INTERNATIONAL JOURNAL OF INNOVATIVE RESEARCH & DEVELOPMENT

ISSN 2278 – 0211 (Online)

Spectrophotometric Determination of Ciprofloxacin Using Charge-Transfer Complexation Technique

Igboasoiyi A.C.
Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmacy, University of Uyo, Nigeria
Attih E.E.
Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmacy, University of Uyo, Nigeria
Ofoefule S.I.
Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Uyo, Nigeria.
Umoh E.D.
Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmacy, University of Uyo, Nigeria
Udoh O.C.
Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmacy, University of Uyo, Nigeria

Abstract:
A sensitive and precise spectrophotometric method is described. The method is based on a charge –transfer (C-T) complexation of ciprofloxacin with chloranilic acid. The C-T complex formed absorbed ultraviolet-visible (UV-VIS) light at 520 nm. The calibration curve generated by plotting absorbance against concentration obeyed Beer's law within the range of 5.6 to 120 µg/ml. The regression equation using least square method was A = bc + a that is A = 12c, with a correlation coefficient of r=0.9997 at n=6. The apparent molar absorptivity and Sandall sensitivity were 852.27 L/mol/cm and 0.3886 µg/cm^2 respectively. The limit of detection (LOD) and the limit of qualification (LOQ) were determined as per the current International For Harmonisation (ICH) guideline and were found to be 2.50 µg/ml and 8.33 µg/ml respectively. The method was validated for accuracy and precision (%RSD and %RE) and, the results obtained which were ≤1.37 and ≤2.75 respectively, were successfully used to analyse ten brands of ciprofloxacin labelled samples A-J. The assay results were statistically compared with those obtained via student t-test and F-test at 95% Confidence level and no significant difference was found. The applicability and accuracy of the method was further ascertained by recovery study via standard addition method. Excellent recoveries within the range stated in the official compendia (95.0-105.0 %) were obtained.

Keywords: *Broad spectrum, bactericidal, charge transfer, ciprofloxacin, chloranilic acid, spectrphotometric.*

1. Introduction

Ciprofloxacin (1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(7-piperazinyl)-3-quinoline carboxylic acid is a second generation fluoroquinolone antibacterial agent with an expanded (broad spectrum bactericidal activity) and acts by inhibiting the a sub-unit of DNA gyrase (tropoisomerase) which is essential in the reproduction of bacteria DNA. Ciprofloxacin is indicated against diseases caused by gram-negative and gram-positive bacteria. It is widely used in the treatment of acute sinusitis (Falagas *et al*, 2008), lower respiratory tract infection (Zuger, 1998), urinary tract infection (Clara, 2009), chronic bacterial prostatitis (Alexander *et al*, 2004) and non-complicated intra abdominal infections caused by *E. coli, P. aeruginosa, Proteus mirabilis* when used in combination with metronidazole. In Nigeria, it is used widely for the treatment of enteric fevers (typhoid fever).

Ciprofloxacin is official in the British and United States Pharmacopoeia. The official method of assay is by high performance liquid chromatography (HPLC). From the literature, several methods have been used to assay ciprofloxacin. These methods, apart from HPLC (Morley and Elrod, 1993; Zalou and Miltiadou, 2002), include: HPTLC (Novakovic *et al*, 2001), capillary electrophoresis (Ahria *et al*, 1993; Wang *et al*, 1997), high performance capillary electrophoresis (Yin and Wu, 1997), fluorimetry (Zhou *et al*,1998), titrimetry and spectrophotometry (Basavaiah *et al*, 2006), chemiluminiscence (Liang and Zang, 1997), potentiometry (Ansec and

Gomiscek, 1992) and voltametry (Di and Jin, 1995). These methods require expensive equipment and highly skilled operations that are hardly affordable by small and medium scale institutions in rural and sub-urban areas hosting the greater population of the people. The pharmaceutical application of charge-transfer complexation technique in drug assay have recently been widely used in uv-spectrophotometry. Some drugs assayed spectrophotometrically using charge-transfer technique include: nortriptilin (Fekria, 2000), nizatidine and ranitidine hydrochloride (Walash, 2004), atorvastatin (Wani *et al*, 2011) and olmersatan medoxomil (Dawish, 2012). Some reasonable work had been done by Mostafa (2002) and Abdel-Gawad *et al*, 1998 on ciprofloxacin and other quinolines, However, bearing in mind massive distribution of counterfeit and fake pharmaceuticals in the African region (Atemkeng *et al*, 2007), any simple and environmental-friendly method developed for the assay of ciprofloxacin in bulk or other pharmaceutical formulations will be complimentary and a critical step in the fight to check the wide spread distribution of fake/counterfeit antibacterials in Africa. In the proposed work, ciprofloxacin in bulk and tablet formulation were assayed spectrophotometrically using chloranilic acid in addition to pharmacopoeia method (weight uniformity test) and non-pharmacopoeia method. Friability test was used to assay tablets from ten (10) brands of ciprofloxacin sold locally and which were labelled samples A-J. These methods were simple, precise, reproducable, devoid of tedious solvent extraction and the hazards associated with the exposure of the environment and the analyst to toxic solvents.

2. Experimental

2.1. Apparatus

Ultraviolet-visible spectrophotometer with matched 1cm quartz cell (uv-1601 PC, Shimadzu, Kyoto, Japan) was used for all UV-VIS spectrophotometric measurements. Water bath (Uniscope,SM 801A). Roche friabilator (MANUS) and thermometer.

Reagents and chemicals: All reagents and chemicals used were Analytical (Analar) grade. Dioxan, chloroform and chloranilic acid (BDA Chemicals Limited, England). Pure ciprofloxacin (BDH Chemicals Limited, England).

2.2. Standard Drug Solution

Two (2) hundred milligrams of pure ciprofloxacin were carefully weighed out and transferred into a 100 ml beaker and 20 ml of distilled water added. The mixture was ultrasonicated for 20 minutes and then fully transferred a 100 ml calibrated volumetric flask and the volume made up to the 100 ml mark. The resulting solution was transferred to a 500 ml capacity beaker, basified with 2 ml solution of 2 M Sodium hydroxide and extracted with five equal portions of 20 ml chloroform using a 1000 ml capacity separating funnel. The resultant chloroform layer was passed through 20 g of anhydrous sodium sulphate to absorb the water molecules present in the chloroform layer.

2.3. Determination of Absorption Spectra of Chloranilic Acid

Twenty (20) millilitre of 1 mg/ml chloranilic acid was diluted with distilled water to obtain 100µg/ml. A 2 ml aliquot of this solution was transferred into a test tube and 3 ml dioxan was added. The solution was shaken to mix well and then scanned using the spectrophotometer in the range of 300-600 nm against a 5 ml dioxan blank.

2.4. Determination of Absorption Spectra of Acceptor-Donor Complex.

Two (2) millilitre of the drug solution was accurately measured and transferred into a calibrated volumetric flask containing 2 ml of chloranilic acid in dioxan. The volume was made up to 5 ml with chloroform and the solution was shaken to mix well. The absorbance was scanned between 300-600 nm against a blank of 2 ml of the drug solution in chloroform.

2.5. General Analytical Procedure

Different 5 ml aliquot of the standard drug solution containing 0.56, 0.72, 0.88, 1.04, 1.20 µg/ml were prepared in equal volumes of chloroform and chloranilic acid, shaken to mix well, allowed to stand for 60 minutes at room temperature and the absorbance read at 520 nm. A standard calibration curve was generated by plotting the absorbance against the concentration of the drug. From the calibration curve, unknown concentrations of the samples and the regression equation were determined.

2.6. Procedure for Tablets

Twenty tablets of each brand of ciprofloxacin procured were singly weighed and crushed into a fine powder using a ceramic mortar and pestle. A quantity equivalent to 100 mg was carefully weighed out and transferred into a 100 ml volumetric flask and 20 ml of distilled water added. The resulting mixture was sonicated for 30 minutes, then made up with distilled water to 100 ml and filtered using Whatman filter paper number 42. The initial 10 ml portion of the filtrate was discarded. The resulting drug solution was basified with 2 ml of 2.0 M sodium hydroxide and then followed by extraction with five (5) portions of 20 ml each of chloroform using 500 ml capacity separating funnel. The chloroform extracts were added together and passed through 20 g of anhydrous sodium sulphate to absorb any residual water in the chloroform layer. The chloroform-drug extract was diluted appropriately to obtain a working concentration of 100 µg/ml, from where a convenient aliquot was analysed as described above in the general procedure. This analysis was used to study the interference of pharmaceutical excipients such as starch, methyl cellulose, sodium citrate, lactose and sodium stearate in the analytical samples.

2.7. Determination of the Resistance of the Tablets to Abrasion (Friability Test)
Twenty (20) tablets from each brand of ciprofloxacin were randomly selected, weighed together (Wo) and placed in a 12 inch high drum and rotated at 25 Rpm for 4 minutes. The tablets were removed from the chamber, dusted and reweighed (W). The abrasion resistance (B) was then calculated for each brand of ciprofloxacin tablet using the formula: $B=\{1-W/W_o\}\times100$ (Ofoefule, 2002)

3. Results and Discussion
The therapeutic importance, clinical success and the electron-donating capability of ciprofloxacin informed its use for this method development. Previous studies involving reactions with polyhalo/polycyanoquinone electron acceptors revealed that chloranilic acid is one of the most efficient reagents in terms of reactivity (Dawish *et al*, 2012; Danish, 2005; Askal, 1997).
Chloranilic acid absorbs maximally at 440nm (table 1).

Wavelength	320	360	400	440	480	520	560	600
Absorbance	0.804	0.952	0.996	0.960	0.940	0.810	0.841	0.810

Table 1: Absorption characteristics of chloranilic acid.

However, the interaction between ciprofloxacin and chloranilic acid in dioxane produced a golden yellow chromogen that had an absorption maximum at 520nm (table 2).

Wavelength	320	360	400	440	480	520	560	600
Absorbance	0.274	0.486	0.543	0.610	0.654	1.138	1.121	1.030

Table 2: Absorption characteristics of ciprofloxacin-chloranilic acid complex.

This absorption maximum was due to the formation of CT complex. This complex was formed from the radical anion of chloranilic acid. The lone pair of electron was donated by ciprofloxacin as represented in the donor-acceptor-scheme below.

$$D + A \underset{\text{complex}}{=} [D\text{-}A] \overset{\text{polar}}{\underset{\text{solvent}}{=}} \underset{\text{radical ions}}{D^+ + A^-}$$

3.1. Optimization of Experimental Conditions
The experimental conditions for the complex formation and the appropriate colour development were studied and optimized. Each variable was altered in turn while keeping the other variables constant and then observing the effect of each variable on the formation of the complex and subsequent absorbance.

3.1.1. Reaction Time
The reaction time optimized. It was discovered that the optimum time for the complex to fully develop and stabilize was 30 minutes, after which the complex started losing stability, confirmed by the decrease in absorbance (table 3)

Time (min)	5	10	20	30	60	120	180	240	1440
Absorbance	0.080	0.082	0.085	0.089	0.085	0.084	0.084	0.077	0.070

Table 3: Effect of time on ciprofloxacin-chloranilic acid complex.

3.1.2. Temperature
The temperature of 20^oC was found to be the most suitable for the formation of CT complex between ciprofloxacin and chloranilic acid. Increase in the laboratory ambient temperature above showed marked instability in the formed complex. This is indicated by the decreased intensity of the coloured complex formed, hence the decrease in the absorbance of the complex at 520nm (table 4)

Temperature 0^oC	5	10	20	30	40	50	60
Absorbance	0.145	0.158	0.187	0.151	0.148	0.146	0.140

Table 4: Effect of temperature on ciprofloxacin-chloranilic acid complex.

The absorbance of the complexes formed, were determined while varying the concentration and the volume of chloranilic acid. It was discovered that 2ml of 5.0×10^{-3} M solution of chloranilic acid was found to be most suitable.

3.2. Solvent Used
Previous studies have shown that polar solvents produce CT complexes with higher molar absorptivity than non-polar solvents (Saleh *et al*, 2003, Wani *et al* 2011). Two polar solvents (methanol and ethanol) and two non-polar solvents (chloroform and dioxane) were used. For this particular experiment dioxane was found most suitable producing a golden-yellow coloured complex, suggesting that

the species involved in the complex formation is the undissociated form. Chloranilic acid exists in three ionic forms, the yellow-orange (golden-yellow) H_2A, the dark purple HA^- and the pale violet A^{2-}.

Stoichiometry of the Ciprofloxacin-Chloranilic acid CT Complex

Job's method of continuous variation was used to determine the mole ratio of ciprofloxacin and chloranilic acid. From Job's plots obtained it was clear that [ciprofloxacin]:[chloranilic acid] ratio was 1:1.

From the equation, **a**D + **b**A = D**a**A**b ;** where **a** is the number of moles of the donor (D) and **b** that of the acceptor (A).

If the concentration of the donor (D) and that of the acceptor (A) is varied but the total combined analytical concentration is constant then (D) = (A) = constant.

From Job's plot the CT complex (ciprofloxacin- chloranilic acid) is 1:1. This means that only one site of interaction was actually involved in the formation of CT complex despite the fact that there could be more than one possible electron-donating site in the ciprofloxacin molecule. This finding, supports the fact that the interaction of ciprofloxacin with chloranilic acid takes place only at one site which is the nitrogen of the piperazine ring.

4. Validation of the Proposed Method

4.1. Linearity and Sensitivity

Under optimum conditions of this reaction, calibration curve for the determination of ciprofloxacin in tablets by the proposed method was generated by plotting the observed absorbance versus the concentration of ciprofloxacin. Beers law was observed in the concentration range of 5.6µg/ml and 120µg/ml. The regression equation for the result was derived using the least square method.

A = bC + a (A = 0.12c), r = 0.9997 (n = 6)

Where **A** = absorbance, **C** = concentration, in µg/ml and **b** the slope and **a** the intercept. The apparent molar absorptivity, Sandell's sensitivity and sensitivity parameters, such as limit of detection (LOD) and limit of quantification were determined as per the current ICH guidelines, 2005 and recorded in table 5.

Parameter	Value
Wavelength	520 nm
Linear range	5.6 – 120 µg/ml
Molar absorptivity	852.7 L/mol/cm
Sandell sensitivity	0.3886 µg/cm^2
Limit of detection	2.50 µg/ml
Limit of quantification	8.333 µg/ml
Slope	0.12
Regression coefficient	0.9997

Table 5: Results of measurement of analytical and optical parameters

The limit of detection using the formula 3σ/slope and limit of quantification w× σ/slope; where σ is the standard deviation of five blank determinations and s is the slope of the calibration curve.

Precision and Accuracy

The precision and accuracy of the purposed method were evaluated by preparing analyzing solutions containing three different concentrations of ciprofloxacin in five replicates. The percentage relative error (% R.E.) were determined. The % R.E. was calculated using the formula:

% R.E. = [amount formed-amount taken]/amount taken] × 100.

The assay procedure was repeated seven times within the same day (intra-day precision) and for five different days (inter-day); and the % RSD and % R.E. were obtained for repeatability and intermediate precision (table 6).

Proposed Method	CPF Taken	Intra-day Precision & Accuracy			Inter-day Precision & Accuracy		
		CPF Formed	% RSD	% R.E.	CPF Formed	% RSD	% R.E.
Spectrophotometry (CT)	2.0	2.02	1.01	1.00	2.04	1.00	2.00
	4.0	4.06	1.01	1.51	3.89	1.37	2.75
	6.0	5.94	0.95	1.00	5.95	0.42	0.83

Table 6: Evaluation of intra-day and inter-day precision accuracy

4.2. Selectivity

The proposed method was evaluated for selectivity. Common pharmaceutical excipients such as tale, glucose, alginate and starch were used to prepare a placebo blank, from which a suitable aliquot was analysed as described in the procedure for tablets above. Most of the excipients were not very soluble in dioxane and chloroform and therefore had no interference with results indicating a very high selectivity of this method in the assay of ciprofloxacin.

Application of the Proposed Assay Method in Tablet Formulations

To evaluate the analytical practicability of the proposed method for the quantification of ciprofloxacin in commercially available tablets. The results obtained were statistically compared with the official method by applying student's t-test for accuracy and student's F-test for precision (table 7).

S/N	Sample	Label Claim (mg/tablet)	Reference Method	Proposed Method (% found ± SD)	t	F
1.	A	500	99.70 ± 1.16	99.99 ± 0.86	1.44	1.62
2.	B	500	99.70 ± 1.16	100.22 ± 0.83	0.36	1.94
3.	C	500	99.82 ± 1.05	99.92 ± 0.85	0.65	1.53
4.	D	500	99.92 ± 0.85	99.97 ± 0.42	0.29	1.27
5.	E	500	99.70 ± 1.16	99.80 ± 0.61	0.80	1.07
6.	F	500	99.70 ± 1.16	99.97 ± 0.94	0.18	1.50
7.	G	500	99.70 ± 1.16	100.04 ± 1.23	0.20	1.12
8.	H	500	99.70 ± 1.16	99.99 ± 0.87	1.44	1.83
9.	I	500	99.70 ± 1.16	99.47 ± 0.86	1.44	1.82
10.	K	500	99.70 ± 1.16	97.99 ± 0.86	1.44	1.83

Table 7: Results of analyses of dosage form (tablet)

The student's t-test and F-values at 95% confidence level were lower than the tabulated values showing a good congruence between the proposed method and the official method. Recovery Studies.

Recovery studies via standard addition method, was performed to further ascertain the accuracy and validity of proposed method. This was done by spiking up a specific quantity of a pre-analyzed tablet powder with pure ciprofloxacin at three concentration levels and the total of both is analyzed using the proposed method. The percentage recovery of the pure ciprofloxacin ranged between 99.35 to 102.2% with standard deviation of 1.00 – 2.15 (table 8).

Sample	Amount of Drug (mg)	Amount of Pure Ciprofloxacin Added (mg)	Total Amount Found (mg)	Recovery of Pure Drug (% ± SD)
A	40.20	20.00	61.80	104.0 ± 2.00
	40.20	40.00	81.35	102.5 ± 1.76
	40.20	60.00	109.90	103.0 ± 1.09
E	41.00	20.00	61.65	103.3 ± 1.63
	41.00	40.00	82.10	102.8 ± 1.38
	41.00	60.00	101.20	102.3 ± 1.60
D	45.10	20.00	61.22	101.1 ± 0.55
	45.10	40.00	86.20	102.8 ± 1.38
	45.10	60.00	106.20	101.8 ± 0.92
G	50.10	20.00	70.50	101.0 ± 1.63
	50.10	40.00	91.10	102.5 ± 1.25
	50.10	60.00	110.00	103.3 ± 1.67
C	50.10	20.00	70.51	102.1 ± 1.00
	50.10	40.00	91.10	102.5 ± 1.25
	50.10	60.00	112.15	103.4 ± 1.71
I	50.10	20.00	70.40	101.5 ± 1.06
	50.10	40.00	91.30	103.0 ± 1.05
	50.10	60.00	112.10	101.6 ± 1.67
F	50.10	20.00	70.65	102.7 ± 1.63
	50.10	40.00	91.30	103.3 ± 1.50
	50.10	60.00	112.40	103.8 ± 1.92
K	50.10	20.00	70.52	102.0 ± 1.48
	50.10	40.00	91.10	102.5 ± 1.77
	50.10	60.00	111.00	101.6 ± 1.06
H	50.10	20.00	70.50	102.0 ± 1.48
	50.10	40.00	91.30	103.0 ± 1.50
	50.10	60.00	112.10	103.3 ± 1.67
B	50.10	20.00	70.40	102.0 ± 1.00
	50.10	40.00	91.30	102.5 ± 1.23
	50.10	60.00	112.10	103.3 ± 1.67

Table 8: Results of the Recovery Study by the Standard Addition Method

4.3. Robustness

To evaluate robustness, some parameters such as wavelength range, temperature change and the reaction time were interchanged and varied slightly. The capacity of the method to perform remained unaffected by small deliberate variations.

5. Conclusion

Ciprofloxacin formed a complex with choranilic acid, confirmed by a shift in the maximum absorbance of chloranilic acid from 428nm to 520nm. The proposed method was used in the determination of ciprofloxacin tablets which yielded percentage recoveries within the range stated in the official compendium (95.0-105.0 %) . The method is suitable for the determination of ciprofloxacin in bulk or tablet form.

The method is simple, direct, sensitive, quick and does not require special experimental conditions such as heating time, tedious solvent extraction steps. It also uses simple and inexpensive analytical equipment. The method is therefore recommended for the determination of ciprofloxacin in bulk and pharmaceutical preparations.

6. References

1. Ahria, K.D. and Chanter, V.C (1993). Validation of capillary electrophoresis method for the determination of a quinoline antibiotic and its related impurities. J. Chromatogr. 652: 459-463.
2. Alexander, S, Paul, T.U. and John, C.(2004). Ciprofloxacin or tamsolutsin in men with chronic prostatis (chronic pelvic pain syndrome: a randomized, double-blind trial. Annals of internal medicine. 141(8): 581-589.
3. Askal, H.F. (1997). Spectrophotometric study of the charge-transfer complexes of some pharmaceutical butryophenone. Talanta, 44: 1749-1755.
4. Ansec, H. and Gomiscue, S. (1992). Study of the prospect for a ciprofloxacin PVC-coated wire ion selective electrode on quinoline4-ones. Anal. Chem. 268:307-9.
5. Basavaiah, K., Nagegowda, P., Somershekar, B.C. and Ramakrishna, V (2006). Spectrophotometric and titrimetric determination of ciprofloxacin based on reaction with cerium (IV) sulphate. Science Asia 32:
6. 403-409.
7. Dawish, I.A. (2005). Kinetic spectrophotometric analysis for determination of trimetazidine dihydrchloride. Anal Chim. Acta 551:222-23.
8. Dawish, I.A., Wani, T.A., Khalil, Y.N., Al-shaikh, A and Al-Morshadi, N. (2012). Development of a novel 96-microwell assay with high throughput for determination of olmersartan medoxomil in its tablets. Chemistry Central Journal, 6:1.
9. Di, J.W. and Jin, M. (1995). Study on the determination and electrode mechanism of ciprofloxacin by LSP. Fenxi Shinyanshi IX, 33-6.
10. Falagas, M.I.(2008). Respiratory fluoroquinolones for the treatment of Community –acquired pneumonia, a meta-analysis of randomized controlled trials. CMAJ 1 79(12): 1269-77.
11. Fekria, M. (2000) Spectrophotometric Determination of nortriptyline hydrochloride in bulk form and tablet. Journal of Pharmaceutical Chemistry 19(7): 213-217.
12. Liang, Y.D., Li, J.Z. and Zang, Z.I. (1997) . Flow injection Chemiluminiscence determination of ciprofloxacin hydrochloride. Fenxi Huaxe 25, 1307-10.
13. Morley, J.A. and Elrod, L. (1993). Determination of fluoroquinolone antibacterials as N acyl derivatives. Chromatographia 37, 295-9
14. Novakovic, J., Neomerak, K, Nova, H and Filka, K. (2001). An HPTLC method for the determination and the purity control of ciprofloxacin HCL in coated tablets. J. Pharm Biomed Anal 25:957-64.
15. Ofoefule S.I. (2002). A Textbook of Pharmaceutical Technology an Industrial Pharmacy. pp 58-65.
16. Saleh, G.A., Askal, H.F., Dawish, I.A. and El-Shorbagi, A.N. (2003). Spectroscopic analytical study for the charge-transfer complexation of certain cephalosporins with chloranilic acid. Anal. Sci. 19:281-287.
17. The British Pharmacopoeia (1999). Her Majesty's Stationary Office, London. 2, p.1714.
18. The United States Pharmacopoeia (1999). United States Pharmacopoeial Convention 12601. Twinbrook Parkway, Rockville, MD 20852 p.420.
19. Walash, M. (2004). Spectrophotometric determination of H_2-receptor antagonists. International Journal of Analytical Chemistry 17(3):36-43.
20. Wang, P.L., Feng, Y.L. and Chen, L.A. (1997). Validation of capillary electrophoresis method for the determination of quinolone antibiotic and its related impurities. Michrochem. J. 56:229-35
21. Wani, T.A., Khalil, N.Y., Abdel-Rhaman, H.M. and Danish, I.A. (2011). Novel microwell-based spectrophotometric assay for determination of atovastatin calcium in its pharmaceutical formulation. Chemistry Central Journal 5:57.
22. Yin, C. and Wu, Y.T. (1997). Determination of four quinolones by high performance capillary electrophoresis. Yauwu Fenxi Zazhi 17:371-3.
23. Zalou, A. and Miltiadou, N. (2002). Sensitive L.C. determination of ciprofloxacin in pharmaceutical preparations and biological fluids with fluorescence detection. J. Pharm. Biomed Anal 28:559-68.
24. Zhou, C.J., Liu, N. and Guo, Y.E. (1998). Fluometric determination of the content of ciprofloxacin hydrochloride ointments. Yauwu Fenxi Zazhi 18:200-1.
25. Zuger, A. (1998). Ciprofloxacin for acute exacerbations of chronic bronchitis. Journal Watch (Geneva) 1103:4