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DETERMINATION OF CIPROFLOXACIN IN TABLETS FROM EU AND BOSNIAN MARKETS

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ABSTRACT

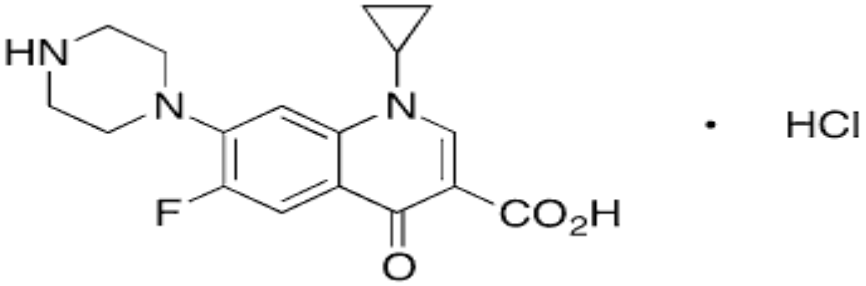
The subject of this study are six samples of ciprofloxacin hydrochloride film tablets, through product identification and characterization, in accordance with applicable pharmacopoeias and guidelines. Objectives of the thesis are: Test the process parameters of ciprofloxacin hydrochloride film tablet and test the content of ciprofloxacin hydrochloride film tablets.

KEYWORDS: Ciprofloxacin Hydrochloride, Spectrophotometric Assay, Pharmaceutical Analysis, Fluoroquinolone.

INTRODUCTION

Ciprofloxacin, a synthetic fluoroquinolone, has a bactericidal action. Ciprofloxacin belongs to the second generation of fluoroquinolones. It has in vitro activity in a wide range of gram-negative and gram-positive microorganisms. The bactericidal action is achieved by the inhibition of topoisomerase II (DNA gyrase) and topoisomerase IV (both type II topoisomerase) required for bacterial DNA replication, transcription, repair, and recombination.[1]

Ciprofloxacin retained part of its bactericidal activity after RNA inhibition and protein synthesis using rifampin and chloramphenicol. These observations suggest that ciprofloxacin may have two bactericidal mechanisms, one mechanism resulting from the inhibition of the DNA rays and another mechanism that may be independent of the synthesis of RNA and protein.[2]



Ciprofloxacin hydrochloride, chemically, 1-Cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4- dihydroquinoline-3-carboxylic acid hydrochloride. It is pale yellow, crystalline powder, slightly hygroscopic. Soluble in water, slightly soluble in methanol, very slightly soluble in anhydrous ethanol, practically insoluble in acetone, in ethyl acetate and in methylene chloride.[3]

MATERIAL AND METHODS

Ciprofloxacin hydrochloride was from BP standard. Water was from Millipore system. As analytical equipment were used UV Spectrophotometer Shimadzu, Digital weighing balance Mettler Toledo and Ultra sonicator Sonis. To determine appearance, uniformity of mass, uniformity of dosage units, subdivision of tablets and assay content of Ciprofloxacin hydrochloride in

conventional tablet available from EU and Bosnian market, randomly select products and labeled as sample 1 to sample 6. All samples were 500 mg strength. Also, samples 1 to 3 were from EU market, and samples 4 to 6 were from Bosnian market.

Tests

Appearance. Samples of 20 tablets from each batch were randomly selected and their properties analyzed such as color, shape, shape of the surface, the presence of the described grooves and monograms all on based on visual observation.

Uniformity of mass. Uniformity of mass was tested according to European Pharmacopoeia. Individually point to twenty randomly selected dosage forms, or if each one is one the preparation separately packaged takes up the contents of 20 packs, and calculates the average mass. Only two average masses may deviate more than the permissible percentage deviation, according to European Pharmacopoeia, and no average mass may deviate by more than twice values of permitted percentage of deviation.[4]

Uniformity of dosage units. The test for mass variation is applicable for film-coated tablets, containing 25 mg or more of an active substance comprising 25 per cent or more, by mass, of the dosage unit and calculate the acceptance value according European Pharmacopoeia 2.9.40.[5]

Subdivision of tablets. Tablets may bear a break-mark or break-marks and may be subdivided in parts, either to ease the intake of the medicinal product or to comply with the posology. In the latter case, subdivision must be assessed and authorised by the competent authority. In order to ensure that the patient will receive the intended dose, the efficacy of the break-mark(s) must be assessed during the development of the product, in respect of uniformity of mass of the subdivided parts. Each authorised dose must be tested using the following test. Take 30 tablets at random, break them by hand and, from all the parts obtained from 1 tablet, take 1 part for the test and reject the other part(s). Weigh each of the 30 parts individually and calculate the average mass. The tablets comply with the test if not more than 1 individual mass is outside the limits of 85 per cent to 115 per cent of the average mass. The tablets fail to comply with the test if more than 1 individual mass is outside these limits, or if 1 individual mass is outside the limits of 75 per cent to 125 per cent of the average mass.[6]

Selection of Analytical Wavelenth for Assay Determination

From the standard stock solution, a mixture of dilutions ranging between 5 µg/ml to 12 µg/ml were prepared and scanned within the wavelength range of 500-190 nm on spectrum mode, using water as blank. Ciprofloxacin hydrochloride shows λ_{max} at 278 nm.

RESULTS AND CONCLUSION

Appearance

From these visual observations, we can say that all samples are of adequate appearance, without any flaws and damage (Figure 1). Detailed observations of the appearance of the tested samples are in Table 1.

Figure 1: Appearance of tested samples.

Table 1: Detailed observations of the appearance.

Parameter	*Sample 1*	*Sample 2*	*Sample 3*	*Sample 4*	*Sample 5*	*Sample 6*
Shape and colour	Oblong, white	Oblong, white	Oblong, white	Oblong, green	Oblong, green	Oblong, white
Surfaces	Biconvex, with brake line on side	Biconvex, with brake line on side	Biconvex, with brake line on both side	Biconvex, with brake line on side	Biconvex, with brake line on side	Biconvex, with brake line on side
Engraving	/	„CIP 500“ on one side	/	/	/	
Damage	/	/	/	/	/	

Uniformity of mass

From the below results, all the tested samples satisfy the criteria defined by the European Pharmacopoeia Requirement 2.9.5.

Table 2: Uniformity of mass for tested samples.

Sample No	*Sample 1*	*Sample 2*	*Sample 3*	*Sample 4*	*Sample 5*	*Sample 6*
1.	786.50	763.46	780.49	898.14	879.61	776.10
2.	787.42	776.09	772.53	892.65	896.20	776.14
3.	781.44	776.64	778.53	899.65	870.85	778.87
4.	784.71	780.31	782.36	895.96	858.06	785.42
5.	782.68	779.72	786.56	883.47	889.79	790.27
6.	786.50	763.25	780.44	898.02	879.50	776.02
7.	787.47	775.92	772.45	892.15	896.07	776.06
8.	781.43	776.44	778.46	899.50	870.79	778.92
9.	784.71	780.15	782.25	895.84	858.01	785.36
10.	782.70	779.50	786.46	883.43	889.66	790.16
11.	786.48	763.17	780.38	897.95	879.45	775.97
12.	787.47	775.77	772.35	892.08	896.03	776.03
13.	781.47	776.36	778.39	899.44	870.74	778.87
14.	784.70	780.02	782.18	895.79	857.93	785.33
15.	782.73	779.37	786.37	883.44	889.62	790.12
16.	786.50	763.02	780.32	897.88	879.33	775.91
17.	787.49	775.63	772.29	892.02	896.97	776.02
18.	781.46	776.28	778.34	899.34	870.69	778.92
19.	784.69	779.91	782.14	895.74	857.92	786.25
20.	782.74	779.26	786.31	883.41	889.56	790.13
Average mass of film coated tablets	**784.56**	**775.01**	**779.98**	**893.80**	**878.84**	**781.34**
Min (mg)	**781.43**	**763.02**	**772.29**	**883.41**	**857.92**	**775.91**
Max (mg)	**787.49**	**780.31**	**786.56**	**899.65**	**896.97**	**790.27**
Min (%)	**99.60**	**98.45**	**99.01**	**98.84**	**97.62**	**99.30**
Max (%)	**100.37**	**100.68**	**100.84**	**100.66**	**102.06**	**101.14**

Uniformity of dosage units

From the below results, all tested samples meet the criteria defined by the European Pharmacopoeia 2.9.40. Acceptable values of parameter L are less than 15.

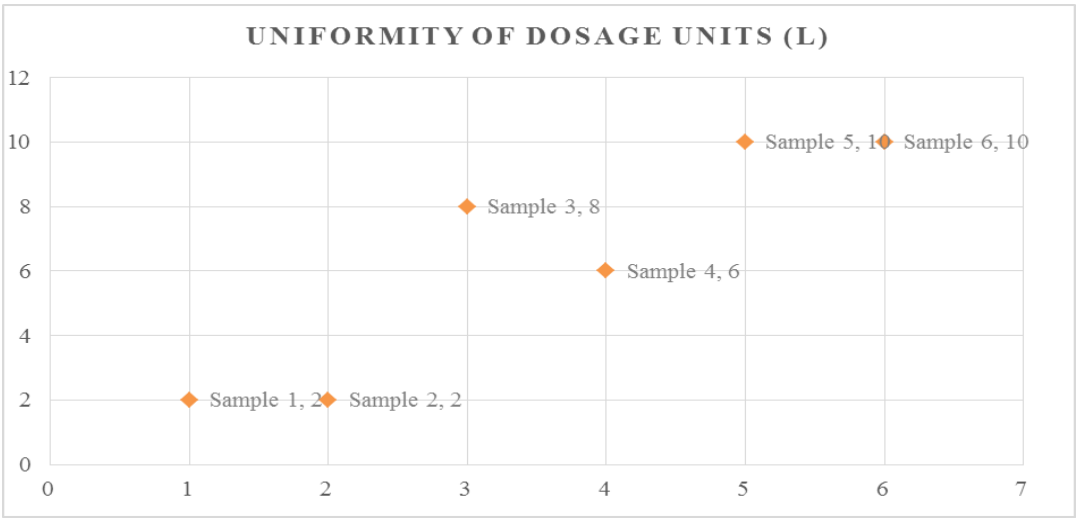


Figure 2: Uniformity of dosage units for tested samples.

Subdivision of tablets

The uniformity of the weight of the half tablets on the test samples was done according to the general procedure described in Ph.Eur. monograph 0478- Subdivision of tablets. 30 film tablets were randomly taken from each sample tested, one half was used for further work and the other was discarded.

Table 3: Subdivision of tablets for tested samples.

Mass of the half tablets (mg)	*Sample 1*	*Sample 2*	*Sample 3*	*Sample 4*	*Sample 5*	*Sample 6*
m1	397,15	392,08	367,60	431,61	400,32	361,12
m2	397.49	387.90	392.89	436.02	429.66	395.38
m3	389.43	389.88	341.20	464.83	416.20	370.55
m4	385.22	375.90	435.79	460.94	468.71	393.65
m5	383.56	384.95	417.71	461.54	457.33	376.24
m6	363.44	386.12	399.10	429.30	428.30	407.56
m7	322.60	385.48	372.06	468.76	430.60	416.95
m8	372.33	377.00	386.47	461.95	448.16	403.33
m9	408.96	402.39	363.68	430.98	439.78	377.51
m10	400.41	384.09	417.64	414.05	466.18	397.22
m11	397.20	392.02	367.59	431.51	400.25	361.09
m12	397.41	387.86	392.82	435.93	429.72	395.35
m13	389.35	389.76	341.21	464.77	416.04	370.51
m14	385.21	379.85	435.76	460.90	468.68	393.64
m15	383.46	384.88	417.66	461.44	457.24	376.23
m16	363.42	386.08	399.13	429.25	428.29	407.53
m17	422.55	385.41	372.04	468.73	430.67	416.97
m18	372.25	376.94	386.42	461.85	448.05	403.28
m19	408.96	402.36	363.63	430.90	439.72	377.62
m20	400.33	384.02	417.59	414.05	466.14	397.18
m21	397.20	391.97	367.56	431.45	400.20	361.98
m22	397.39	387.80	392.80	435.96	429.60	395.31
m23	389.26	389.68	341.13	464.78	415.91	370.51
m24	385.20	375.81	435.72	460.81	468.62	393.63
m25	383.47	384.79	417.63	461.31	457.18	376.28
m26	363.36	386.06	399.05	429.17	428.24	407.53
m27	422.55	385.44	371.98	468.71	430.62	416.90
m28	372.08	376.93	386.38	461.78	448.03	403.35
m29	408.93	402.32	363.58	430.87	439.64	377.62
m30	394.49	386.88	388.13	448.10	441.92	394.12
Average	**388.49**	**386.75**	**388.40**	**447.08**	**437.67**	**389.87**
Min (mg)	**322.60**	**375.81**	**341.13**	**414.05**	**400.2**	**361.09**
Max (mg)	**422.55**	**402.39**	**435.79**	**468.76**	**468.71**	**416.97**
Min (%)	**83.04**	**97.17**	**87.83**	**92.61**	**91.44**	**92.62**
Max (%)	**108.77**	**104.04**	**112.20**	**104.85**	**107.09**	**106.95**

Spectrophotometric assay determination

Verification of method was tested in the range from 5 µg/ml to 12 µg/ml, with linear relationship r=0.9978 (Figure 3). From the below results, we see that all samples meet the quality requirements of the ICH 3AQ11a guidelines, Specifications and Control Tests on Finished Products, as well as BP requirements 95.0% - 105.0% (samples 1 and 2) and USP requirements 90.0% -110.0% (samples 3, 4, 5 and 6).[7,8,9]

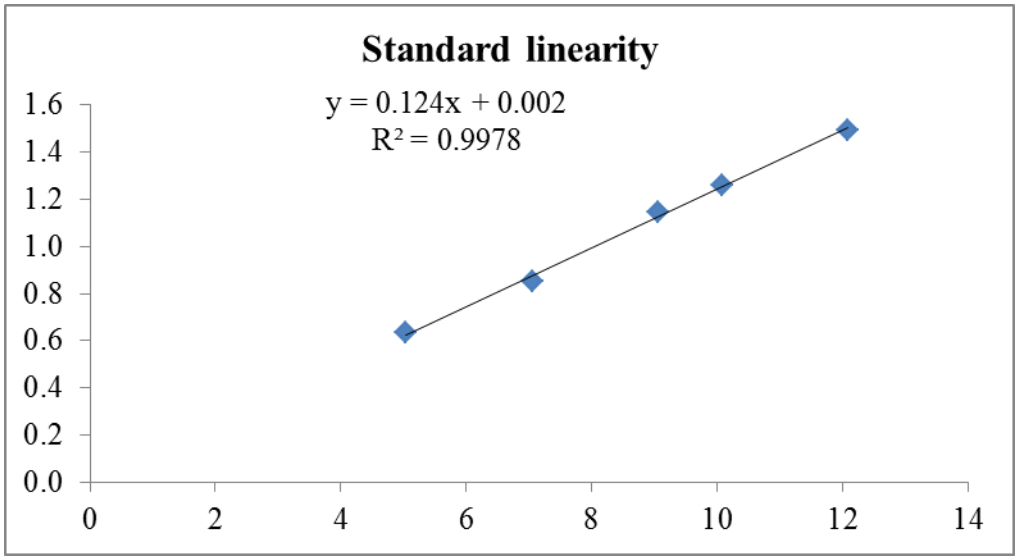


Figure 3: Standard calibration curve.

Table 4: Linearity data of Ciprofloxacin hydrochloride.

Standard solutions	*Concentration (µg/ml)*	*Absorbance*
1	5.04	0.6347
2	7.05	0.8524
3	9.07	1.1423
4	10.07	1.2575
5	12.09	1.4937

Table 5: Data regarding tested samples.

	Apsorbanca	*µg/ml*	*%*	*mg*
Sample 1	1.2807	10.31	102.40	512.02
Sample 2	1.2669	10.20	101.30	506.49
Sample 3	1.3495	10.87	107.91	539.57
Sample 4	1.3252	10.67	105.97	529.84
Sample 5	1.3361	10.76	106.84	534.20
Sample 6	1.3613	10.96	108.86	544.29

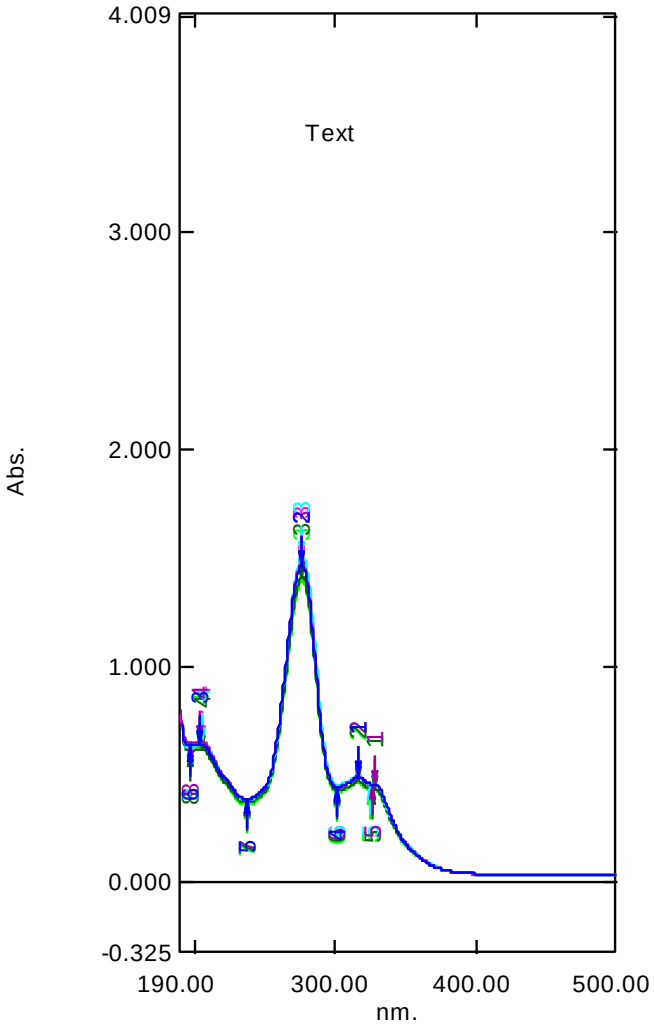


Figure 4: Wavelength of Ciprofloxacin hydrochloride standard and sample solutions.

CONCLUSION

Official pharmacopoieses provide monographs that make it easy to set up specification requirements. The aim of this study was to demonstrated quality of Ciprofloxacin hydrochloride tablets from EU and Bosnian market. After the experimental work and the processing of results we can conclude all tested samples of Ciprofloxacin hydrochloride tablets correspond to the appearance, uniformity of mass, uniformity of dosage units and subdivisopn of tablets. Also, a simple and sensitive spectrophotometric method was used for assay determination of Ciprofloxacin in film coated tablets, and this method can be used routine control. And the main conclusion is that there is no difference in quality requirement between samples from EU and Bosnian market.

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