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NOVEL RP-TLC DENSITOMETRIC METHOD FOR THE SIMULTANEOUS DETERMINATION OF CIPROFLOXACIN, CHLOROCRESOL, CLOTRIMAZOLE, AND FLUOCINOLONE ACETONIDEIN CREAM DOSAGE FORM

Mohammad Marouf[1], Ghoufran Kawas[1], Amir Alhaj Sakur [2]*

[1]Department Chemistry, Faculty of Science, Tishreen University, Syria
[2]Department of Analytical and Food Chemistry, Faculty of Pharmacy, University of Aleppo, Syria

*Corresponding author E-mail**:** profsakur@gmail.com

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ABSTRACT

A simple, rapid, specific, and accurate reverse-phase thin-layer chromatography (RP-TLC) method was developed and validated for simultaneous quantification of Ciprofloxacin, Clotrimazole and Fluocinolone acetonide, in presence of Chlorcresol as preservative material in their combined dosage form (Cream), it is very challenging to carry out the simultaneous estimation of all four compounds together. In the developed method, chromatography was performed on TLC plates with precoated silica gel60 RP-18 F_{254} using triethylamine–ethylamine–methanol–acetonitrile–dichloromethane–ethylacetate (7:5:15:15:18:40) v/v, as mobile phase. Densitometric evaluation was performed at 254 nm. The R_F values were 0.363, 0.634, 0.738 and 0.864 for ciprofloxacin, Chlorcresol, clotrimazole and fluocinolone acetonide, respectively. The polynomial regression data for the calibration plots showed good linear relationship in the concentration range 10.0–37.5 g per spot for ciprofloxacin, 2.0–7.5 g per spot for Chlorcresol, 20–75 g per spot for Clotrimazole, and 0.4–1.5 g per spot for fluocinolone acetonide. **Conclusions:** The developed method was validated and found to be simple, specific, accurate and precise and can be used for routine quality control analysis of titled drugs in combination in cream formulation. The suitability of this TLC method for quantitative determination of drugs was proved by validation in accordance with the requirements of the International Conference on Harmonization (ICH) guidelines (Q2B).

INTRODUCTION

Clotrimazole (CLO), fig(1,a)is designated chemically as 1-[(2-Chlorophenyl)(diphenyl) methyl]-1Himidazole. [1,2] is compound of Benzene and Substituted Derivatives class (fig. 1a) and is used to an antifungal medication commonly used in the treatment of fungal infections (of both humans and other animals) such as vaginal yeast infections, oral thrush and ringworm. It is also used to treat athlete's foot and jock itch. It inhibits the biosynthesis of ergosterol and other sterols required for cell membrane production [3-6].

Ciprofloxacin Hydrochloride (CIP),fig(1,b) is1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid]; [1–2]Ciprofloxacin Hydrochloride is the hydrochloride salt form of ciprofloxacin, a fluoroquinolone related to nalidixic acid with antibacterial activity. Ciprofloxacin hydrochloride exerts its bactericidal effect by interfering with the bacterial DNA gyrase, thereby inhibiting the DNA synthesis and preventing bacterial cell growth[7-8]. Ciprofloxacin has been linked to rare but convincing instances of liver injury that can be severe and even fatal. Pale yellow, crystalline

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powder soluble in water and in ethanol, slightly hygroscopic[9].

Fluocinolone acetonide (FLU), fig(1,c)6α-Fluorotriamcinolone; 6α,9α-Difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione). Fluocinolone Acetonide (FLU) is a corticoid, which is an inflammation reducer, an antipruritic, and has vasoconstrictor properties. White or almost white, crystalline powdersoluble in acetone and in ethanol. [1–4].

Chlorocresol: (CHC), fig(1,d) 4-chloro-3-methyl-Phenol, possesses disinfectant and antiseptic properties, It also used as preservative in creams and other preparations[2– 4].Studies have reported many methods concerning the determination of separate formulations containing either CLO, CIP or FLU. Various analytical methods have been reported for the estimation of CLO, CIP and FLU as alone as well as in combination with other drugs.

For CLO such as spectrophotometry[10-12] ,, HPLC and RP-HPLC. [13-15], HPTLC [16], electrochemical detection [17-18].

For CIP such as spectrophotometry [19–25],TLC [26,27], HPTLC [28-29], HPLC [30-31], CE [32], Electorochemistry [33-37].

The methods reported for the determination of FLU are UV [38,39],GC [40],TLC [41],HPTLC[42], and HPLC [43 - 45].But no TLC method , has yet been reported for the simultaneous quantification of CLO, CIP, FLU and CHC in their combined dosage form. Thus, the aim of the present work was to develop and validate a new simple, rapid, selective, , reproducible, cost-effective and stability indicating RP-TLC method for simultaneous determination of CIP, CHC, CLO and FLU in (Cream) formulation dosage form.

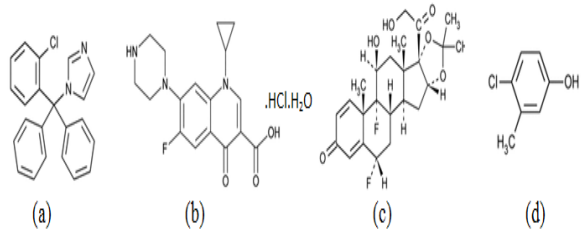

Figure 1: The chemical structure of (a) Clotrimazole, (b) Ciprofloxacin HCl, (c) fluocinolone acetonide and (d) Chlorocresol.

2. MATERIALS AND METHODS:

2.1. Materials, Reagents, and Solutions

Pharmaceutical grade clotrimazole, ciprofloxacin HCl, fluocinolone acetonide and Chlorocresol(99%) (supplied by Lyphar, Shaanxi, China). Methanol, isocratic HPLC grade (Scharlab S.L., Spain).Trimethylamine, ethylamine, acetonitrile, dichloromethane, ethylacetate, and analytical grade analytical grade (Merck, Germany) .All the reagents used were of AR grade. Combined cream dosage form (NEW CIPROMAC-FC) topical cream, manufactured by TORQUE PHARMACEUTICALS PVT LTD, INDIA. were procured from the local market in India.

2.2. Apparatus:

The HPTLC system consisted of a Shimadzu "dual wavelength flying spot scanning" densitometer CS-9301 PC (Tokyo, Japan, 2000) was used for TLC plates scanning. Digital Water Bath of Heidolph Laborota (Germany) was used to incubate solutions. UV-254 nm chamber was used for UV development experiments. Pre-coated TLC plates, C_{18} GF-254 (10 × 10 cm) (Merck, Germany). Hamilton 5-µL micro-syringe (Switzerland) was used to apply samples on TLC plates. Glass TLC developing chamber (20 × 20 × 10 cm).

3. PROCEDURE:

3.1. Preparation of Solutions

3.1.1. Preparation of Standard Stock Solutions

Stock solutions prepared by dissolving 500 mg of CLO, 250 mg of CIP, 50 mg of CHC and 10 mg of FLU, separately in 25mL volumetric flask, in least amount of mixture methanol :water (9:1)v/v, and complete to 25 mL with the mixture. To obtain solutions contain (20 mg/mL) of CLO,(10 mg/mL) of CIP,(2 mg/mL) of CHC and (0.4 mg/mL) of FLU.

3.1.2Preparation of Standard mixture Solutions:

A suitable amounts of the last mentioned standard stock solutions, were taken in series of 10mL volumetric flasks, made up to the mark with mixture methanol: water (9:1) v/v, to prepare a standard mixture solutions of CIP, CHC, CLO and FLU, in the concentration range (2.5-7.5)mg/mL for CIP, (0.5-1.5)mg/mL

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for CHC, (5-15)mg/mL for CLO and (0.1-0.5)mg/mL for FLU.

3.1.3. Preparation of Sample Solution

2g of pharmaceutical preparation (NEW-CIPROMAC-FC) Topical antifungal antibacterial cream equivalent to 10mg Ciprofloxacin, 2 mg of Chlorcresol, 20 mg, of Clotrimazole and 0.2 mg of Fluocinolone acetonide , was transferred to a 10 ml mixture of methanol: water (9:1)v/v was added,sonicate for 15 minute, cooled and filtered through whattman filter paper.

4. RESULTS AND DISCUSSION:

4.1. Optimization of Chromatographic Conditions: Few trials were carried to determine CIP, CLO and FLU in presence of CHC as preservative material, in dosage form. The optimum condition of separation were determined.The pre-coated TLC plates RP-18 F254 (10 cm × 10 cm, 250 µm thickness) were used. 5 µL on spots from each standard mixture solutions and 25 µL on spots of sample solution, were applied on TLC plates. Solutions were applied on TLC plates as 3mm spots, 5 mm from the bottom edge and the side, 15 mm between the spots, the Chromatograms were run to the solvent front of 80 mm by ascending development in the densitometer CS-9301 PC (Tokyo, Japan, 2000) (program version 2.00) twin-through chamber previously saturated for 30 min with triethylamine–ethylamine–methanol–acetonitrile–dichloro methane–ethylacetate (7:5:15:15:18:40)v/v% as the mobile phase (run time 20 min). After development, the plates were removed immediately and dried in an oven at 60°C for 1h. Densitometric scanning at λ = 254 nm was performed with a Shimadzu TLC Scanner in the absorbance mode. The silt dimension was kept at 4.0 mm × 0.45 mm and a scanning rate of 20 mms^{-1} was employed. The chromatograms were integrated using the densitometer CS-9301 PC (Tokyo, Japan, 2000) (program version 2.00), fig. (2,3).

The Separation factors for analyzed compounds were calculated. Table 1.

4.2. Method Validation

4.2.1. Linearity and range

Five concentrations were chosen in the ranges of corresponding of the analytical concentration of CIP, CHC,CLO and FLU.The linearity of peak area responses versus concentrations was demonstrated by linear least square regression analysis. The linear regression equations were as shown in Table 2.

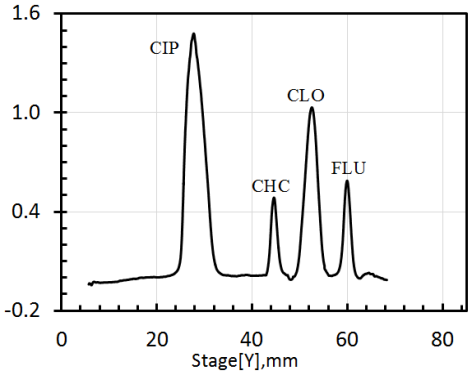

Figure 2: Densitometry TLC chromatogram of standard mixture of CIP, CHC, CLO and FLU with concentration (25,5,50,1) µg/spot respectively.

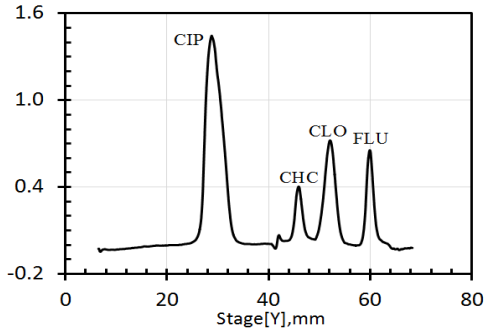

Figure 3: Densitometry TLC chromatogram of cream sample

4.2.2. Accuracy

Accuracy was assessed using 9 determinations over 3 concentration levels covering the specified range (75,100 and 125%). Accuracy was reported in Table 3 as percent recovery by the assay of known added amount of analyte in the sample

Fixed dose combination of CIP,CHC, CLO and FLU is approved for marketing in India in the brand names of (NEW-CIPROMAC-FC) Topical antifungal antibacterial cream . The ratio is maintained 500, 100, 1000 and 10 mg in 100g cream, CIP, CHC,CLO and FLU concentrations respectively**.** The resultant sample solution was used for chromatographic development and scanning followed by analysis. The analysis was repeated in triplicate.

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Table 1: Separation factors for analyzed compounds

Parameter	CIP	CHC	CLO	FluA
Retardation factor, R_f	0.363±0.004	0.634±0.005	0.738±0.005	0.864±0.006
Resolution (R_S)	-	2.88	1.56	1.51
Selectivity (α)	-	3.07	1.63	2.22
Theoretical plates Number (N)	125	1708	608	6750

Table 2: Linear regression data for analysis of CIP, CHC, CLO and FLU by the developed TLC method (*n* = 3).

Item	CIP	CHC	CLO	FLU
Linear range, µg/spot	10.0 - 37.5	2.0 - 7.5	20 - 75	0.4 - 1.5
Detection limit , µg/spot	0.30	0.06	0.5	0.05
Quantitation limit , µg/spot	0.90	0.18	1.50	0.15
Regression Data:				
Slope	1508.4		282.88	6.307
Intercept (a)	784.54		175.67	207.88
Correlation Coefficient , r^2	0.9985	0.9978	0.9992	0.9986

y = a C+b where C is the concentration of the compound (µg/spot) and Y is the drug peak area.

Table 3: Accuracy (recovery%) of drugs in sample.

Cocn.	SD%			
Drug	CIP	CHC	CLO	FLU
75%	98.48±0.22	101.22±0.17	98.88±0.22	100.38±0.20
100%	99.63±0.29	99.18±0.24	99.63±0.22	99.60±0.42
125%	101.33±0.42	100.56±0.29	101.08±0.52	101.15±0.50

Table 4. Assay of CIP, CHC, CLO and FLU inTopicalCream (n=3).

Drug	Label claim (mg/100g)	Amount found (mg/100g)	Recovery%	SD%
CIP	500	485.59	101.89	1.37
CHC	100	101.62	101.62	1.62
CLO	1000	987.88	98.79	1.23
FLU	10	10.17	101.70	1.89

Determinations of CIP, CHC, CLO and FLU in pharmaceutical preparation Cream using proposed Method were calculated in Table4.

5.CONCLUSION

The simultaneous estimation of CIP, CHC, CLO and FLU from combined dosage form is a very challenging task due to structural similarity of CLO and CIP and to the wide difference in the polarity of CLO, CIP, and FLU. Here, an RP-TLC method was developed and validated as per ICH[46] guidelines for the simultaneous estimation of CIP, CHC,CLO and FLU. A good percentage recovery for all the four drugs showed that the developed method was free from the interference of excipients used in the formulation. The developed method can be successfully used for the simultaneous quantification of CIP, CHC, CLO and FLU in routine quality control analysis of pharmaceutical dosage forms.

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