneous determination of Camylofin dihydrochloride and Diclofenac potassium. Helium was used as a carrier gas. Oven temperature was kept 180°C and increased at a rate of 10°C $min^{-1}$ to 280°C and held at 280°C for 15.0 minutes. Injector temperature and detector temperature were kept at 250°C and 280°C respectively. The split ratio was kept at 50:1.

**Preparation of Standard Solutions**

The stock solution of Camylofin dihydrochloride (1250 µg $mL^{-1}$) was prepared by dissolving 125.6 mg of Camylofin dihydrochloride (99.9 %) in methanol in a standard 100mL volumetric flask (stock solution A). The stock solution of Diclofenac potassium (1250 µg $mL^{-1}$) was prepared by dissolving 125.9 mg of Diclofenac Potassium (99.8 %) in methanol in a standard 100mL volumetric flask (stock solution B). Internal standard (benzoic acid) stock solution (5000 µg $mL^{-1}$) was prepared by dissolving 498.6 mg of benzoic acid in methanol in a 100mL standard volumetric flask (stock solution C).

Transferred 10.0 mL of each stock solution A, B & C to a 50 mL volumetric flask and diluted up to the mark with methanol. This is working standard solution.

**Preparation of Sample solution**

For analysis of the tablet dosage form, twenty tablets were weighed individually and their average weight was determined. The tablets were crushed to fine homogenous powder and quantity equivalent to ten tablets were transferred in a 200mL volumetric flask. Added about 100 mL of Methanol to the volumetric flask, shaken for 10 minutes and then sonicated for 15 minutes. The solution was allowed to stand at room temperature for 20-30 minutes and filtered through Whatman no. 41 filter paper. The residue was washed with Methanol and the combined filtrate was made up to the mark with the same solvent.

5.0 mL of filtrate was quantitatively transferred to a 50 mL volumetric flask, 10.0 mL of internal standard solution was added to it, and solution was diluted up to the mark with methanol. The identities of both the compounds were established by comparing retention time of the sample solution with those of standard solution.

**RESULTS AND DISCUSSION**

**Optimization of chromatographic conditions**

To develop a suitable GC method for the analysis of camylofin dihydrochloride and Diclofenac Potassium in their dosage form, different capillary columns were tried [18]. The criteria employed for selecting the columns for the analyses of the drugs were cost involve, time required for the analysis, better separation of the components. Chromatographic separation was preformed with Agilent Technologies 6890N Network Gas chromatography system, equipped with auto sampler and a flame ionization detector. Chromatograms and data were recorded by means of Empower software. RTX-5 capillary column (Crossbond 50% diphenyl-95% dimethyl polysiloxane) was used for analysis. The column dimension was 30m x 0.53mm, 1.5µm. The system was run at a flow rate of 1.5mL $min^{-1}$, 1 µL of sample was injected in the chromatographic system and flame ionization detector was used for simultaneous determination of Camylofin dihydrochloride and Diclofenac potassium. Helium was used as a carrier gas. Oven temperature was kept 180°C and increased at a rate of 10°C $min^{-1}$ to 280°C and held at 280°C for 15.0 minutes. Injector temperature and detector temperature were kept at 250°C and 280°C respectively. The split ratio was kept at 50:1. A summary of method development and optimization is described in Table 1.

**Table 1**: **Summary of optimization of chromatographic conditions**

| Column used | Carrier gas | Flow rate | Observation | Result |
|---|---|---|---|---|
| DBWax,30mx0.53mm, 1.0µm capillary column | Helium | 1.2 mL $min^{-1}$ | No peaks observed | Method rejected |
| DB624,30mx0.32mm, 1.8µm capillary column | Helium | 1.2 mL min-1 | Peak shape for both components not good | Method rejected |
| RTX1,30mx0.53mm, 1.0µmcapillary column | Helium | 1.5 mL min-1 | Poor resolution and low response | Method rejected |
| RTX5,30mx0.53mm, 1.5µmcapillary column | Helium | 1.5 mL min-1 | Good resolution and good peak shape | Method accepted |

System suitability test parameters for Camylofin dihydrochloride and Diclofenac Potassium by the proposed GC method

System suitability tests are used to verify that the reproducibility of the equipment is adequate for the analysis to be carried out. System suitability tests were performed as per the USP 31 to confirm the suitability and reproducibility of the system. The % RSD values were found to be satisfactory and meeting the requirements of USP 31 (RSD less than 2.0 %).

**Table 2: Results of System suitability**

| Parameters | Benzoic Acid | Camylofin dihydrochloride | Diclofenac Potassium |
|---|---|---|---|
| Resolution | NA | 6.5 | 3.6 |
| Tailing factor | 1.0 | 1.1 | 1.0 |
| Theoretical plates | 5414 | 4521 | 3554 |
| % RSD | NA | 0.82 | 0.61 |

**Method Validation**

The method validation was carried out as per ICH guidelines. Various method validation parameters were performed.

**Specificity**

Specificity of the method was evaluated by injecting diluents, placebo, individual Camylofin dihydrochloride and Diclofenac Potassium and sample solution in to the GC system to check any interference to the peaks.

No peak was observed at the retention time of Camylofin dihydrochloride, Diclofenac Potassium and Benzoic acid in diluents and Placebo chromatogram. Hence the method was specific.

**Linearity**

Linearity was evaluated by analysis of working standard solutions of Camylofin dihydrochloride and Diclofenac Potassium of seven different concentrations.

Linearity was evaluated by analysis of working standard solutions of Camylofin dihydrochloride and Diclofenac Potassium of seven different concentrations. The range of linearity for Camylofin dihydrochloride and Diclofenac Potassium were from 125 µg $mL^{-1}$ to 375 µg $mL^{-1}$ (250 µg/mL is 100% level). The peak area ratio and concentration of each drug was subjected to regression analysis to calculate the calibration equations and correlation coefficients. Figure 3 and 4 represents the linearity plots of Camylofin

dihydrochloride and Diclofenac Potassium respectively. The regression data obtained for the Camylofin dihydrochloride and Diclofenac Potassium is represented in Table 3. The result shows that within the concentration range mentioned above, there was an excellent correlation between peak area ratio and concentration.

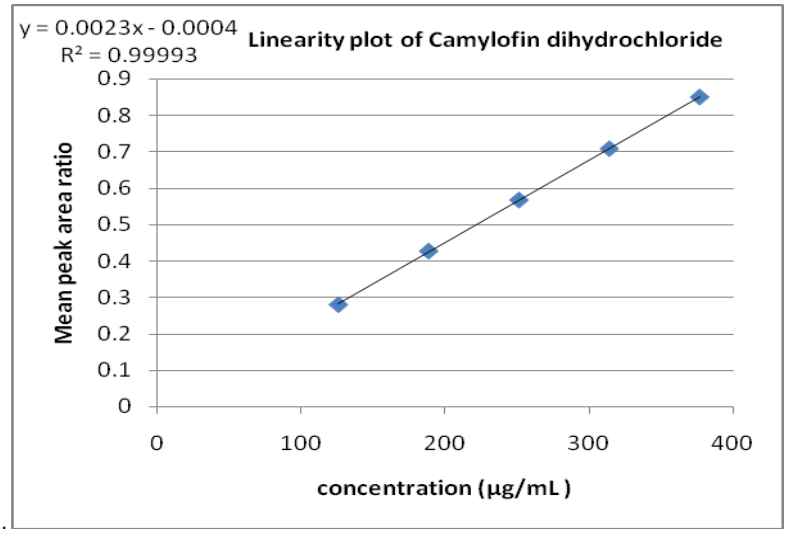


**Fig. 3: Linearity plot of Camylofin dihydrochloride**

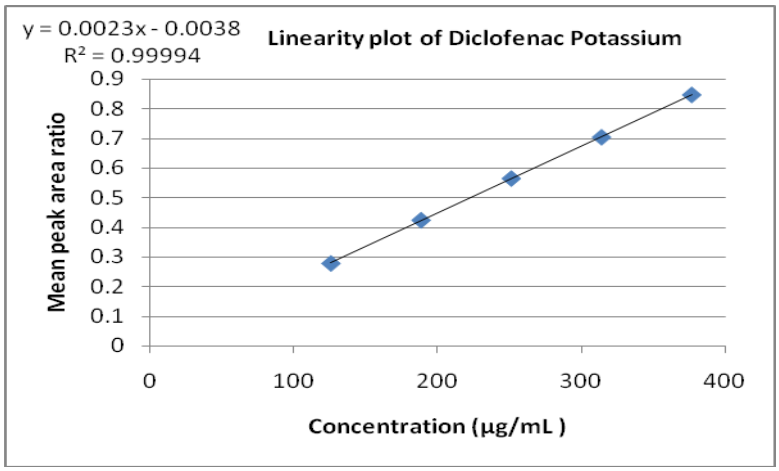


**Fig. 4: Linearity plot of Diclofenac Potassium**

**Table 3: Results of Linearity study**

| Analyte | Slope | Intercept | Correlation coefficient ($r^2$) (n=5) |
|---|---|---|---|
| Camylofin dihydrochloride | 0.0023 | -0.0004 | 0.99993 |
| Diclofenac Potassium | 0.0023 | -0.0038 | 0.99994 |

**LOD and LOQ / Sensitivity**

Sensitivity was determined by establishing the limit of detection (LOD) and limit of quantification (LOQ). The limit of detection (LOD) and limit of quantitation (LOQ) were established at signal-to-noise ratio of 3:1 and 10:1 respectively.

The LOD and LOQ of Camylofin dihydrochloride and Diclofenac Potassium was experimentally determined by six injections of each drug. The LOD of Camylofin dihydrochloride and Diclofenac Potassium was found to be 1.2 µg $mL^{-1}$ & 1.1 µg $mL^{-1}$ respectively. The LOQ of Camylofin dihydrochloride and Diclofenac Potassium was found to be 2.1 µg $mL^{-1}$ & 1.9 µg $mL^{-1}$ respectively.

**Accuracy**

Accuracy was determined over the range 50% to 150% of the sample concentration. Calculated amount of Camylofin dihydrochloride and Diclofenac Potassium from standard stock solution was added in placebo to attain 50%, 100% and 150% of sample concentration. Each sample was prepared in triplicate at each level. Blank and standard preparations were injected and chromatograms were recorded.

Accuracy was expressed as the percentage of analytes recovered by the assay. Table 4 lists the recoveries of the drug from a series of spiked concentrations. The results indicate the method is highly

accurate for simultaneous determination of Camylofin dihydrochloride and Diclofenac Potassium.

**Precision**

Repeatability was studied by carrying out system precision. System precision was determined from results for six replicate injections of the mixed standard solutions. Method precision was determined from results from six independent determinations at 100% of the test concentrations of Camylofin dihydrochloride and Diclofenac Potassium in the product.

**Ruggedness (Intermediate Precision)**

Ruggedness study was demonstrated by injecting five individual sample preparations at 100% of the test concentrations of Camylofin dihydrochloride and Diclofenac Potassium on different day using another column and system.

Ruggedness study was done by injecting six individual sample preparations at 100% of the test concentrations of Camylofin dihydrochloride and Diclofenac Potassium on different day and different GC system. The mean % Assay obtained was compared with mean % Assay of precision study. The relative standard deviation (RSD) was less than 2%. Refer Table 6.

**Solution stability**

The solution stability of Camylofin dihydrochloride and Diclofenac Potassium was carried out by leaving the test solutions of sample in a tightly capped volumetric flask at room temperature for 120 hours. The same sample solutions were assayed for 24 hours interval up to the study period against freshly prepared standard solution.

The % assay of Camylofin dihydrochloride and Diclofenac Potassium were checked in the test solutions. The % difference of assay of Camylofin dihydrochloride and Diclofenac Potassium with respect to initial assay during solution stability experiment was within 2.0. No significant changes were observed in the content of Camylofin dihydrochloride and Diclofenac Potassium during solution stability experiment. Sample solutions used during the experiment were stable upto the study period of 120 hours. The results are reported in Table 7.

**Table 4: Accuracy of the method**

| Analyte | Recovery Level (%) | Amount added (µg mL$^{-1}$) | Amount recovered ( µg mL$^{-1}$ ) | RSD (%) n= 3 | (%) Recovery |
|---|---|---|---|---|---|
| Camylofin dihydrochloride | 50 | 125.14 | 124.58 | 0.42 | 99.56 |
| | 100 | 250.28 | 251.73 | 0.31 | 100.58 |
| | 150 | 375.42 | 376.28 | 0.38 | 100.23 |
| | 50 | 125.78 | 127.16 | 0.59 | 101.10 |
| Diclofenac Potassium | 100 | 251.56 | 253.34 | 0.46 | 100.71 |
| | 150 | 377.34 | 380.84 | 0.62 | 100.93 |

**Table 5: Results of Precision experiment**

| Results | Camylofin dihydrochloride | Diclofenac Potassium |
|---|---|---|
| Drug found in mg/tab (mean) | 25.21 | 24.95 |
| % Mean Assay | 100.84 | 99.80 |
| % RSD | 0.52 | 0.44 |

**Table 6: Ruggedness of Assay experiment**

| Results | Camylofin dihydrochloride | Diclofenac Potassium |
|---|---|---|
| Drug found in mg/tab (mean) | 24.96 | 24.68 |
| % Mean Assay | 99.84 | 98.72 |
| % RSD | 0.52 | 0.59 |
| % Difference w.r.t. Precision | 1.00 | 1.08 |

**Table 7: Results of Solution stability**

| Condition | % Assay of Camylofin dihydrochloride | % Difference w.r.t. initial assay | % Assay of Diclofenac Potassium | % Difference w.r.t. initial assay |
|---|---|---|---|---|
| Initial | 99.82 | NA | 100.12 | NA |
| 24 hours | 99.56 | 0.26 | 100.32 | 0.20 |
| 48 hours | 99.15 | 0.67 | 99.85 | 0.27 |
| 72 hours | 98.82 | 1.00 | 99.35 | 0.77 |
| 96 hours | 98.92 | 0.90 | 99.29 | 0.83 |
| 120 hours | 98.89 | 0.93 | 99.32 | 0.80 |

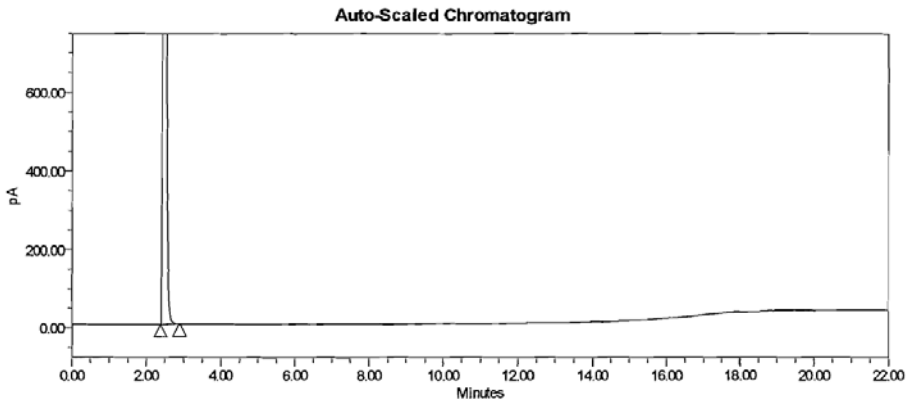


**Fig. 5: Chromatogram of Placebo preparation**

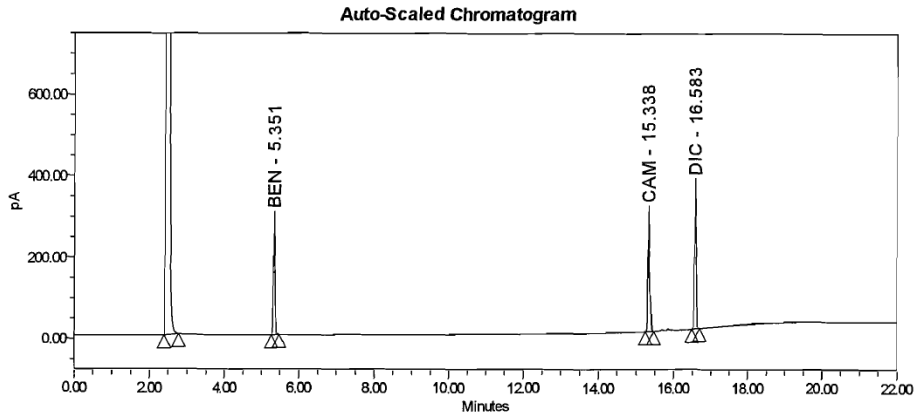


**Fig. 6: Chromatogram of Camylofin dihydrochloride (CAM) and Diclofenac Potassium (DIC) with Benzoic acid (BEN) as internal standard in standard preparation**

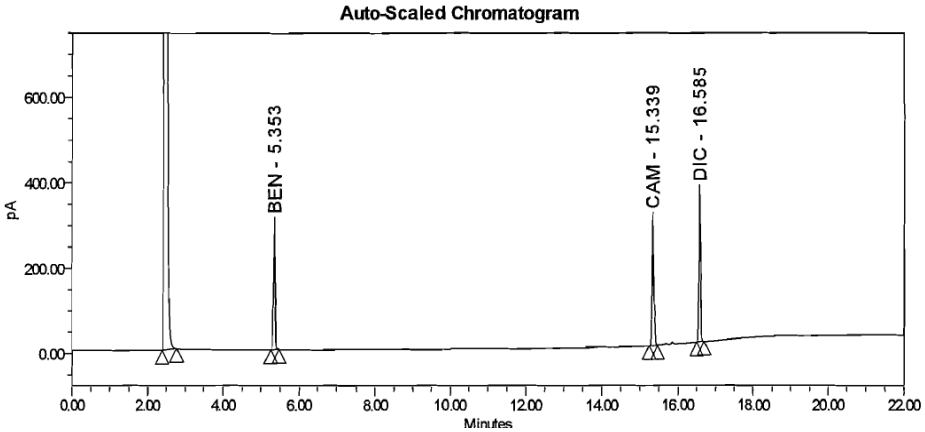


**Fig. 7: Chromatogram of Camylofin dihydrochloride (CAM) and Diclofenac Potassium (DIC) with Benzoic acid (BEN) as internal standard in sample preparation**

**Stress Testing (Forced Degradation study)**

To further confirm the stability indicating nature of the method, the drug was subjected to stress conditions as per the ICH recommended test conditions [19, 20].

To study the effect of acid, 5 mL of 2 M HCl was added to the sample and the mixture was kept for 48 hours. To study the effect of base, 5 mL of 1 N NaOH solution was added to the sample and the mixture kept for 3 hours. To study the effect of oxidizing conditions, 5 mL of 3% v/v $H_2O_2$ was added to the sample and the mixture was kept for 48 hours.

To study the effect of temperature sample was kept in an oven at 80°C for 5 days.

To study the effect of light sample was and kept in a photo stability chamber for 5 days.

The % degradation of Camylofin dihydrochloride in acid hydrolysis, base hydrolysis, oxidation, thermal and photolytic was 13.16, 16.50, 3.58, 4.91 and 5.60 respectively with respect to the control sample. The % degradation of Diclofenac Potassium in acid hydrolysis, base hydrolysis, oxidation, thermal and photolytic was 4.05, 7.98, 3.94, 2.03 and 5.04 respectively with respect to the control sample. The mass balance was found to be more than 97.0%. The peaks of the degradation products were well resolved from the principle peaks. The results of stress studies are tabulated in Tables 8(a) and 8(b).

**Table 8(a): Summary of forced degradation results for Camylofin dihydrochloride**

| Stress condition | Time | % Assay of Camylofin 2HCl | % Degradation w.r.t control | Mass balance (% assay+ % degradation products) |
|---|---|---|---|---|
| Control | NA | 100.14 | NA | 100.00 |
| Acid hydrolysis (2 M HCl) | 48 h | 86.98 | 13.16 | 97.56 |
| Base hydrolysis (1 N NaOH) | 3 h | 83.64 | 16.50 | 97.12 |
| Oxidation (3% H2O2) | 48 h | 96.56 | 3.58 | 98.00 |
| Thermal (80°C) | 5 day | 95.23 | 4.91 | 98.84 |
| Light (photolytic degradation) | 5 day | 94.54 | 5.60 | 98.69 |

**Table 8(b): Summary of forced degradation results for Diclofenac Potassium**

| Stress Condition | Time | % Assay of Camylofin 2HCl | % Degradation w.r.t control | Mass balance (% assay+ % degradation products) |
|---|---|---|---|---|
| Control | NA | 99.86 | NA | 100.00 |
| Acid hydrolysis (2 M HCl) | 48 h | 91.11 | 4.05 | 97.56 |
| Base hydrolysis (1 N NaOH) | 3 h | 90.87 | 7.98 | 97.12 |
| Oxidation (3% H2O2) | 48 h | 95.87 | 3.94 | 98.00 |
| Thermal (80°C) | 5 day | 97.89 | 2.03 | 98.84 |
| Light (photolytic degradation) | 5 day | 91.87 | 5.04 | 98.69 |

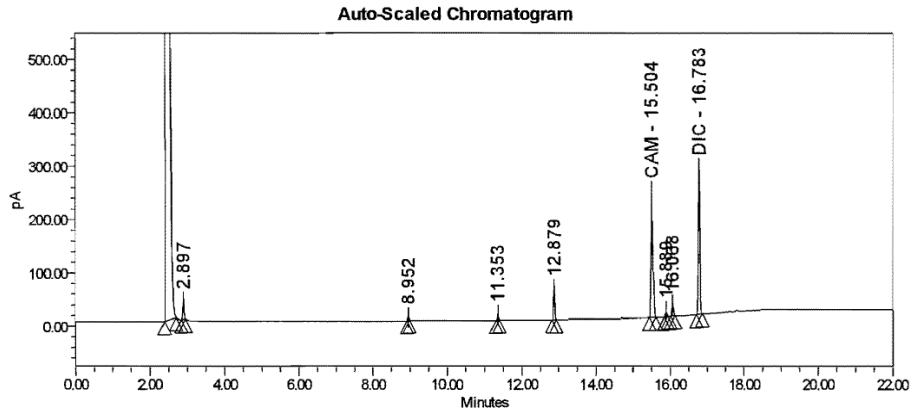


**Fig. 8: Acid hydrolysis forced degradation condition: Chromatogram of Camylofin dihydrochloride (CAM) and Diclofenac Potassium (DIC)**

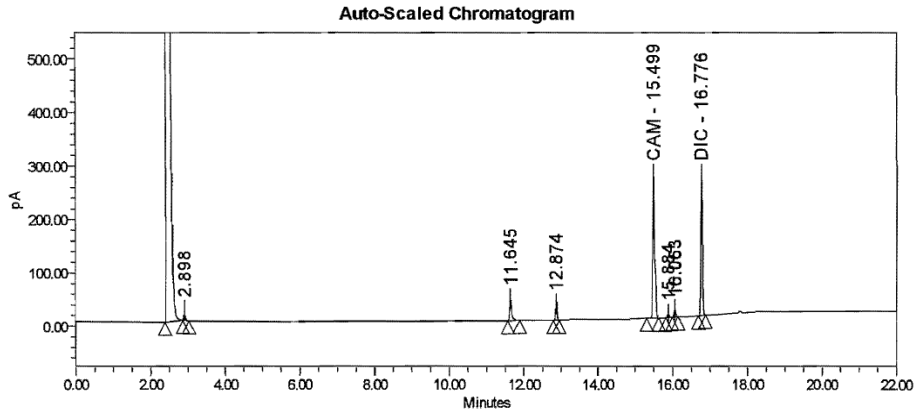


**Fig. 9: Base hydrolysis forced degradation condition: Chromatogram of Camylofin dihydrochloride (CAM) and Diclofenac Potassium (DIC)**

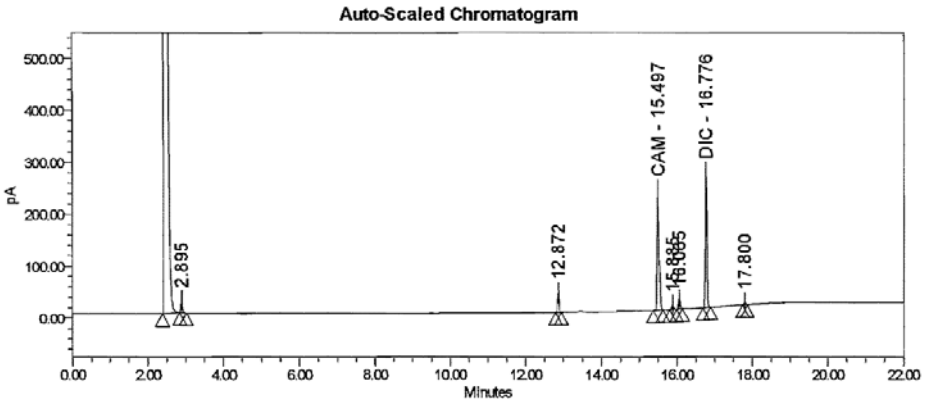


**Fig. 10: Oxidation forced degradation condition: Chromatogram of Camylofin dihydrochloride (CAM) and Diclofenac Potassium (DIC)**

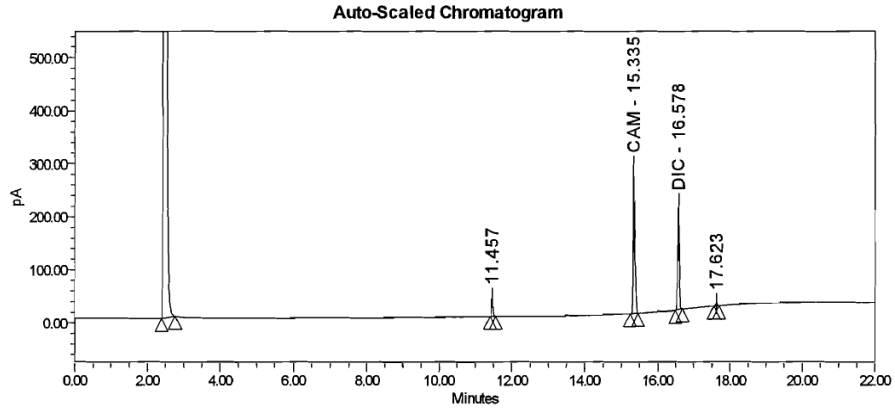


**Fig. 11: Thermal forced degradation condition: Chromatogram of Camylofin dihydrochloride (CAM) and Diclofenac Potassium (DIC).**

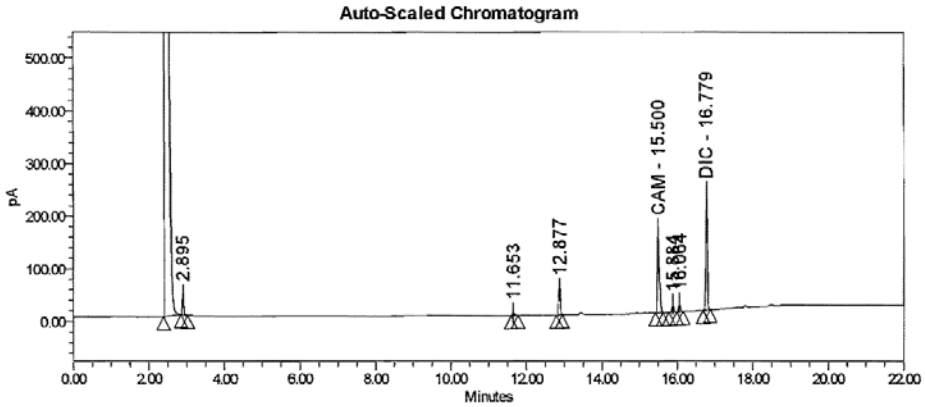


**Fig. 12: Photolytic degradation condition: Chromatogram of Camylofin dihydrochloride (CAM) and Diclofenac Potassium (DIC)**

## CONCLUSIONS

The method after being completely validated showed satisfactory data for all the method validation parameters. Method validation study showed that the method is specific, linear, accurate, easily reproducible and can be used for simultaneous determination of Camylofin dihydrochloride and Diclofenac Potassium from pharmaceutical preparations. Stress testing showed that all degradation products were well separated from Camylofin dihydrochloride and Diclofenac Potassium, confirming its stability indicating capability. The method seems to be suitable for quality control in the pharmaceutical industry because of its sensitivity, simplicity and selectivity.

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