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University of AL-Qadisiyah
College of Pharmacy

Comparative evaluation study of different manufacturers from ciprofloxacin tablets in Iraqi market

A Thesis

Submitted to the Department of Pharmaceutical chemistry and the Committee of under Graduate Studies of the College of Pharmacy/University of AL-Qadisiyah in Partial Fulfillment of the Requirements for the Degree of Bachelor of Science in Pharmacy.

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2017 A.D.

1438 A.H.

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

هُوَ الَّذِي يُرِيكُمْ آيَاتِهِ وَيُنَزِّلُ لَكُمْ

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صدق الله العظيم

سورة غافر الاية ﴿١٣﴾

Supervisor certificate

I certify that this the **"*Comparative evaluation study of different manufacturers from ciprofloxacin tablets in Iraqi market* "**, was prepared under my supervision at the University of AL-Qadisiyah, College of Pharmacy as a partial fulfillment of the requirements for the degree of Bachelor of Science in Pharmacy.

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Advisor: ***Dr. Hussein Abdelamir Mohammad***
Department: ***Pharmaceutical chemistry***
Date:

In view of the available recommendation, I forward this thesis for the debate by the examining committee.

Signature:
Name:
Chairman of the Committee of Graduate Studies in the College of Pharmacy
Date:

جمهورية العراق

وزارة التعليم العالي

والبحث العلمي

جامعة القادسية/ كلية الصيدلة

تقييم ومقارنة مختلف العالمات التجارية من أقراص سيبروفلوكساسين المتاحة تجاريا في السوق العراقية

أطروحة

قدمت إلى قسم الكيمياء الصيدالنية ولجنة الدراسات االولية بكلية الصيدلة / جامعة القادسية في الوفاء الجزئي بمتطلبات درجة طلبة العلوم في الصيدلة

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2017 A.D.

1438 A.H.

Digitation

To.....

MY Father.....

MY Mother.....

MY Brother &

MY Sisters.....

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List of Abbreviation

Abbreviation	Meaning
CF1	CiproHEXAL
CF2	Ciprofloxin
CF3	Cipropham
CF4	SIFLOKS
CF5	CiproXENE
$NaH_2Po_4.2H_2o$	Sodium phosphate monobasic
Na_2HPo_4	Sodium phosphate dibasic
USP	United States Pharmacopeia
EP	European Pharmacopeia
AUC	Area under the curve
Log P	Logarithm of portion coefficient
CSF	Cerebrospinal fluid
Hcl	Hydrochloric acid
API	Active pharmaceutical ingredient
Absor.	Absorbance
Conc.	Concentration
D\S	Dissolution\Solubility
Sol.	Solution
D	Deviation
D%	Deviation percent
Fig.	Figure
C.U	Content uniformity
T.W	Tablet weight
D	Diameter
T	Thickness
Tab.	Tablet
Kg	Kilogram
g	Gram
mg	Milligram
mL	Milliliter
µg	Microgram
IV	Intravenous
IM	Intramuscular
hr	Hour
min	Minute
sec	Second

Abstract

The in vitro evaluation of the physical characteristics of the pharmaceutical products ensures their quality as well as bioavailability. Ciprofloxacin Hcl, a widely used antibiotic to treat different types of bacterial infections, was chosen for this in vitro comparative study of different pharmaceutical company. The present study compared the content uniformity, weight variation, hardness, friability, thickness, diameter, disintegration and dissolution ability of five brands of ciprofloxacin Hcl tablets exported to Iraqi market to confirm whether they follow guidelines USP [9]. All five brands of ciprofloxacin HCl tested can meet the specification of the USP for content uniformity, weight variation, hardness, friability, thickness, diameter, disintegration and dissolution [9]. The average hardness of the products varies 15.5 kg to >20 kg and the friability 0.0 %. All the brands had shown disintegration time 2 to 20 minutes while they showed 99.2 to 100 % release of active ingredient within 50 to 60 minutes in dissolution testing. This may confirm the absorption of the drug from gastrointestinal tract for optimum therapeutic effect.

CHAPTER ONE
INTRODUCTION

1.1. Introduction:-

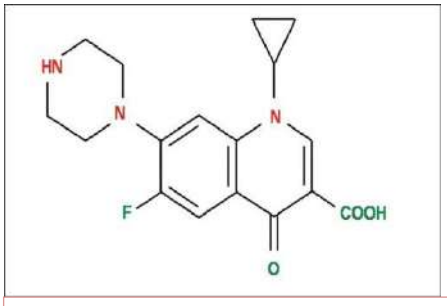
Ciprofloxacin is a broad-spectrum bactericidal anti-infective agent of the second-generation fluoro-quinolone class [1].

Uses:- Ciprofloxacin is used to treat different types of bacterial infections. This includes bone and joint infections, intra-abdominal infections, certain type of infectious diarrhea, respiratory tract infections, skin infections, typhoid fever, and urinary tract infections[2].

***Adverse reactions*: -** nausea, vomiting, diarrhea, abdominal pain, rash, headache, and restlessness [2].

***Serious adverse effects*:-** drug-induced psychosis, immunogenic hypersensitivity reaction, peripheral neuropathy, raised intracranial pressure, seizure, tendinitis, traumatic, or non-traumatic rupture of tendon. [3] Acute renal failure has also been described, mostly in cases related to overdose [4,5],but sometimes at ciprofloxacin dosages within therapeutic schedules[6,7].Because of its potency, broad-spectrum activity and general safety, ciprofloxacin is usually reserved as a drug of last resort to treat antibiotic-resistant infections

***Systematic (IUPAC) Name:-** 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-quinoline-3-carboxylic acid[8]



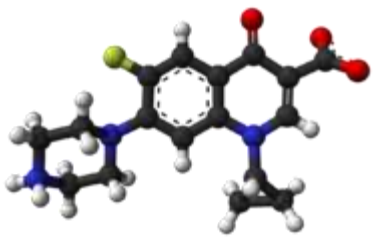


Fig. 1. Structure of ciprofloxacin. **- 3D** Structure of ciprofloxacin

1.2. Chemical Properties:-

1.2.1. *Salts, Isomers, and Polymorphs:*

The United States Pharmacopeia (USP) [9] contains a monograph for ciprofloxacin hydrochloride and the European Pharmacopeia (EP) [10] has a monograph for the anhydrous form of ciprofloxacin hydrochloride.

The hydrochloride and the free base are in regular therapeutic use. Stoichiometric metallic complexes between ciprofloxacin and metals have been reported but they are not in regular therapeutic use [11,12].

Polymorphic forms and stereoisomers have not been reported.

1.2.2. *Dissociation Constants:-*

Ciprofloxacin is a zwitter-ionic molecule containing two proton-binding sites. At 37°C, values of **pKa1** and **pKa 2** are **6.2** and **8.59**, respectively, have been reported [13]. At 25° C, **pKa** values of **6.8** and **8.73–8.76** were reported [14].

1.2.3. *Partition Coefficient:*

The n-octanol/pH 7.0 buffered solution partition coefficient (log P) of ciprofloxacin was reported as 0.94 at 37° C and 1.70 at 25°C and pH 7.2, [14, 15].

1.2.4. *Solubility:*

As other fluoroquinolones ciprofloxacin is zwitter-ionic and exhibits a ‘‘U’’ shaped pH-solubility profile, with high solubility at pH values below 5 and above 10, and minimum solubility near the isoelectric point, which is close to neutral **Fig.2**(see below). The USP reports the aqueous un-buffered solubility of ciprofloxacin hydrochloride, which has a final acidic pH [9]. The solubility in phosphate buffer was informed at pH 6.8 and 7.5 and 37°C [16]. Several pH-solubility profiles of ciprofloxacin hydrochloride have been reported at 25°C [17,18]. The data and the corresponding dose solubility ratios (D/ S) are summarized in **Table 1** for the usual range of tablet strengths (see below). The intrinsic solubility of ciprofloxacin, that is, the solubility of the neutral form, also has been determined at different temperatures [13, 19].

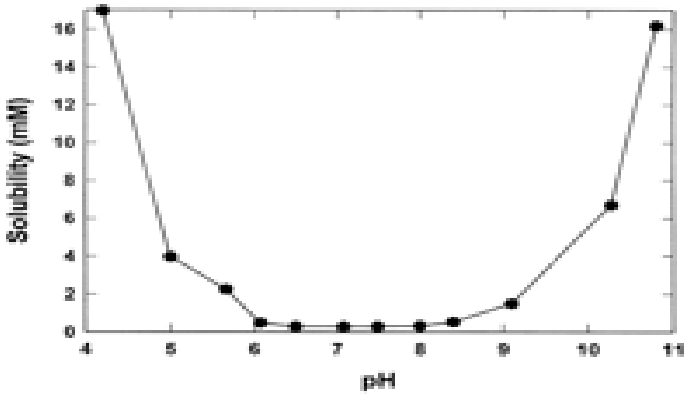


Figure 2. Solubility of ciprofloxacin in aqueous solutions buffered in the pH range between 4 and 11

Table 1. *Solubility of Ciprofloxacin Hydrochloride and Corresponding D/S Ratios for Three Usual Tablet Strengths*

				D/S Ratio (mL)		
Ph	°C	Medium	Solubility (mg/mL)	250 mg	500 mg	750 mg
3–4.5	25	Water	10–30	8–25	17–50	25–75
4.5	25	Water + NaOH to indicated pH	3.5	71	143	214
6.8	25	Water + NaOH to indicated pH	0.0813	3075	6150	9225
6.8	37	Phosphate buffer	0.17	1470	2941	4412
6.84	25	Water + NaOH to indicated pH	0.088	2840	5682	8523
7.5	25	Water + NaOH to indicated pH	0.0702	3536	7072	10,608
7.5	37	Phosphate buffer	0.16	1562	3125	4687

1.3 .Physical properties:-

1.3.1. *Color:*

Faint to light yellow crystalline powder [20]

1.3.2. *Melting point:*

The melting point at which ciprofloxacin is decomposes at 225-257°C [21]

1.3.3. *Solubility:*

Soluble in dilute (0.1N) hydrochloric acid; practically insoluble in ethanol [20]
In water, 30 mg/mL at 20 °C [22]

1.3.4. *Stability:*

Ciprofloxacin hydrochloride ophthalmic solution should be stored in tight, light-resistant containers at 2-25 °C. When stored as directed, the commercially available ophthalmic solution has an expiration date of 24 months following the date of manufacture. Ciprofloxacin hydrochloride ophthalmic ointment should be stored at 2-25 °C. Ciprofloxacin hydrochloride and hydrocortisone otic suspension should be stored in light-resistant containers below 25 °C; freezing should be avoided. Ciprofloxacin hydrochloride and dexamethasone otic suspension should be stored at 15-30 °C and protected from light; freezing should be avoided [23].

Ciprofloxacin hydrochloride tablets should be stored in tight containers at a temperature < 30 °C. The drug should be protected from intense UV light. Ciprofloxacin microcapsules for oral suspension & the diluent provided by the manufacturer should be stored at <25 °C & protected from freezing. Following mixture with the diluent, ciprofloxacin oral suspension should be stored at <30 °C & protected from freezing, & is stable for 14 days when stored at room temperature or in a refrigerator [24].

The compatibility of 10 mg/ml ciprofloxacin injection in 0.9% sodium chloride and 5% dextrose sol. were /mixed/ with other injectable drugs, including amikacin sulfate, aminophylline,clindiamycin phosphate, gentamicin phosphate, tobramycin sulfate and metronidazole sol. were stored for up to 48 hr at room temperature and under refrigeration. 8 hr. after amikacin was mixed with ciprofloxacin in sodium chloride sol. and refrigerated; the drug conc. was 89% of the original. Admixtures of the precipitate formed immediately whenever ciprofloxacin was mixed with aminophylline or clindamycin. Results indicate/ that ciprofloxacin was in-compatible with aminophylline and clindamycin, and that its compatibility with amikacin depended upon the vehicle and storage temperature [25].

The physical and chemical compatibilities of ciprofloxacin lactate infusion with other commonly used IV admin. Drugs /was investigated, only heparin, furosemide and teicoplanin were found to be incompatible with ciprofloxacin, Ciprofloxacin lactate [26].

1.4. *Dosage Form:-* shown in the **table 2.**

Table 2: Dosage form of ciprofloxacin			
No.	Dosage Form	Trade Name	Conc.
1	Vial	Ciprofloxacin	200(10mg/ml) & 400mg/40ml
2	Coated Tab.	Tyflox	250 & 500 mg
3	Eye Drop	Ciloxan	0.3%
4	Eye Ointment	Ciloxan	0.3%
5	Eye Solution	Ciprofloxacin	0.3%
6	Oral Suspension	Cipro 5%	10g/100ml & 5g/100ml
7	Otic Solution	Ciprofloxacin	0.2%
8	Otic Suspension "in companion with Hydro."	Cipro. HC Otic	Cipro 0.2% &Hydro. 0.1%

1.5. *Pharmacokinetics* [27, 28, 29]*:-*

1.5.1 .*Absorption:*

Ciprofloxacin given as an oral tablet is rapidly and well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70% with no substantial loss by first pass metabolism. Ciprofloxacin maximum serum concentrations and area under the curve are shown in the **Table 3** for the 250 mg to 1000 mg dose range.

Table 3: Maximum Serum Conc. And Area Under The Curve Of Ciprofloxacin		
Dose (mg)	Maximum serum Conc. Of ciprofloxacin (mg./mL)	Area under the curve (AUC), (mg*hr./mL)
250	1.2	4.8
500	2.4	11.6
750	4.3	20.2
1000	5.4	30.8

Maximum serum concentrations are attained 1 to 2 hours after oral dosing. Mean concentrations 12 hours after dosing with 250, 500, or 750 mg are 0.1, 0.2, and 0.4 μg/mL, respectively. The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Serum concentrations increase proportionately with doses up to 1000 mg. A 500 mg oral dose given every 12 hours has been shown to produce an area under the serum concentration time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours. A 750 mg oral dose given every 12 hours has been shown to produce an AUC at steady-state equivalent to that produced by an intravenous infusion of 400 mg given over 60 minutes every 8 hours. A 750 mg oral dose results in a C_{max} similar to that observed with a 400 mg I.V. dose. A 250 mg oral dose given every 12 hours produces an AUC equivalent to that produced by an infusion of 200 mg ciprofloxacin given every 12 hours.

1.5.2. *Distribution:*

The binding of ciprofloxacin to serum proteins is 20 to 40% which is not likely to be high enough to cause significant protein binding interactions with other drugs. After oral administration, ciprofloxacin is widely distributed throughout the body. Tissue concentrations often exceed serum concentrations in both men and women, particularly in genital tissue including the prostate. Ciprofloxacin is present in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses, sputum, skin blister fluid, lymph, peritoneal fluid, bile, and prostatic secretions. Ciprofloxacin has also been detected in lung, skin, fat, muscle, cartilage, and bone. The drug diffuses into the cerebrospinal fluid (CSF); however, CSF concentrations are generally less than 10% of peak serum concentrations. Low levels of the drug have been detected in the aqueous and vitreous humors of the eye.

1.5.3. *Metabolism:*

Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin.

1.5.4. *Excretion:*

The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. After a 250 mg oral dose, urine concentrations of ciprofloxacin usually exceed 200 µg/mL during the first two hours and are approximately 30 µg/mL at 8 to 12 hours after dosing. The urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately 300 mL/minute, exceeds the normal glomerular filtration rate of 120 mL/minute. Thus, active tubular secretion would seem to play a significant role in its elimination. Co-administration of probenecid with ciprofloxacin results in about a 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its concentration in the systemic circulation. Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after oral dosing, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1 to 2% of the dose is recovered from the bile in the form of metabolites. Approximately 20 to 35% of an oral dose is recovered from the feces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination. With oral administration, a 500 mg dose, given as 10 mL of the 5% CIPRO Suspension (containing 250 mg ciprofloxacin/5mL) is bioequivalent to the 500 mg tablet. A 10 mL volume of the 5% CIPRO Suspension (containing 250 mg ciprofloxacin/5mL) is bioequivalent to a 5 mL volume of the 10% CIPRO Suspension (containing 500 mg ciprofloxacin/5mL).

1.5.5. *Drug-drug Interactions:*

When CIPRO Tablet is given concomitantly with food, there is a delay in the absorption of the drug, resulting in peak concentrations that occur closer to 2 hours after dosing rather than 1 hour whereas there is no delay observed when CIPRO Suspension is given with food. The overall absorption of CIPRO Tablet or CIPRO Suspension, however, is not substantially affected. The pharmacokinetics of ciprofloxacin given as the suspension are also not affected by food. Concurrent administration of antacids containing magnesium hydroxide or

aluminum hydroxide may reduce the bioavailability of ciprofloxacin by as much as 90%.

Concomitant administration of ciprofloxacin with theophylline decreases the clearance of theophylline resulting in elevated serum theophylline levels and increased risk of a patient developing CNS or other adverse reactions. Ciprofloxacin also decreases caffeine clearance and inhibits the formation of paraxanthine after caffeine administration.

Concurrent administration the ciprofloxacin, with multivalent cation-containing products such as magnesium/aluminum antacids, sucralfate, Videx® (didanosine) chewable/buffered tablets or pediatric powder, other highly buffered drugs, or products containing calcium, iron, or zinc may substantially decrease its absorption, resulting in serum and urine levels considerably lower than desired.

The concomitant administration of ciprofloxacin with the sulfonylurea glyburide has, on rare occasions, resulted in severe hypoglycemia.

Ciprofloxacin, have been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.

Ciprofloxacin, have been reported to enhance the effects of the oral anticoagulant warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored. Probenecid interferes with renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly

1.6. Aim of Study:-

The aim of study is to comparatively evaluate and assess the quality of different brands of ciprofloxacin 500 mg tablets commercially available tablet in Iraqi market.

CHAPTER TWO
EXPERIMENTS

2. Experiments

2.1. Material and requirement:

The materials used in the research are shown in table (4).

Table 4: *Materials Used In The evaluation ciprofloxacin tablets.*

No.	Materials	Supplier
1	CiproHEXAL	Salutos Pharma GmbH, Germany
2	Ciprofloxacin	Bristol Laboratories Ltd.
3	Cipropharm	Ph. International Co. Amman- Jordan
4	SIFLOKS	Zentiva, Kirkiareli - TURKEY
5	CIPROXENE	Medical Bahri Company, Syria
6	Ciprofloxacin powder	**Lap.medico,India**
7	Sodium phosphate monobasic	**Qualikems**
8	sodium phosphate dibasic	**Qualikems**
9	hydrochloric acid (Hcl)	SDFCL, s d line-CHEM limiTEd

Table 5: Batch No. , Mfg. Date& Exp. Date *of the five ciprofloxacin companies*

	Batch No.	Mfg. Date	Exp. Date
CF1"Hexal"	EC 9936	02/2014	02/2017
CF 2"Bristal"	AZR025001		09/2018
CF 3"Pharma I."	15179	04/2015	04/2018
CF 4"Zentiva"	008053	06/2013	06/2017
CF 5 "MB¥C"	115	10/2015	09/2018

2.2. Instruments:

The instruments used in the study are shown in table (6).

No.	Instruments	Manufacturer
1	Sensitive Balance	Germany
2	Vernier Caliper	**China**
3	YD-1 Hardness	China
4	UV-VIS Spectrophotometer	Germany
5	Disintegration Tester	China
6	Friability Tester	China
7	Dissolution Tester	China

Table 6: *Instruments Used In The evaluation ciprofloxacin tablets.*

2.3. Methods

2.3.1. Method used for the estimation of Calibration curve of ciprofloxacin Hcl in 0.1 N HCl [30]*:*

A spectrophotometric method based on the measurement of absorbance at 276 nm in 0.1 N Hcl was used in the present study for the estimation of ciprofloxacin Hcl

Materials:-

1. Ciprofloxacin Hcl **2.** Hydrochloric acid

Standard solution:

10 mg of ciprofloxacin Hcl was dissolved in 0.1 N Hcl in 100 ml of volumetric flask and the solution was made up to volume with 0.1 N Hcl.

Procedure:

The standard solution of ciprofloxacin Hcl was subsequently diluted with **0.1 N Hcl** to obtain a series of dilutions containing **1, 2, 3, 4 and 5 ml** of ciprofloxacin Hcl in **0.1mg/ ml** solution.

Conc. After Dilution:-

1. 0.1(mg/ml) × 1 ml = Conc. (mg/ml) × 50 ml => Conc. = 0.002 mg/ml

2. 0.1(mg/ml) × 2 ml = Conc. (mg/ml) × 50 ml => Conc. = 0.004 mg/ml

3. 0.1(mg/ml) × 3 ml = Conc. (mg/ml) × 50 ml => Conc. = 0.006 mg/ml

4. 0.1(mg/ml) × 4 ml = Conc. (mg/ml) × 50 ml => Conc. = 0.008 mg/ml

5. 0.1(mg/ml) × 5 ml = Conc. (mg/ml) × 105 ml => Conc. = 0.005 mg/ml

2.3.2. Method used for estimation the calibration curve of ciprofloxacin Hcl in buffer phosphate (PH 6.8) at 37 °C [30]*:-*

A spectrophotometric method based on the measurement of absorbance at 276 nm in 6.8 PH of buffer phosphate was used in the present study for the estimation of ciprofloxacin HCl.

Materials:-

1. Ciprofloxacin Hcl

2. Buffer Phosphate " Sodium phosphate monobasic ($NaH_2 PO_4 .2H_2 O$), sodium phosphate dibasic ($Na_2 HPO_4$)"

Preparation of Buffer Phosphate:-

Dissolve 2 g of Sodium phosphate monobasic ($NaH_2 PO_4 .2H_2 O$) in 1000 ml of distilled water, 2 g of sodium phosphate dibasic ($Na_2 HPO_4$) in 1000 ml of distilled water

Then, we mix these two solutions (250 ml of "$Na_2 HPO4$" with 650 ml of $NaH_2 PO_4 .2H_2 O$) to obtain Buffer Phosphate has PH 6.8

Standard solution:

10 mg of ciprofloxacin Hcl was dissolved in 100 ml of 6.8 PH Buffer Phosphate the solution was made up to volume in volumetric flask.

Procedure:

The standard solution of ciprofloxacin Hcl was subsequently diluted with **Buffer Phosphate "6.8 PH"** to obtain a series of dilutions containing **1, 2, 3, 4 and 5 ml** of ciprofloxacin Hcl in **0.1 mg/ ml** solution

Conc. After Dilution:-

1. 0.1(mg/ml) × 1 ml = Conc. (mg/ml) × 35 ml => Conc. = 0.003 mg/ml

2. 0.1(mg/ml) × 2 ml = Conc. (mg/ml) × 35ml => Conc. = 0.006 mg/ml

3. 0.1(mg/ml) × 3 ml = Conc. (mg/ml) × 35ml => Conc. = 0.009 mg/ml

4. 0.1(mg/ml) × 4 ml = Conc. (mg/ml) × 35ml => Conc. = 0.011 mg/ml

5. 0.1(mg/ml) × 5 ml = Conc. (mg/ml) × 40 ml => Conc. = 0.013 mg/ml

2.4. Evaluation ciprofloxacin tablets

2.4.1. Weight Variation:-

To ensure the consistency of dosage units, each unit in a batch should have drug substance content within a narrow range around the label claim. In weight variation test, measurement of contents is done by estimation of contents based on weight. If it is used correctly, this WV test can be used to measure content uniformity (CU) (USP) [9]. There are some conditions in which the weight difference can determine the percentage difference in the API in the individual dosage units. Hence this WV test can be useful in the quality control of drug production [30, 31].

Requirement:

1- Five brands of ciprofloxacin tablets.

2- Sensitive Balance **Fig.3**.

Fig.3: Sensitive Balance

Procedure:

1.10 tablets from each of five brands of ciprofloxacin tablets are previously selected at random were weighed.

2. Tablets were weighed individually and the average weight was determined.

3. The percentage of deviation of its weight from the average weight was determined for each tablet.

4. The deviation if individual weight from the average weight should not exceed the limits given below.

Average weight of Tablet	Deviation %	Number Of Tablets
More Than 250mg	± 5%	Maximum 18 Minimum 2

Average weigh = Total weight/ No. of Sample

Deviation **(D)** = | tablet weight – average weight |

D % = (D / average weight) *100

2.4.*2. Thickness and diameter*:-

Tablet thickness is important for tablet packaging, very thick tablet affect packaging either in blisters or plastic container. The tablet thickness is determined by diameter of the die, the amount of fill permitted to enter the die and the force pressure applied during compression [32].

Requirement:

1- Five brands of ciprofloxacin tablets.
2- Vernier calipers **Fig.4**.

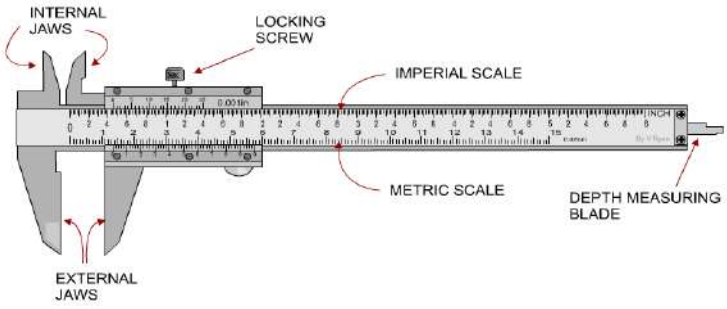


Fig.4: Vernier calipers.

Procedure:

1. Ten tablets from each of five available brands of ciprofloxacin tablets were selected and were tested for diameter, thickness.
2. The values of each tablet on their diameter, thickness are recorded.
3. The deviation of tablets' diameter and thickness are calculated. The deviation of individual unit from the mean diameter should not exceed ± 5% for tablets with diameter of less than 12.5 and ± 3% for diameter of 12.5 mm or more.

2.4.3. *Hardness Test:-*

The resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. **Tablet hardness** is defined as the load required crushing or fracture a tablet placed on its edge. Sometime it is also termed as tablet crushing strength. The hardness test was performed using YD-1 type hardness tester [33].

Requirement:

1- Five brands of ciprofloxacin tablets.
2- Hardness Tester **Fig.5**.

Fig.5: YD-1 Hardness Tester.

Procedure:

The standard method used for tablet hardness testing was compression testing. For each brand, the hardness of **3 tablets** was determined by using hardness tester. The tablet was placed between two jaws that crush the tablet. The machine measured the force applied to the tablet and the crushing strength that just causes the tablet to break was recorded.

2.4.4. *Friability of tablets:-*

Friability (the condition of being Friable) testing is a method, which is employed to determine physical strength of tablets upon exposure to mechanical shock and attrition. In simple words, friability test tells how much mechanical stress tablets are able to withstand during their manufacturing, distribution and handling by the customer. Throughout pharmaceutical industry, friability testing has become an accepted technology and the instrument used in to perform this process is called Friabilator or Friability Tester [33].

Requirements:

1- Five brands of ciprofloxacin tablets.
2- Sensitive Balance.
3- Friabilator tester **Fig.6.**

Fig.6: CS-2 friabilator tester.

Procedure:

1. Take 10 tablets from each of five available brands of ciprofloxacin tablets, get them cleaned the dust using a cloth, weight them a put in a friability tester.
2. Turn on the apparatus by pressing the knob “mains” a set the rotation speed to 25 rpm.
3. Start the rotation of the device by pressing “start/stop” button.
4. End the rotation after 4 minutes by re-pressing “start/stop” button.
5. 10 tabs are taken out of the drum and cleaned with a cloth, then weighed before and after the test, then calculated the **Friability %** , the weight variation must not be less than 0.5 to 1.0 % for an conventional tablet.

Friability % = (initial weight- final weight) Initial weight

2.4.5. *Content uniformity test:-*

Content uniformity test is a pharmaceutical analysis parameter for the quality control of tablets. Multiple tablets are selected at random and a suitable analytical method is applied to ensure that every dosage form contains equal amount of drug substance i.e. active pharmaceutical ingredient within a batch.

Mainly it is used for testing the consistency of amount of active pharmaceutical ingredient within individual units of tablets [34,35].

Requirements:

1- Five brands of ciprofloxacin tablets.
2- Solution of 0.1 mg/ml from Hcl.
3- UV-VIS Spectrophotometric apparatus **Fig.7**.

Fig.7: UV-VIS Spectrophotometric apparatus

Procedure:

1. Take tablet from each of five available brands of ciprofloxacin tablets; crush the tablet to become powder.
2. Added the powder in beaker contains 1000 ml solution from 0.1 mg/ml of Hcl.
3. Take sample from the solution and measuring the absorbance by UV-spectrophotometric method.
4. The conc. Of the sample obtain by using the equation of stander curve "**y = 113.4x – 0.0028**", after using the value of absorbance that's obtain from UV-spectrophotometric apparatus, used in known the Content of drug in each tablet.

2.4.6. *Disintegration test:-*

Is a method to evaluated the rate of disintegration of solid dosage form, **Disintegration test** define as the state in which no residue of the unit under test remain on the screen of the apparatus or, if a residue remains, it consists of fragments of disintegrated parts such as insoluble coating of the tablet.

Requirements:

1- Five brands of ciprofloxacin tablets.

2- Solutions:

- Sol. Of 0.1 N,
- Sol. Of 6.8 PH of PO_4

3- Disintegration tester **Fig.8**.

Fig.8: BJ-2 Disintegration tester

Method:

The instrument contain six tube placed in beaker, which it contain solution and this beaker placed in water bath which was maintained at 37±5°C, Three from each of Five available brands of ciprofloxacin tablets were placed in tube of specified dimensions (one tablet for each tube) the tubes were raised and lowered in solution by specific and same procedure and we took the time when all tablets dissolved in it Maximum time for film coated tablet to disintegrate is (30 min) according to (USP [9]).

2.4.7. *Dissolution test:-*

Dissolution is defined as the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition. It's considered as one of the most important quality control tests performed on pharmaceutical dosage forms. Dissolution behavior of drugs has a significant effect on their pharmacological activity.

Requirements:

1- Five brands of ciprofloxacin tablets.

2- Solutions:

- Sol. Of 0.1 N,
- Sol. Of 6.8 PH of PO_4

3- Dissolution apparatus **Fig.9**.

Fig.9: RC-3Dissolution tester

Method:

1. Paddle method was applied.
2. Prepare 900 ml of (**1-** Sol. Of 0.1 N Hcl, **2-** Sol. Of 6.8 PH of PO_4) was used as dissolution media and added to each of three vessels. The water-bath temperature was fixed & confirmed to be 37±0.5 °C before starting the experiment.
3. The apparatus was then a started and after that when we starting rotation at 100 rpm for 30min, one tab. from same code were placed in the vessel immediately and allowed to sink to the bottom.
4. Withdraw 5 ml samples and replace it with dissolution fluid every 5 min. for 30 minutes and every 10 min. for another 30 minutes and transfer them to tubes and labeled, take 1ml from these 5ml and dilute it to 100 ml using dissolution media.

5. Measure the absorbance of the solution by using UV-spectrophotometric apparatus and use it to calculate the concentration of ciprofloxacin.
6. Plot a graph of the concentration of ciprofloxacin in solution against the time of the sample was taken [36,37].

CHAPTER THREE
RESULT AND DISCUSSION

3. Result and Discussion

3.1. *Calibration curve of ciprofloxacin Hcl in 0.1 N Hcl:-*

The absorbance of these solutions was measured at 276 nm using UV-VIS spectrophotometer against blank. The concentrations of ciprofloxacin Hcl and the corresponding absorbance are given in the **Table 7.** The absorbance were plotted against concentration of ciprofloxacin Hcl as shown in **Fig.10**

Table 7: *Absorbance and Concentration of ciprofloxacin Hcl in 0.1 N Hcl*

No. of sample	Absorbance	Ciprofloxacin Hcl concentration (mg/ml)
1	0	0
2	0.224	0.002
3	0.445	0.004
4	0.699	0.006
5	0.900	0.008
6	0.55	0.005

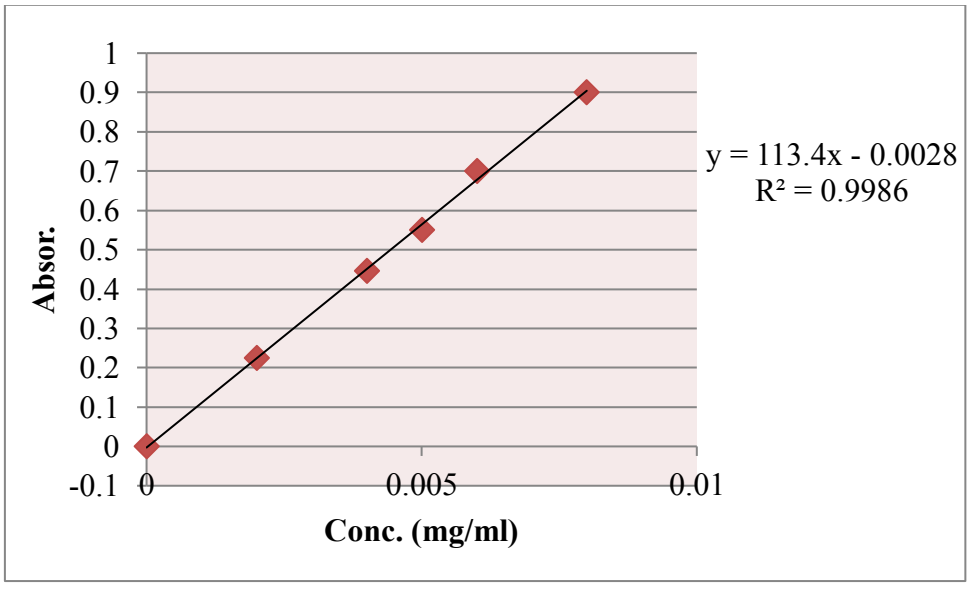


Fig. 10: *Calibration curve of* ***ciprofloxacin Hcl*** *in* ***0.1 N Hcl***

3.2. *Calibration curve of ciprofloxacin Hcl in buffer phosphate at PH 6.8:-*

The absorbance of these solutions was measured at 276 nm using UV-VIS spectrophotometer against blank. The concentrations of ciprofloxacin Hcl and the corresponding absorbance are given in the **Table** 8 the absorbance were plotted against concentration of ciprofloxacin HCl as shown in **Fig.11**

Table 8 : *Absorbance and Concentration of ciprofloxacin Hcl in Buffer Phosphate at 6.8 PH*

No. of sample	Absorbance	Ciprofloxacin Hcl concentration (mg/ml)
1	0	0
2	0.227	0.003
3	0.453	0.006
4	0.677	0.009
5	0.941	0.011
6	0.974	0.013

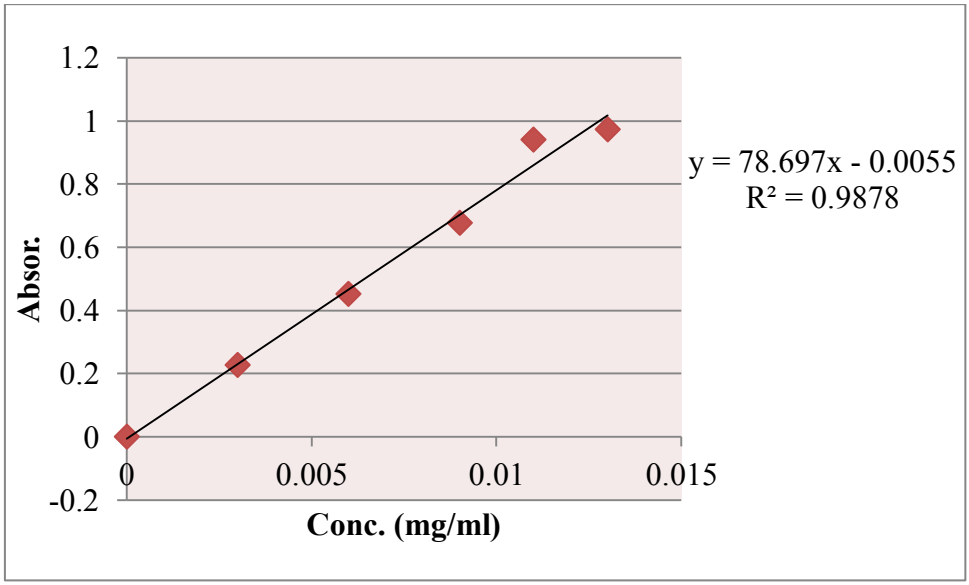


Fig.11: *Calibration curve of* ***ciprofloxacin Hcl*** *in* ***Buffer Phosphate*** *(PH 6.8 at 37° C)*

3.3. Evaluation of ciprofloxacin tablet

3.3.1. Weight Variation test:-

In order to ensure good manufacturing practices (GMP), appropriate size of the tablets and the content uniformity of the formulation weight variation test was carried out according to the procedure discussed in the experimental section. The United States Pharmacopoeia (USP) provides criteria for tablet weight variation of intact dosage units [9]. As can be noted in the **Table 9,** all brands complied with the specification for uniformity of weight which states that, weights of not more than 2 tablets should not differ from the average weight by more than 5 % and none deviates by more than twice that percentage.

The Values that result from ***Weight Variation test*** are shown in table (9).

Table 9: *Weight variation of five brands of ciprofloxacin tablets.*

No. Of sample	**CF1** "hexal"		**CF2** "bristal"		**CF3**"pharma. I"		**CF4** "Zentiva"		**CF5** "MB&C"	
	T.W	D%	T.W	D%	T.W	D%	T.W	D%	T.W	D%
1	0.863	0.208	0.766	1.238	0.252	3.576	0.795	3.207	0.754	4.083
2	0.864	0.093	0.765	1.367	0.251	3.165	0.781	1.389	0.784	0.267
3	0.868	0.370	0.777	0.181	0.241	0.945	0.773	0.351	0.778	1.030
4	0.868	0.370	0.78	0.567	0.237	2.589	0.772	0.221	0.795	1.132
5	0.86	0.555	0.758	2.269	0.264	8.508	0.765	0.688	0.796	1.259
6	0.862	0.324	0.773	0.335	0.226	7.111	0.753	2.246	0.798	1.514
7	0.865	0.023	0.792	2.114	0.242	0.534	0.775	0.610	0.778	1.030
8	0.863	0.208	0.777	0.181	0.222	8.755	0.761	1.207	0.795	1.132
9	0.872	0.833	0.792	2.114	0.249	2.343	0.765	0.688	0.792	0.751
10	0.863	0.208	0.776	0.052	0.249	2.343	0.763	0.948	0.791	0.623
Total	8.648		7.756		2.433		7.703		7.861	
Average	0.8648		0.7756		0.2433		0.7703		0.7861	

T.W: Tablet Weight, ***D%***: Deviation Percentage

3.3.2. *Hardness Test:-*

The experiment shows all the tablets hardness uniform in range of 12.3 kg to >20 kg. If the tablets are too hard" as in ***CF3& CF5***" it may not disintegrate in required period of time and if it too soft, it may break during the handling of manufacturing, or packaging process. The hardness of tablets is important to withstand the mechanical shocks

during the tablets manufacturing, packaging and transport. Averagely, all the tablets are strong enough to withstand the pressure applied.

The Values that result from ***Hardness Test*** are shown in table (10).

Table 10: *Hardness of five brands of ciprofloxacin tablets.*

No. of tab.	CF1 "hexal"	CF2 "bristal"	CF3 "pharma. I"	CF4 "Zentiva"	CF5 "MB&C"
1	18.3	12.6	>20	14.7	>20
2	20.4	12.3	>20	13.3	>20
3	20.4	12	>20	15.8	>20
Mean	19.7 kg	12.3 kg	>20 kg	14.6 kg	>20 kg

3.3.3. *Friability test:-*

The United State Pharmacopoeia states that the friability value of tablets should be less than 1% and as such all the brands of ciprofloxacin Hcl tablets passed this Friability specification (USP) [9]. Friability test can be performed in order to monitor the resistance of tablets to stresses like mechanical shocks and abrasion during the manufacturing, packing and transportation processes. Such stresses can lead to capping, chipping, abrasion or even breakage of the tablets. It is therefore important that the tablet is formulated to withstand such stress without damage. Weight values are presented in the **Table 11**. All the brands of ciprofloxacin Hcl were coated. They showed 0.0 % (Table 11) loss of weight after the friability test.

The Values that result from ***friability test*** are shown in table (11).

Table 11: *Friability values of five brands of ciprofloxacin* ***tablets.***

Weight of tablet in "g"		CF1 "hexal"	CF2 "bristal"	CF3 "pharma. I"	CF4 "Zentiva"	CF5 "MB&C"
	Before	8.58	7.78	7.83	7.67	7.92
	After	8.58	7.78	7.83	7.67	7.92
Friability %		0.0 %	0.0 %	0.0 %	0.0 %	0.0 %

3.3.4. *Thickness and diameter test*:-

In order to investigate the size uniformity and shape, diameters and thickness Test of tablets of various formulations were measured by using Vernier calipers. The results are shown in the **Table 12**. From the Table it can be mentioned here that the average diameter is 17.09 to 20.2 mm and the average value of thickness is 5.3 to 6.3 mm respectively. These results for all the brands of ciprofloxacin Hcl are affected by ***two parameters:*** (1) the Compression pressure, and (2) the flim coating of the tablet.

The Values that result from ***Thickness and diameter test*** are shown in table (12).

Table 12: *thickness and diameter of five brands of ciprofloxacin* tablets

No. of Sample	CF1 ”hexal”		CF2 ”bristal”		CF3 ”pharma. I”		CF4 ”Zentiva”		CF5 ”MB&C”	
	D	T	D	T	D	T	D	T	D	T
1	19.20	6.42	18.79	5.87	20.19	5.90	20.19	5.05	17.11	6.03
2	19.20	6.42	18.78	5.87	20.19	5.89	20.17	5.11	17.11	6.03
3	19.20	6.26	18.78	5.89	20.20	5.89	20.14	5.14	17.11	5.98
4	19.20	6.26	18.78	5.89	20.18	5.88	20.13	5.95	17.10	6.06
5	19.19	6.27	18.78	5.89	20.20	5.90	20.13	5.95	17.09	6.02
6	19.19	6.27	18.77	5.81	20.20	5.90	20.11	5.14	17.09	6.12
7	19.19	6.27	18.77	5.81	20.20	5.91	20.11	5.14	17.09	6.06
8	19.17	6.23	18.78	5.80	20.22	5.90	20.11	5.12	17.08	6.00
9	19.17	6.25	18.78	5.80	20.20	5.91	20.11	5.12	17.08	6.06
10	19.17	6.25	18.73	5.78	20.20	5.90	20.11	5.16	17.08	6.06

Thickness and diameter test: (in millimeters=mm)

3.3.5. *Content uniformity test:-*

Content uniformity test was developed in vitro to show: that the release of the drug from the tablet is as close as possible to 100%, the results are shown in the **Table 13.**the accepted amount dissolved in 30min is not less than 80% in USP [9].

The Values that result from ***Content uniformity test*** are shown in table (13).

Table 13: *Conc. and Content % of five brands of ciprofloxacin*		
Sample No.	Conc. (mg)	Content %
CF1"hexal"	499	99.8
CF2"bristal"	497	99.4
CF3"pharma. I"	496	99.2
CF4"Zentiva"	500	100
CF5"MB&C"	496	99.2

3.3.6. *Disintegration test:-*

From this test, in average, a ***ciprofloxacin*** "***Bristal***" tablet would need < 1 min while ***CIPROXENE*** "***Pharma I.***" need at last 20 min. to be fully disintegrate, the results are shown in the **Table 14.** This different in disintegration time may be occur as a result the presence of additional ingredients in the compassion of tablets, ***ciprofloxacin*** "***Bristal***", ***SIFLOKS "Zentiva" & Cipropham*** "***Pharma I.***" content super disintegrate as compare with the ***CIPROXENE"MB¥C"*** that content little amount of disintegrate agent and the different in compression pressure during the manufacture proses can also produce this different. The standard set for this experiment was to have the tablet disintegrate not more than one hour in water medium. So, all five brands of ciprofloxacin tablets have succeeded this test. Multiple parameters to really imitate our body system upon drug intake, some of these parameters include the different ***pH*** and ***motility*** in different parts of gastrointestinal tract. The disintegration time in both media {acidic "Hcl" shown in table (14) & basic "buffer phosphate" shown in table (15)} has approximately the same mints to disintegrate completely. This result is not guarantee to be the same as in an actual person. It might be lot faster since the motility of human GI tract was quite vigorous.

The Values that result from ***Disintegration test*** in Hcl "acidic media" are shown in table (14).

Table 14: *Disintegration time of five brands of ciprofloxacin tablets in 0.1 N of Hcl at 37°C.*

Sample	Disintegration time
CF 1"hexal"	12 min.
CF 2"bristal"	40 sec.
CF 3"pharma. I"	5 min.
CF 4"Zentiva"	2 min. & 53 sec.
CF 5"MB&C"	18 min. & 30 sec.

The Values that result from ***Disintegration test*** in *Buffer Phosphate "6.8 PH* " basic media" are shown in table (15).

Table 15: *Disintegration time of five brands of ciprofloxacin tablets in Buffer Phosphate "6.8 PH at 37°C".*

Sample	Disintegration time
CF 1"hexal"	12 min.
CF 2"bristal"	55 sec.
CF 3"pharma. I"	3min. & 59 sec.
CF 4"Zentiva"	2 min. & 5 sec.
CF 5"MB&C"	20 min. & 11 sec.

3.3.7. *Dissolution test:-*

Figures 12 & 13 shows the dissolution profiles of the selected tablets of ciprofloxacin in 0.1 N Hcl & buffer phosphate sol. at PH 6.8, respectively. In all cases, the amount of ciprofloxacin released in 20 minutes was not less than 80% of the labeled amount. This is in accordance with the pharmacopoeia requirements where it is stated that at least 80% of the ingredients are to be released within 30 minutes of dissolution. The only exceptions **CF5** "MB&C" was dissolve more slowly than the other companies, so that the effectiveness of its will be delay.

These results suggest that the formulation and/or the manufacturing process can affect the dissolution and thus the bioavailability of the drug product. Proper drug formulation will allow for the drug to reach its site

of absorption, the upper part of the GI tract (duodenum/jejunum) in a solution form.

The Values that result from ***dissolution test*** in Hcl "acidic media" are shown in table (14).

Table 16: Conc. *and* Dissolution Rate percent *of five brands of ciprofloxacin tablets in Hcl at 37*°C**.**

Time. of Sample	CF1 "hexal"		CF 2 "bristal"		CF3 "pharma. I"		CF 4 "Zentiva"		CF 5 "MB&C"	
	Conc.	D %	Conc.	D %	Conc.	D %	Conc.	D %	Conc.	D %
5 min.	65	13	330	66	248	49.6	416	83.2	48	9.6
10 min.	270	54	365	73	305	61	437	87.4	195	39
15 min.	386	77.2	394	78.8	418	83.6	469	93.8	256	51.2
20 min.	420	84	431	86.2	436	87.2	471	94.2	314	62.8
25 min.	464	92.8	445	89	455	91	481	96.2	389	77.8
30 min.	476	95.2	469	93.8	469	93.8	486	97.2	402	80.2
40 min.	495	99	471	94.2	487	97.4	490	98	475	95
50 min.			483	96.6	495	99	497	99.4	483	96.6
60 min.			487	97.4	500	100			491	98.2

D.R %:- Dissolution Rate percent. Conc.:- Concentration (mg/ml).

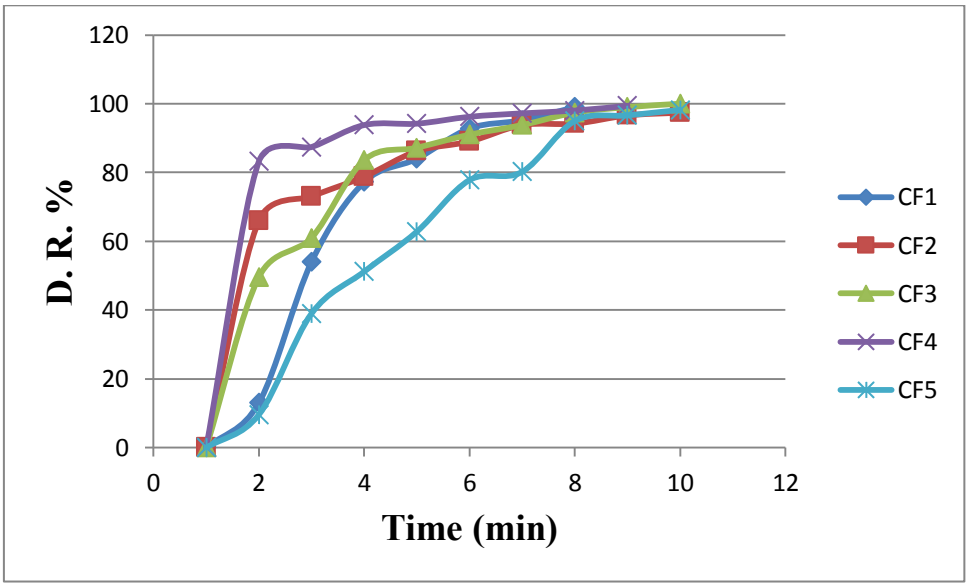


Fig.12: *Dissolution time in* ***Hcl at 37*** **°C**.

The Values that result from ***Dissolution test*** in *Buffer Phosphate "6.8 PH* " basic media" are shown in table (16).

Table 17: Conc. *and* Dissolution rate percent. *Of five brands of ciprofloxacin tablets in Buffer Phosphate "6.8 PH at 37°C".*

Time. of Sample	CF1 "hexal"		CF 2 "bristal"		CF3 "pharma. I"		CF 4 "Zentiva"		CF 5 "MB&C"	
	Conc.	D %	Conc.	D %	Conc.	D %	Conc.	D %	Conc.	D %
5 min.	65	13	473	94.6	366	73.2	417	83.4	74	14.8
10 min.	301	60.2	480	96	434	86.8	427	85,4	162	32.4
15 min.	335	67	493	98.6	445	89	461	92.2	255	51
20 min.	414	82.2	499	99.8	478	95.6	469	93.8	291	58.2
25 min.	449	89.8			485	97	484	96.8	297	59.4
30 min.	481	96.2			496	99.2	497	99.4	317	63.4
40 min.	494	98.8			498	99.6	507	101.4	321	64.2
50 min.	501	100.2							326	65.2
60 min.									346	69.2

D.R %:- Dissolution Rate percent, Conc.:- Concentration (mg/ml).

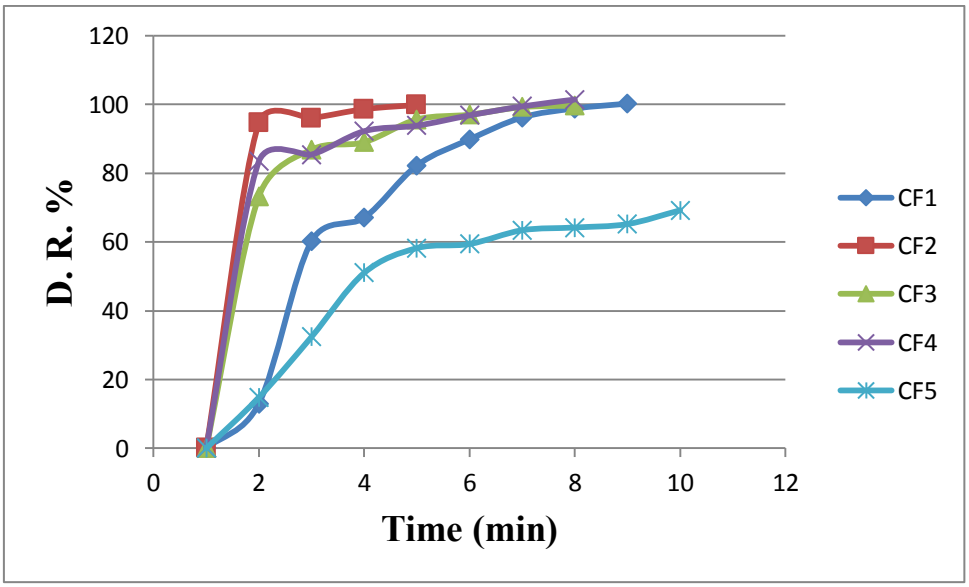


Fig.13: *Dissolution time in* ***Buffer Phosphate "6.8 PH at 37 °C".***

CHAPTER FOUR
CONCLUSION

Conclusion

All the tablets of five brands of ciprofloxacin displayed uniformity in terms of, weight variation ”not more than 2 tablets should not differ from the average weight by more than 5 %”, thickness and diameter met the acceptable range the pharmacopoeia (USP) [9]. They also met USP [9] standards in friability test as no any friable occur and the friability percentage for all brands are 0.0%. In hardness test the brands **CF2** and **CF4** met the acceptable range while **CF1**, **CF3** & **CF5** more than the range of the pharmacopoeia (USP) [9]. All the brands of ciprofloxacin tablet complied with the official specification for content uniformity as stipulated by the (USP) [9]. They also met USP [9] standards in disintegration test and dissolution test, with the exception of **CF5** that’s take time more than the other to disintegrate and so that, to dissolve. Therefore it can be concluded that all the brands of the ciprofloxacin HCl tested have uniform weight and also sufficient physical stability to maintain physical integrity over time and they will also be capable of withstanding the rigors of mechanical shocks encountered in its production, packaging, shipping and dispensing. Disintegration and dissolution test suggest that the product might sufficiently release in the GIT followed by proper absorption from the GIT and thus provide desired therapeutic activity to the patient.

CHAPTER FIVE
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REFERENCES

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الخلاصة

التقييم في المختبر من الخصائص الفيزيائية للمنتجات الصيدلانية يضمن جودتها وكذلك التوافر البيولوجي. سيبروفلوكساسين هكل، وهو مضاد حيوي يستخدم على نطاق واسع لعلاج أنواع مختلفة من الالتهابات البكتيرية، وقد تم اختياره لهذه الدراسة المقارنة في المختبر من شركة أدوية مختلفة. قارنت الدراسة الحالية توحيد المحتوى، تباين الوزن، الصلابة، القابلية للتفتيت، سمك، قطر، تفكك، قدرة حل خمس علامات تجارية من سيبروفلوكساسين أقراص هكل المصدرة إلى السوق العراقية لتأكيد ما إذا كانت تتبع المبادئ التوجيهية USP [9]. جميع العلامات التجارية الخمس من سيبروفلوكساسين حمض الهيدروكلوريك اختبار يمكن أن تلبي مواصفات USP لتوحيد المحتوى، تباين الوزن، صلابة، القابلية للتفجير، سمك، قطر، تفكك وحل [9]. متوسط صلابة من المنتجات يتراوح 15.5 كجم إلى> 20 كجم والتصلب 0.0٪. وقد أظهرت جميع العلامات التجارية تفكك الوقت 2 إلى 20 دقيقة في حين أظهرت 99.2 إلى 100٪ الإفراج عن العنصر النشط في غضون 50 إلى 60 دقيقة في اختبار الذوبان. هذا قد يؤكد امتصاص الدواء من الجهاز الهضمي للحصول على أفضل تأثير علاجي.