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Development and validation, of Fluocinolone Acetonide, Miconazole Nitrate, Chlorocresol, Methyl paraben and Propyl Paraben, form cream formulation dosage form, by using RPHPLC with UV/PDA detector

[1] Bhaskar Musmade, [2]Durgesh Yadav, [3] Shrinivas Bhope, [4] Kishan Lohar*
[1][2][3] Sava Healthcare Limited, Research and development Centre, Chinchwad MIDC, Pune, Maharashtra India.
[4]Department of Chemistry, Shrikrishna Mahavidyalay Gunjoti, Maharashtra, India.
[3] Dr.kslohar@rediffmail.com

***Abstract:* - A precise, robust and accurate method was developed for estimation of Fluocinolone Acetonide, Miconazole Nitrate, Chlorocresol, Methyl paraben and Prolyl Paraben, from cream dosage form. The gradient was optimized on BDS Hypersil C18, 250 x 4.6 nm 5µm column, operated at 45°C and mobile phase A and B were selected as monobasic phosphate buffer pH 7.2 and Acetonitrile, pumped at 1.5 ml/min. flow rate. All the solutions were injected at 20 µl injection volume and monitored at 238 nm. The Methylparaben, Propylparaben, Chlorocresol, Fluocinolone acetonide and Miconazole were eluted at about 4, 9, 9.8, 11and 25 minutes respectively. The recoveries were found between 98.0 to 102.0 % for each analytes. The method was found linear from 50 to 150 % of sample concentration and linear regression curves, (r2) were more than 0.999 for all the analytes. The developed method was remains unchanged after deliberate variation in method parameters hence proved the method robustness. The developed method is time saving, cost effective hence can be used in pharmaceutical industries for simultaneous estimation of these compounds from cream and other dosage forms.**

I. INTRODUCTION

IUPAC name of Fluocinolone acetonide is a Pregna-1,4-diene-3,20-dione, 6,9-difluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-, (6α,11β,16α)-;6α,9-Difluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione, cyclic 16,17-acetal with acetone [67-73-2].It is used topically in treatment of varieties of skin disease and anti-inflammatory in nose, eyes nose disorders [1].It is used in Gel, cream , ointment , and lotion pharmaceutical dosage form[2]. It is practically insoluble in water, soluble in acetone and in ethanol.

The IUPAC name of miconazole is 1-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-1-Himidazole It is a imidazole antifungal agent used in topical as well as intravenous infusion[3].It is soluble in methanol, acetonitrile and insoluble in water[4]. It is very slightly soluble in Water, freely soluble in Methanol, soluble in Ethanol (96 per cent).

Chlorocresol is used as bactericidal and closely related to carbolic acid .In many pharmaceutical dosage forms it is used as preservative content [5]. It is slightly soluble in water, very soluble in ethanol (96 per cent), freely soluble in fatty oils. It also dissolves in solutions of alkali hydroxides.

The methyl Paraben and propyl Paraben also used as preservative content in most of the pharmaceutical dosage forms. The preservative contents plays vital role in stabilizing the active content and prevent from degradation.

After intensive literature review it was observed that no reported method had been done for these molecules simultaneously in cream and ointment dosage form. The reported methods were available for estimation of Fluocinolone acetonide and Miconazole in combination dosage form [1, 16] but preservative contents not estimated from the same methods .There were some method for individual determination of Fluocinolone acetonide or combination with other drugs from cream, ointment and other dosage form [2,8-11,17], while some reported methods were available for Miconazole nitrate individually or with combination other drug substance in pharmaceutical dosage forms [14,15,18,19]. Presently no reported method were observed for simultaneous estimation, of Fluocinolone acetonide, Miconazole nitrate, Chlorocresol, Methyl paraben and Prolyl Paraben from the Pharmaceutical cream and ointment dosage form. Determination of such five content in single HPLC method is challenging work in terms of

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resolutions, column efficiency, and recovery, hence this developed work will helpful to researchers for saving the development cost and time, also save the routine analysis cost in pharmaceutical industries. Considering this advantage this method can be use in quality control laboratories for routine analysis. The developed method was successfully validated as per ICH guideline [20].

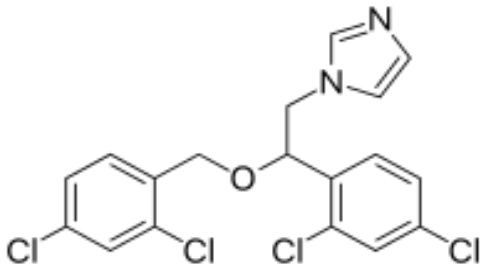

Figure 1a Fluocinolone Acetonide

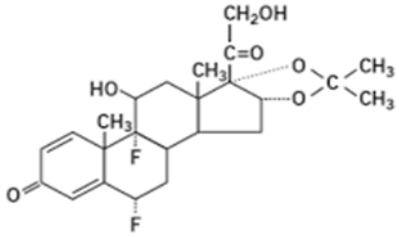

Figure 1b Miconazole Nitrate

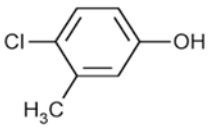

Figure 1c Chlorocresol

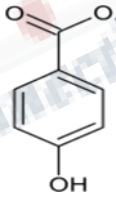

Figure 1d Methyl Paraben

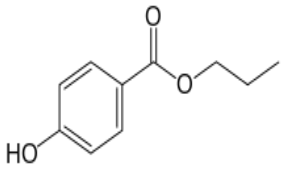

Figure 1e Propyl Paraben

Chemicals, reagents and equipment

HPLC grade Methanol and Acetonitrile (Make- Rankem), AR grade Triethylamine (Make- Rankem), and Orthophosphoric acid (Make- Rankem) was used for diluent and mobile phase preparation. The calibrated pH meter (Make- Mettler Toledo) used for pH measurement. The separation of all the analytes were achieved on BDS Hypersil C18, 250 x 4.6 mm, 5µ column (Make-Thermo Scientific). The complete development and validation study was performed by using LC-2010CHT, with VU/visible detector (Make-Shimadzu, Japan) liquid chromatographic system. Intermediate precision and selectivity study was performed on Alliance 2695 with PDA detector (Make- Waters, USA). The analytical balance HTR-220E (Make SANSUI) and XP26 (Make- Mettler Toledo) was used for weighing purpose.

II. MATERIALS AND METHODOLOGY

The qualified working standard of Fluocinolone acetonide (FL.), Miconazole nitrate (MI), Chlorocresol (CH), Methyl Paraben (MP) and Propyl Paraben,(PP) having % purity 99.8, 99.5, 99.7, 99.4 and 99.6% respectively, were used for entire development and validation study.

Preparation of mobile phase A

Accurately pipetted 2 mL of Triethylamine was transferred in to a 1000 mL of water, the mixture was well mixed and the pH was adjusted to 7.2 with dilute Orthophosphoric acid. 10 ml of acetonitrile was added to the mixture and the mixed well, and the solution was sonicated and filtered through a 0.45µ filter.

Mobile phase B

The pure acetonitrile was used as a mobile phase B.

Diluent:

The mixture of mobile phase A and B in ratio of (15:85) % v/v was used as diluent.

Method optimization:

The development of the study was initiated by using Inertsil ODS 250 x 4.6mm, 5 micron column and phosphate buffer as a mobile phase but the base line noise, extra peaks was observed and the resolution not achieved. Some trials were taken on RP18 and Sun fire C18 column but the peak shape and resolution was not achieved as per system suitability criteria. Finally Hypersil BDS C18, 250 x 4.6 mm, 5 µm, column was optimized at 45°C and chromatograms were monitored at 238nm based on the optimum response of all analytes. The mobile phase was pumped at 1.5 ml/minutes flow rate and all the solutions were injected at 20□L injection volume. The gradient was optimized for better separations of analytes and mentioned in Tablet 1. The retention time of FL MI, CH, MP, PP, were obtained at about 10.8 min., 25.5 min., 9.8 min., 9.3 min., and 4.3 minutes respectively.

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Table 1 Gradient program:

Time (minutes)	% Mobile phase :A	% Mobile phase : B
0.01	65	35
30.0	5	95
33.0	5	95
33.10	65	35
38.0	65	35

Fluocinolone Acetonide Standard Stock Solution

20 mg Fluocinolone Acetonide working standard was weighed and transferred in to a 100 mL volumetric flask added about 65 mL of diluent and sonicated to dissolve completely. The flask was removed and volume was adjusted up to the mark with diluent and mixed well and labeled as standard stock solution A.

Miconazole Nitrate Standard Stock Solution

200 mg Miconazole Nitrate working standard was transferred in to a 25 mL volumetric flask, added about 15 mL of diluent, the resulting solution was sonicated to dissolved the content completely , the flask was allow to cool and volume was adjusted up to the mark with diluent and mixed well and labeled as standard stock solution B.

Chlorocresol Standard Stock Solution:

25 mg Chlorocresol working standard was transferred in to a 25 mL volumetric flask, add about 15 mL of diluent and sonicated to dissolve the content completely. The flask was allowed to cool and the volume was adjusted up to the mark with diluent and mixed well, and labeled as standard stock solution C.

Methyl Paraben Standard Stock Solution

100 mg Methyl Paraben working standard was transferred in to a 50 mL volumetric flask, added about 35 mL of diluent and the mixture was sonicated to dissolve the content completely, the flask was remove and allow to cool and final volume was adjusted with diluent and mixed well and labeled as standard stock solution D.

Propyl Paraben Standard Stock Solution

20 mg Propyl Paraben working standard was transferred in to a 100 mL volumetric flask, about 75 mL of diluent was added in to the flask, and the mixture was allow to sonicate to dissolve the content completely. The flask was removed and volume was adjusted with diluent and mixed well and labeled as standard stock solution E.

Mixed standard Solution preparation

Accurately pipetted 2 mL of stock A, 10 mL of stock B, 4 mL of stock C, 5 mL of stock D, 5 mL of stock E was transferred in to a 100 mL volumetric flask, and diluted up to the mark with diluent and mixed well.

Sample Preparation

1 g of sample was transferred in to a 25 mL of volumetric flask, added about 15 mL of diluent, the mixture was vortexed for 15 minutes followed by sonicated for 20 minutes with intermittent shaking. The flask was allowed to cool at room temperature and the volume was adjusted with diluent and mixed well. The solution was transferred in to 250 ml separating funnel and added 50 mL n-Hexane, the mixture was shacked well and allowed to stand for 10 min till complete separation of two layers. The aqueous layer (lower layer) was collected in another 250 ml separating funnel by discarding the organic layer (n-Hexane layer), and the same procedure was repeated two times. The aqueous layer was filtered through 0.45 µ filter by discarding first 3 ml of filtrate and used.

Placebo solution

Placebo was prepared as per sample preparation procedure by excluding label clam of estimated analyte.

Method Validation

The developed method was validated as per ICH guideline and the findings were reported in results and discussion.

Accuracy

Accuracy of the method was carried out in terms of recovery of analytes from 50 to 150% of sample concentration. The pure working standard solutions were spiked in the placebo at 50%, 100% and 150% levels and injected in triplicate in the HPLC system.

Precision, repeatability and intermediate precision

Precision is nothing but the injector accuracy of HPLC system. Precision of the method was checked by injecting six replicate injections of standard solution and calculate the % relative standard deviation. The RSD of six injections of standard solution should not be less than 2 % for all the analytes. The method precision was performed by preparing and injecting six samples and calculates the RSD of % assay obtained from six sample preparations for all the analytes. The intermediate precision was conducted by using different HPLC system, column, and analyst on different days. The six samples were prepared and injected in the HPLC system and the RSD of % assay obtained from six sample preparations were calculated.

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Selectivity

Selectivity study is carried out to prove the ability of a method to assess unequivocally the analyte in the presence of components which may be expected to be present in sample.

The diluent, placebo, standard solution, individual standard solution and sample solution were injected to check the selectivity the developed method. The interference at the retention time of each analytes from diluent and placebo solution was checked, as well as the retention time of individual analytes were confirmed by injecting the individual standard preparation. The peak purity of the individual peak was checked in the standard and sample solution by using PDA detector.

Linearity & Range

It is the ability of the method to obtain the results which are directly proportional to the analyte concentration.

The linearity of the method was carried out by injecting the standard solution by spiking the individual analytes from 50 to 150% of the working concentration. The linearity graph was plotted for average area of individual analyte against the concentration in µg/mL at each level. The correlation coefficient, slope and intercept were calculated.

Robustness

Robustness of the method was proved by varying the deliberate changes in the method variance like , change in mobile phase composition (±5%),change the pH of mobile phase by ±0.2 units, flow rates (±0.1 ml) and change in detection wavelength by ±3 nm. Robustness also conducted by changing the column temperature by ± 5°C and change in gradient program by ±5% of mobile phase B.

Solution stability of Analytical Solutions

The solution stability were studded by keeping of all the solutions at room temperature at different time intervals like , days 0, day1st, day 2nd and day 3rd. After completion of each time point, the sample were analysed against the freshly repaired standard solution and the results were compared against the initial values obtained in method precision study. Calculated the % difference at each time points, the solution was stable till the % difference should not be more than 2%.

III. RESULTS AND DISCUSSION

Accuracy:

The obtained results in the recovery study at 50 to 150% of working concentration of each analytes are summarized in the Tablet 2.

Tablet 2 Recovery study

Sr.no	Compound Name	50% Level	100% Level	150% Level
1	Fluocinolone Acetonide	99.4	100.7	100.4
2	Miconazole Nitrate	98.5	98.1	101.7
3	Methyl Paraben	101.1	101.0	100.3
4	Propyl Paraben	101.0	101.3	101.0
5	Chlorocresol	100.5	100.7	100.4

Method precision and Intermediate precision:

The average and RSD of % assay from six sample preparations in each method precision and intermediate precision were calculated and summarized in Tablet 3.

Tablet 3 Method precision and intermediate precision studies

Sr. No	Fluocinolone Acetonide		Miconazole Nitrate		Methyl Paraben		Propyl Paraben		Chlorocresol.	
	Met.P	Int.P	Met.P	Int.P	Met.P	Int.P	Met.P	Int.P	Met.P	Int.P
Sample -1	99.0	101.0	98.8	100.0	99.2	99.9	99.2	100.4	99.4	99.9
Sample -2	101.0	101.0	101.0	99.1	101.0	100.0	101.2	101.2	101.3	100.7
Sample -3	98.0	101.0	97.8	100.2	98.2	100.9	98.4	101.2	98.4	101.6
Sample -4	99.0	102.0	99.6	101.5	100.1	101.1	100.4	102.0	100.4	101.2
Sample -5	100.0	102.0	99.8	99.7	100.3	100.7	100.4	97.6	100.6	101.5
Sample -6	101.0	98.0	100.7	98.6	101.8	98.9	102.0	98.2	101.8	98.7
Average	99.7	100.8	99.6	99.9	100.1	100.3	100.3	100.1	100.3	100.6
Std.dev	1.2	1.5	1.2	1.0	1.3	0.8	1.3	1.8	1.2	1.1
% RSD.	1.2	1.5	1.2	1.0	1.3	0.8	1.3	1.8	1.2	1.1

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Specificity

During the specificity study it was observed that, no any interfering peaks from the placebo and blank solution found at the retention time of each analytes the peak was pure. The representative chromatograms of blank, mixed standard solution and sample solution were shown in the Figure 3, 4, and 5.

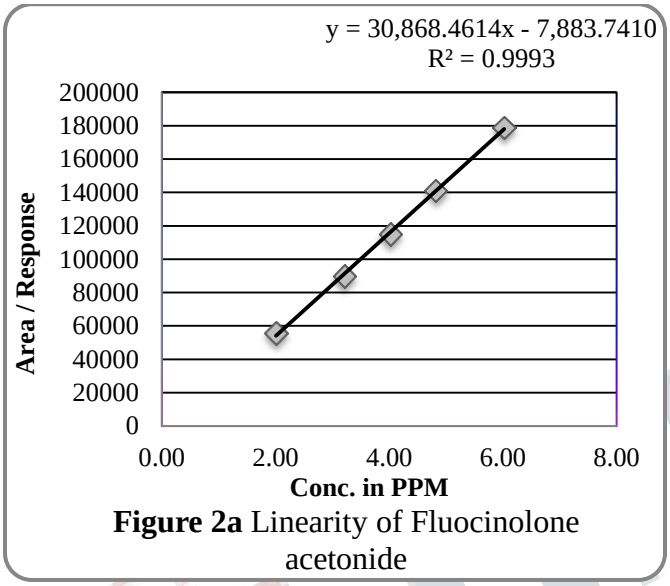

Figure 2a Linearity of Fluocinolone acetonide

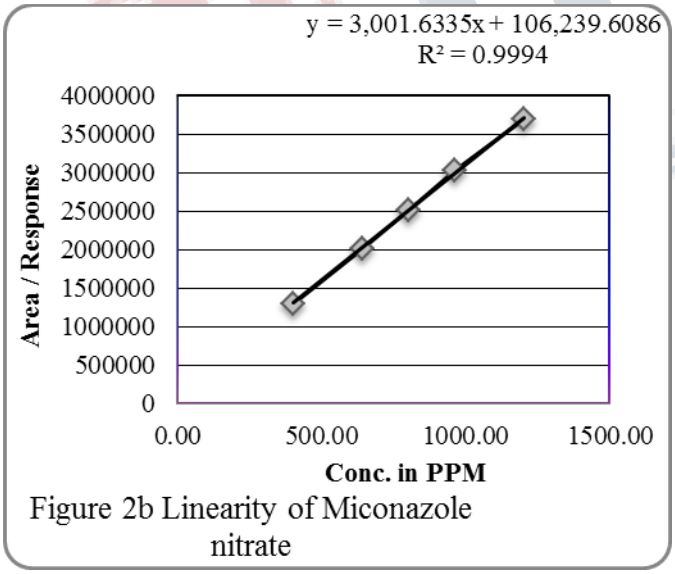

Figure 2b Linearity of Miconazole nitrate

Linearity

The linearity in the area under the curve for each analytes against the concentrations were calculated in terms of correlation coefficient r2 and it was observed that the all the obtained r2 vales were greater than 0.999. The results of linearity were summaries in the Tablet 4.0

Table 4a Linearity of Fluocinolone Acetonide

Conc. in PPM	Area
3.21	89867
4.02	115010
4.82	141173
6.02	178755
Slope	30868.4614
Intercept	-7883.7410
Correlation Coefficient [R]	0.9997
R^2	0.9993

Table 4b Linearity of Miconazole Nitrate

Conc. in PPM	Area
641.86	2018881
802.32	2512899
962.78	3034233
1203.48	3696991
Slope	3001.6335
Intercept	106239.6086
Correlation Coefficient [R]	0.9997
R^2	0.9994

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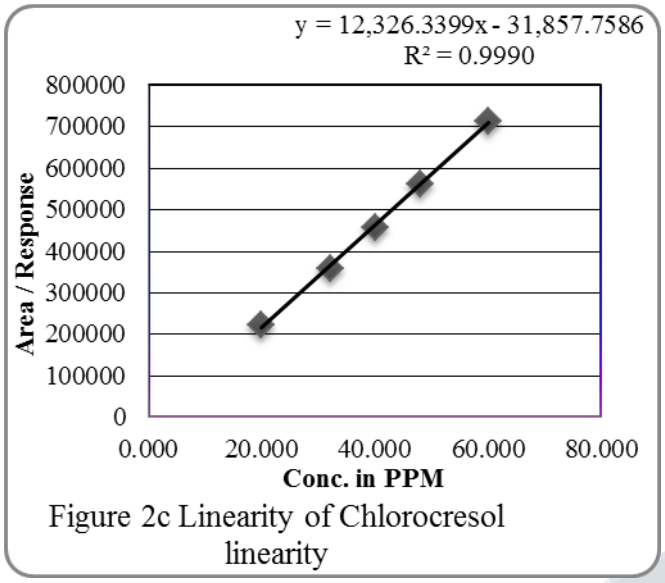

Figure 2c Linearity of Chlorocresol linearity

Tablet 4d Linearity of Methyl Paraben	
Conc. in PPM	Area
50.12	1589876
80.19	2562472
100.24	3272336
120.29	4009108
150.36	5088685
Slope	35065.9186
Intercept	-210512.2813
Correlation Coefficient [R]	0.9996
R^2	0.9993

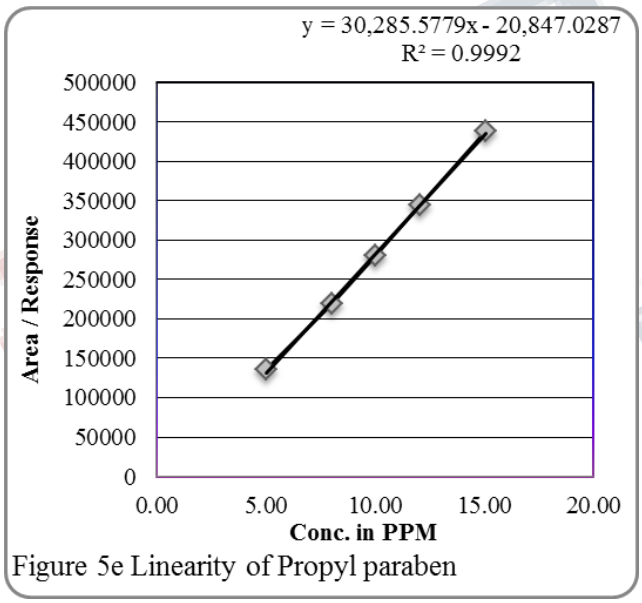

Figure 5e Linearity of Propyl paraben

Tablet 4e Linearity of Propyl Paraben	
Conc. in PPM	Area
5.03	135542
8.04	219085
10.05	280455
12.06	344329
15.08	438507
Slope	30285.5779
Intercept	-20847.0287
Correlation Coefficient [R]	0.9996
R^2	0.9992

Robustness

During the robustness study at various parameters like , change in wavelengths, column temperature , change in mobile phase composition and gradient ratio, change in pH of mobile phase it was observed that no significant variation observation in the system suitability parameters from its initial values, hence the robustness of the developed method was proved. The solutions were found stable up to 24 hrs.at room temperature.

IV. CONCLUSION

The precise and accurate method was developed for the simultaneous determination of Fluocinolone Acetonide, Miconazole Nitrate, Chlorocresol, Methyl paraben and Propyl Paraben, form cream formulation dosage form. The recovery of the method was found between 98 to 102% from 50 to 150%. In the linearity study, the correlation coefficient r2 was found more than 0.999 as well as no any interference were observed during the specificity study. We tried to use

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minimum amount of organic solvents and chemicals in the method also no any hazardous chemicals used, hence the developed works is eco-friendly. This is the first developed method for such five contents in single method which is helpful for the researchers to save the development time and cost.

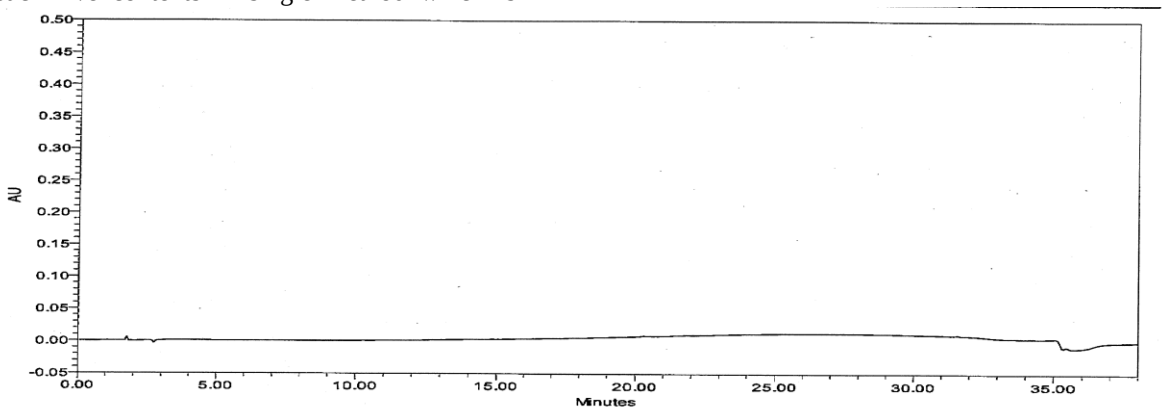

Figure 3 Representative chromatogram of blank.

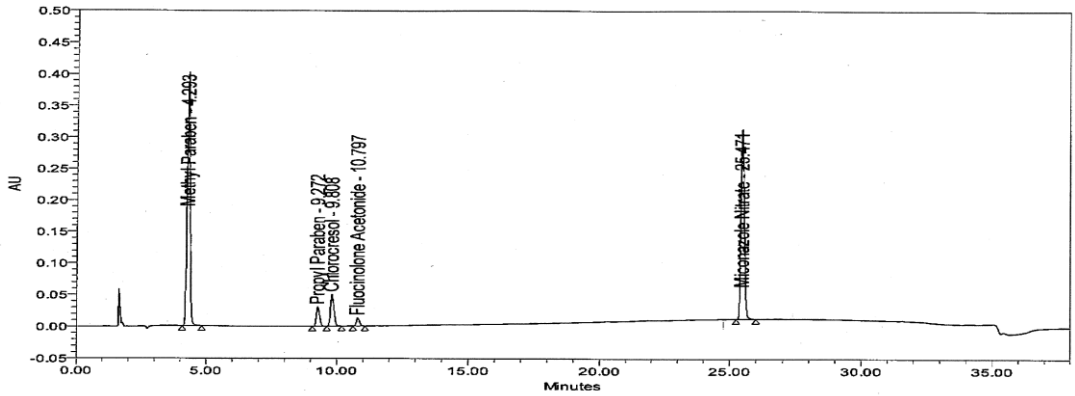

Figure 4 Representative chromatogram of standard solution.

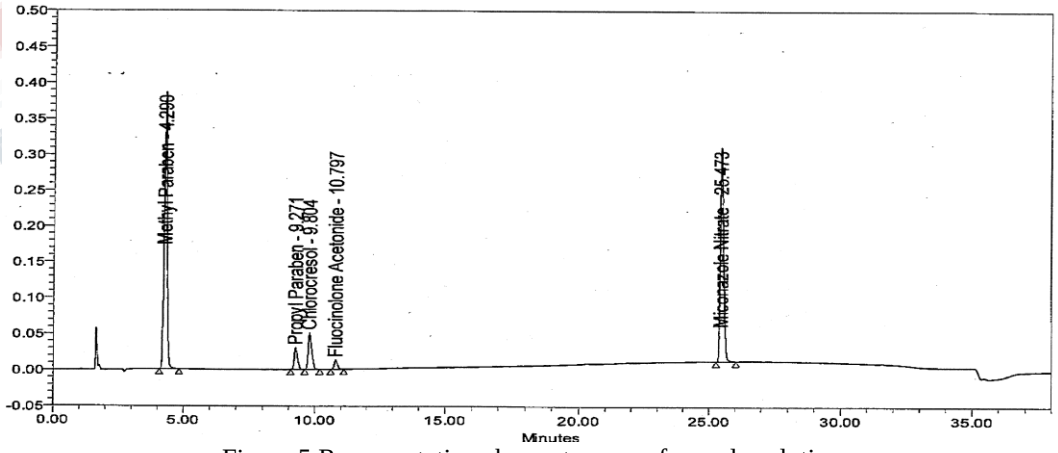

Figure 5 Representative chromatogram of sample solution

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Abbreviations

ICH	International conference on Harmonisation
LOQ	Limit of quantitation
LOD	Limit of detection
RRF	Relative response factor
PPM	Parts per million
NMT	Not more than
EP	European pharmacopeia
FL	Fluocinolone acetonide
MI	Miconazole nitrate
CH	Chlorocresol
MP	Methyl paraben
PP	Propyl paraben
Met.P	Methyl paraben
Int.p	Intermediate precision
RSD	Relative standard deviation

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