The effect of some excipients on the formulation of norfloxacin 400mg tablets

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Received 17/2/2004 ; accepted 5/8/2004

الخلاصة

دواء نورفلوكساسين مضاد حيوي قاتل للجراثيم واسع الطيف ضد سلالات الأحياء المجهرية الموجبة والسالبة لصبغة كرام, ويستخدم في علاج التهاب المجاري البولية الحادة والمزمنة، التهاب المثانة ، التهاب الحوض ،التهاب الاحليل ، التهاب الكلية ،التهاب البروستات ، الحمى التيفوئيدية ، التهاب المعدة والأمعاء الجرثومي . تحتوي الحبوب على ٤٠٠ ملغم من النورفلوكساسين وتزن ٧١٠ ملغم وقطر الحبة ١٢ ملم و هشاشيتها تقل عن ١% وسرعة ذوبان تقل عن عشرة دقائق. تم تحضيرعدة تركيبات منها طريقة العجن بالنشا وطريقة العجن بمادة البولي فاينيل بايروليدون كمادة رابطة والتى اعطت صيغة تركيبية مقبولة , كما تم دراسة تاثير المواد المفتتة على تحرر المادة الفعالة باستخدام مواد تقليدية مثل نشا الذرة, ومواد مفتتة سريعة مثل جلايكوليت الصوديوم النشوي والسيليلوزمجهري التبلور باستخدام طرق مختلفة من الاضافة , وجد ان مادة الكاربوكسي ميثيل سيليلوز كمادة رابطة اعطت صيغة مطابقة للدساتير , كذلك تم اجراء دراسة مقارنة بين الحبوب المحضرة , وحبوب النوروكساسين لشركة الرازي (سوريا)وحبوب النيوفلوكساسين لشركة الاسكندرية (مصر) . وجد إن سرعة تحرر الدواء من الصيغة التركيبية المختارة هي قريبة نوعا ما من سرعة تحرره من حبوب شركة الاسكندرية كما تمت دراسة استقرارية الحبو ب وتحديد تاريخ صلاحية المستحضر في درجات حرارية مختلفة٢٥م ,٤٠ م°, ٥٠ م° , ٧٠ م°,
ووجدت مساوية الى ٣, ٧ سنة - ٧, ٤ سنة- ٢,٤ سنة , واربعة اشهر على التوالي .

ABSTRACT

Norfloxacin a synthetic, broad-spectrum quinolone carboxylic acid derivative, active against Gram negative & Gram-positive bacteria. Used clinically in the treatment of acute and chronic urinary tract infections, cystitis ,urethritis, pyelonephritis, prostatitis& gastroenteritis . This study is concerned with the formulation of 400mg Norfloxacin coated tablets with 710mg weight, 12mm in diameter, less than 10minutes disintegration time, & less than 1 % friability. Many trials were made to prepare a satisfactory tablet formula for the drug by using wet-granulation method with various additives. It was found that Polyvinylpyrrolidone as a binder gives the most satisfactory tablets. The effect of disintegrants on drug release was also investigated on the selected formulas. Conventional corn starch, sodium starch glycolate and microcrystalline cellulose were tried as disintegrants. It was found that cross-caramellose (carboxymethylcellulose) was the best disintegrants. A comparative study on the physical properties of the prepared tablets with Noroxacine (Razi labs,Aleppo.Syria) , Neofloxacin (the Alexandria. Egypt), and Norfloxacin showed that the release of the drug from the selected formula was similar to that obtained from Alexandria. The stability of the prepared tablets was studied at 25°C, 40°C, 50°C, &70°C and the expiration date was calculated and found to be equal to 7.3 years, 4.7 years, and 2.4 years & four months respectively. Key word: Norfloxacin-Pharmacokinetics.Fluoroquinolone- Norfloxacin formulation.

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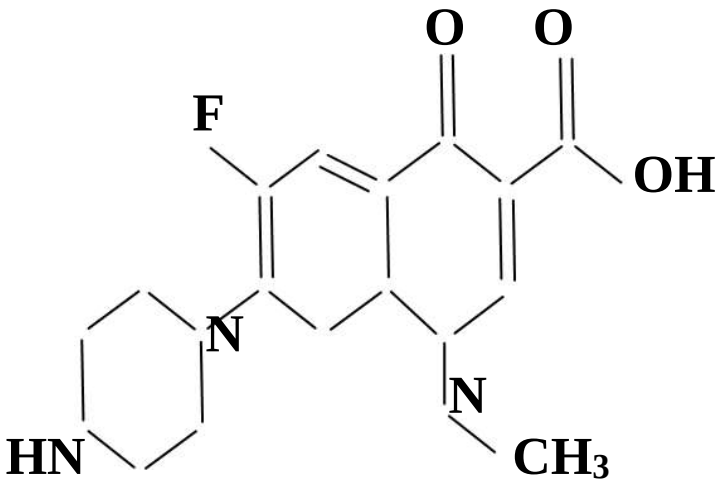
INTRODUCTION :

Quinolone carboxylic acids, a general chemical name is used to describe a group of synthetic agents originated by nalidixic acid and recently joined by many others chemically synthesized compounds with greatly improved activity, such as Norfloxacin[1], ciprofloxacin[2], Gatifloxacin[3], moxifloxacin and trovafloxacin, have all greatly improved the activity against Gram-positive cocci, particularly Pneumococci, and against anaerobes. They are not quite as active as ciprofloxacin against Enterobacteriaceae, and show no substantial improvements in activity against non-fermentative species. Clinafloxacin, gemifloxacin and sitafloxacin have even better activity against Gram-positive cocci and are as active as ciprofloxacin against most Gram-negatives bacteria.Trovafloxacin is more potent than other quinolone against Plasmodium falciparum[4,5,6]. Norfloxacin is active in vitro against Escerichia coli. & Citrobacter , Enterobacter , Klebsiella ,Pseudomonas aeruginosa, Proteus , Providencia , Serratia, Salmonella Shigella &Yersinia spp.[7,8,9,10,11] . Among Gram –positive aerobic bacteria Norfloxacin, is active against Staphylococci including penicillinase producing & non producing strains[12], other gram positive bacteria sensitive to Norfloxacin in vitro are Corynebacterium spp. &Listeria monocytogenes[13], They inhibit specifically the microbial enzyme, DNA gyrase, and is bactericidal. At the molecular level, three specific events are attributed to norfloxacin in E.coli :

1-Inhibition of ATP –dependent DNA supercoiling reaction catalyzed by DNA gyrase, 2-Inhibition of the relaxation of supercoiled DNA, 3-Promotion of double stranded DNA breakage[14,15] .

Noroxin, (Norfloxacin) is available in 400mg plain coated tablets & Chibroxin(Norfloxacin) ophthalmic solution is a synthetic broad spectrum antibacterial agent supplied by (ROBERTS PHARM) as a sterile isotonic solution for topical ophthalmic use , each ml contains 3mg Norfloxacin, also available as ointment. Pandy et all in 1999 published an article titled, development & evaluation of transdermal formulations containing metronidazol and norfloxacin for the treatment of burn wound[16, 17] .

Norfloxacin is 3- quinolone carboxxylic acid 1- ethyl –6- fluro-1, 4- dihydro –1-oxo-7-(1-piperazinyl) .white to pale yellow crystalline powder , freely soluble in acetic acid sparingly soluble in chloroform , very slightly soluble in methyl alcohol & ethyl acetate ; practically insoluble in ether structurally related to Nalidixic acid but with wider antibacterial spectrum & greater activity. Activity may be reduced in acidic media[18].



$C_{16}H_{18}FN_3O_3$ 319.33

Norfloxacin

Norfloxacin a fluoroquinolone, differs from non –fluorinated quinolones by having a fluorine atom at the 6- position & piperazine moiety at the 7- position . It may be analyzed by different methods ; u.v spectrophotometric, high performance liquid chromatography &microbiological method[19, 20, 21] .

Norfloxacin used mainly in the treatment of urinary tract infections such as cystitis, pyelitis, pyelonephritis, urethritis , chronic & acute prostatitis ; other indication have been typhoid fever & paratyphoid fever , gastroenteritis (including travelers diarrhea & shigellosis) ; & use as part of selective digestive tract decontamination regimens in imuonocomproemised (neutropenic) patients[22,23,24,25,26,27] .

Usual dose of norfloxacin is 400 mg once or twice daily . In fasting healthy volunteers, at least 30 – 40 % of an oral dose of Norfloxacin is absorbed. Absorption is rapid following single doses of 200 mg , 400 mg & 800 mg at the respective doses. Mean peak serum & plasma concentrations of 0.8 , 1.5 & 2.4 mcg/ml are attained approximately one hour after dosing[28,29] .

Aim of the work :

This work was carried out to formulate Norfloxacin as a shallow concave coated tablet dosage form through preparing different formulas, and study the effect of different excipients (binders, disintegrants, & diluents) on physical properties of the tablets.

The selected satisfactory formula that comply with the requirements of B.P. 98 & USP XXIV was chosen & investigated for the expiration date & its dissolution in –vitro. The properties of chosen formula were also compared with reference formulas : which are :Neofloxin the Alexendria co- (Egypt) Noroxacine Razi –labs.

MATERIALS AND METHODS :

Materials :

Norfloxacin powder (S.D.I), {Norfloxacin standard supplied by BORAL QUIMICA, S.A. Barcelona (Espana)}, Lactose, Starch, Sodium hydroxide, Phosphoric acid, Acetonitril, Glacial acetic acid, Hydroxypropyl methyl cellulose , blue alum lake ZLT 601, Titanium dioxide, propylene glycole, Ethanol, Microcrystalline cellulose (Avicel PH 101) Polyvinylpyrrolidone (PVP K30), Carboxymethylcellulose sodium salt (C.M.C) ,Hydrochloric acid , Ethanol, Sodium starch glycolate , Magnesium stearate, Talc , Aerosil, polyethyleneglycol, Neofloxin 400mg tablets(Alexandria co Egypt.), Noroxacine400mg tablets(Razi-lab).

Methods :

Calibration curve of norfloxacin : Calibration curve for the drug in phosphate buffer PH 4 was constructed by preparing serial dilutions of the drug from a stock solution. Sample then analyzed spectrophotometrically at its λ 278 nm. The absorbance's were recorded and plotted versus concentrations.

Tablet formulation : Different formulas Table (1) were prepared to find the most satisfactory using wet granulation technique.The binder solution (pvp with alcohol) was added to formulas 1-2-3-5 gradually in the mixing mortar until a satisfactory wetting was achieved .The wet mass then granulated through sieve no.10 and dried in stainless steel tray at 40C for one hour. The granules were then homogenized by passing them through sieve no.16, then mixed in suitable mixer with disintegrants& lubricant for 5min. The final mixture was compressed with tablet compressing machine with multiple punch using 12mm normal punches, & coated with blue film coated suspension in the Accella cota coating machine Table (2) .The same procedure was followed for formula 4 except that the binder was paste starch.

Preparation of film- coated suspension : A predetermined quantity of HPMC was dispersed in small volume of cold deionized water in stainless steel container and stirred vigorously until a homogenous suspension was obtained. Talc powder and titanium dioxide were dispersed in alcohol 96% into a stainless steel container. PEG 6000 was dissolved in warm deionized water & added to the previous dispersion.
Then Color blue alum lake was dispersed in propylene glycol & added.
Pigment suspension was added to the HPMC suspension & homogenized for 5min. The tablets were charged in the accella cota & heated until outlet temperature was 40C, the coating suspension was sprayed continuously on the tablets core until the average weight of 710mg was achieved.
Finally the film-coated tablets were dried in the coated pan for 30 minutes at 60Cº

Specifications of Norfloxacin 400mg tablets :

Hardness: Not less than 9sc and not more than 15sc
Disintegration: Not more than 15 minutes in purified water at 37 ºC
Friability: Not more than 1%
Whole core weight: 700mg
Average film coated tablets weight: 700-710mg
Film coated tablets color: blue
Diameter 12mm

Table 1 . Different formulations for norfloxacin as a shallow concave coated tablet dosage form. (Quantity in mg\ tablet , tablet wt 710 mg)

F	NOR	LAC	ST	PVP	CMC	MCC	S.ST.G	AER.	MG.ST.
1	400	138	58	24	56	-	10	7	7
2	400	138	68	24	56	-	-	7	7
3	400	143	63	24	-	56	-	7	7
4	400	153	107	-	-	-	26	7	7
5	400	167	75	24	20	-	-	7	7

F: Formula, NOR: Norfloxacin, LAC: Lactose,ST: Starch, PVP: Polyvinyl pyrrolidone, CMC: Carboxymethyle cellulose sodium , (Croscarmellose sodium) .MCC: Microcrystalline cellulose . S.ST.G.:Sodium starch glycolate., AER: Aerosil, MG.ST:Magnesium stearate.

Table 2 . Content of film coating suspension for norfloxacin 400mg tablets.

Item	Ingredients
1	Hydroxypropyl methyl cellulose (HPMC)
2	Color blue alum lake ZLT 601
3	Titanium dioxide
4	Propylene glycol
5	Ethanol 96%
6	Talc powder
7	De-ionized water
8	Polyethylene glycol

Weight variations : Twenty tablets were weighted individually and the average weight was calculated .

Assay of Norfloxacin (H P LC)[18] **:**

Mobile phase : Filtered and degassed mixture of phosphoric acid solution (1 in1000) & acetonitril 850:150 was prepared .

Preparation of standard: 100 mg of standard Norfloxacin was dissolved & dilute quantitatively in mobile phase to obtain a solution having a known concentration of about 0.2 mg/ml.

Assay *of the prepared tablets* : 20 tablets are weighed & finely powdered, then an accurately weighed portion of the powder, equivalent to about 100mg of Norfloxacin was placed into a 250ml volumetric flask. 80ml of mobile phase was added, shaken for 5 minutes ,sonicated for 10minutes ,and diluted with phosphoric acid solution (1in1000) to volume, then 10 ml of this solution was transferred to a 25 ml volumetric flask, diluted with mobile phase to volume, mixed and filtered through a filter having a porosity one micrometer. The Norfloxacin content was analyzed by HPLC, by injecting equal volumes of the standard and test preparations (10 microliters) .The peak responses for the major peaks was used to calculate the quantity in mg of C16H18FN3O3 in the portion of tablets using the formula : 500C (rt\rs) in which C is the concentrations , in mg per ml, of USP Norfloxacin Rs in the standared preparation , and rt and rs are Norfloxacin peak responses obtained from the assay preparation and the standard preparation respectively. Assay limit of tablet 90-110%, assay limit of raw material (Norfloxacin) 99-101% according to USP.

Hardness **:** The hardness of Norfloxacin tablets was measured by means of Sch leuniger-2E hardness tester, for test and standard tablets. The load was applied to the tablets, which was held diametrically between the platens of the testing instrument. Tablets generally split in to two halves and applied force could be read using a chart recorder. Determination was made on twenty separate tablets and expressed as means. The unit is KP (kilo pound) & Sc. Stron cobb each 1KP=1.4Sc.

Disintegration : The disintegration of tablets was performed according to B.P 98. method at 37Cº in distilled water. A basket rack assembly containing six open –ended tubes with a 10 mesh screen on the bottom was immersed in 4 glass tubes containing distilled water, placed separately in each tube of the basket and the time for each tablet to disintegrate was recorded. The time below 16 min. indicated good disintegration.

Friability test : By using Roch friabilator, twenty tablets were weighed and placed in the instrument the percentage loss in the weight was measured.

Dissolution rate: The U.S.P. (paddle method, apparatus 2) was used to study the release of the drug for all the prepared tablets. The studies were carried out using, the dissolution medium at 37Cº (900 ml of water in a 1000 ml volumetric flask 2.86 ml of glacial acetic acid was added & 1.0 ml of 50 % (w/w) solution of sodium hydroxide was diluted with water to volume), if necessary, adjusted with glacial acetic acid or the sodium hydroxide solution to pH of 4.0, at 37ºC., with constant stirring speed of 50 rpm. Samples were withdrawn at 5-10 minutes intervals for 60 minutes. The sample volume was replaced immediately by fresh buffer. Samples were filtered by microfilter, diluted and analyzed spectrophotometrically at 278nm for drug content. Time& Tolerances: 30 min. 80% release.

A standard solution was used having known concentration of USP Norfloxacin RS in the same medium .Not less than 80% of the labeled amount of C16H18FN3O3 , is dissolved in 30 min.[18]

Effect of binders & disintegrants : Starch paste & Polyvinylpyrrolidone (P.V.P) were used as binders, carboxy methylcellulose (Croscarmellose sodium) & sodium starch glycolate, with starch were used as disintegrants. The effect of these binder and disintegrants on the hardness, friability, disintegration time, and dissolution rate of the prepared tablets were studied .

Effect of temperature : The effect of temperature on the degradation of norfloxacin was studied by storing the tablets of the selected formula at different temperatures 25ºC, 40ºC, 50ºC, &70ºC. for 6months Samples of tablets were assayed by HPLC method at interval time 1,2,3,4, & 6 months .The disintegration time, hardness, dissolution rate were checked also at interval time .

RESULTS AND DISCUSSION :

Calibration curve of norfloxacin : Fig (1) show the calibration curve of norfloxacin. Straight line was obtained as a result of plotting the absorbances versus concentrations in ug \ml which indicate that it follows Beers-Lamberts law.

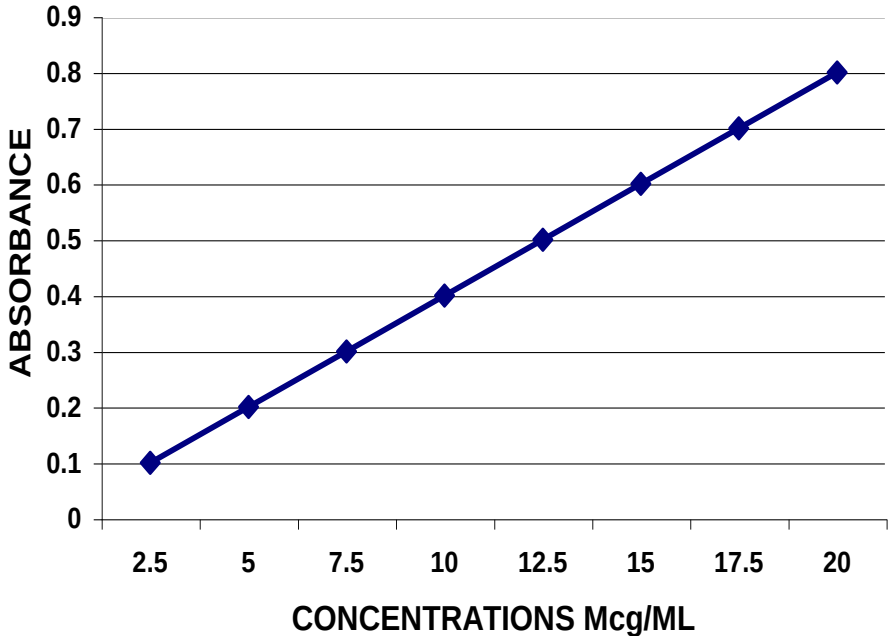


FIG 1 . CALIBRATION CURVE OF NORFLOXACIN

Effect of binders & disintegrants type : Different formulas were prepared (1,2,3,4,5) Table 1 in order to study the effect of binders & disintegrants type on the hardness, friability, disintegration and dissolution rate as shown in Table 1 .The results indicate that the use of different types of binders have an influence on physical properties and drug release of tablets. Formula 1, in which PVP was used as a binder; & sodium starch glycolate as disintegrant showed fast dissolution, good hardness and friability, with 6 minutes disintegration time, which comply the requirements of U.S.P. , also F2 in which starch maize was added as disintegrating agent showed good dissolution, and an acceptable disintegration time (FIG 2 & Table 3).CMC was used in F1, F2 & F5, in 8% for F1 & F2 , showed good results since they fits the requirements of Norfloxacin tablets in the U.S.P. 2.8% of CMC for F5 resulted friable tablets may due to small quantity of CMC). Starch paste used in F4 showed unacceptable hardness, with good disintegration time and friable tablets. Tablets produced using formula 3 had a long disintegration time & non-acceptable tablets in which 8% of avicel was used. Finally one may consider that F1 & F2 are the most satisfactory formulas. (FIG 3 & Table 3) .

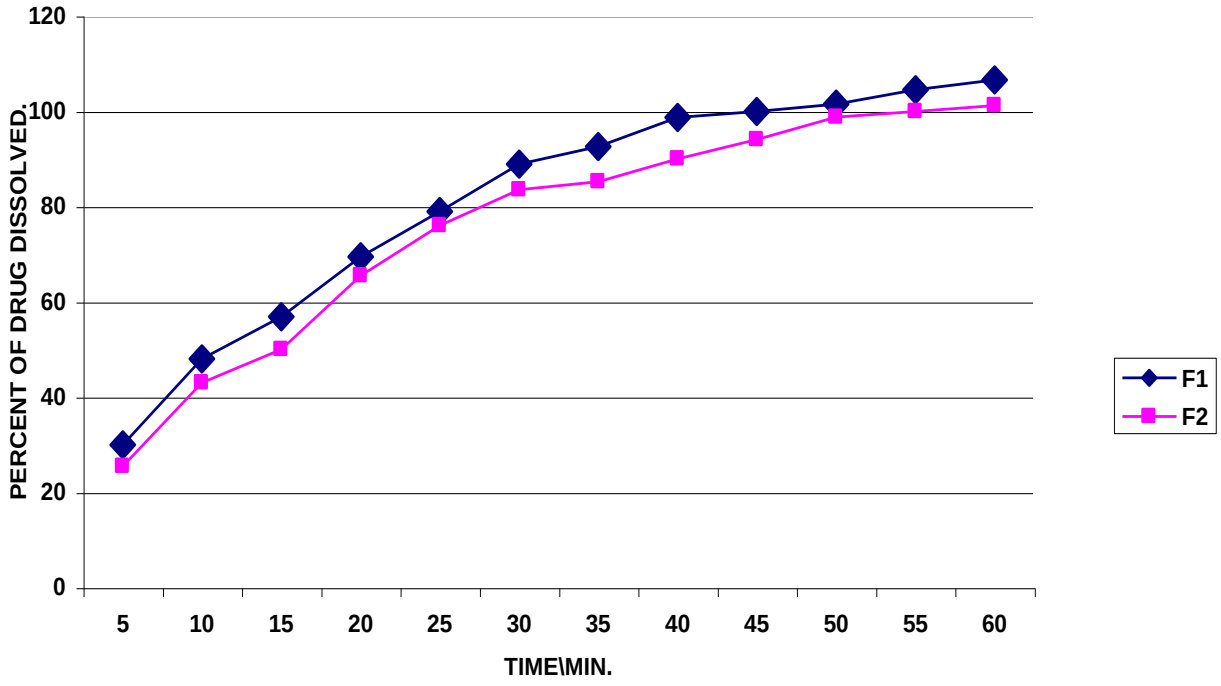


FIG 2 . EFFECT OF SODIUM STARCH GLYCOLATE (DISINTEGRANT) ON THE DISSOLUTION OF NORFLOXACIN FROM FORMULA 1

Table 3 . Physical stability study of 400mg norfloxacin tablets,F1,F2,F3,F4,& F5.

F *	Temp/ °C	Time/Months	Hardness/Sc	Friability%	Disintegration/Min.
1	25	TIME ZERO	8	O.5	6
	40	2	8.2	0.5	6
	50	3	8.5	0.6	6.3
	70	6	8.9	0.6	7
2	25	TIME ZERO	10	0.7	10
	40	2	10	0.7	10.2
	50	3	10.5	0.8	10.7
	70	6	10.8	0.8	11
3	25	TIME ZERO	11	0.9	17
	40	2	11	0.9	17.7
	50	3	11.4	0.95	18.6
	70	6	11.9	1	19.5
4	25	TIME ZERO	12	1.8	12
	40	2	12	1.8	12.5
	50	3	13.8	1.9	13
	70	6	13.9	1.9	13.2
5	25	TIME ZERO	10.5	1.8	18
	40	2	10.5	1.9	19
	50	3	11	1.9	19.2
	70	6	11	1.95	19.8

* FORMULA

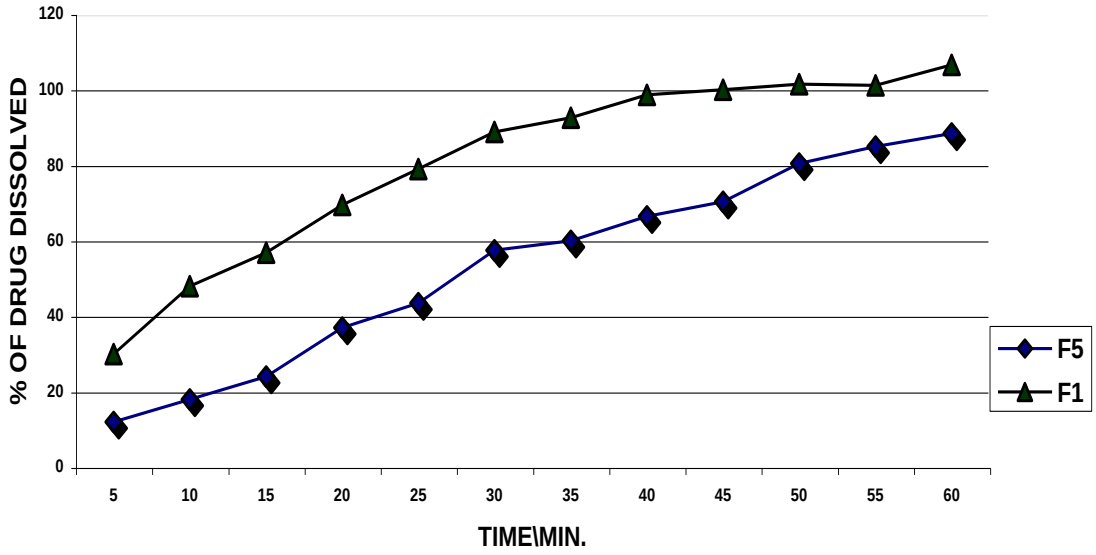


FIG3 . EFFECT OF 8% CARBOXYMETHYLE CELLULOSE ON THE DISSOLUTION RATE OF NORFLOXACIN F1& F5 .

Dissolution study *:* Dissolution rates for all formulas were studied in comparison to AL-RAZI (Noroxacine) ,ALEXANDRIA(Neofloxin) companies as references as shown in Fig 4 .The results obtained from formula 2 were closely related& similar to ALEXANDRIA than formula 1 , although both formulas fit the requirements of norfloxacin tablet release in U.S.P .

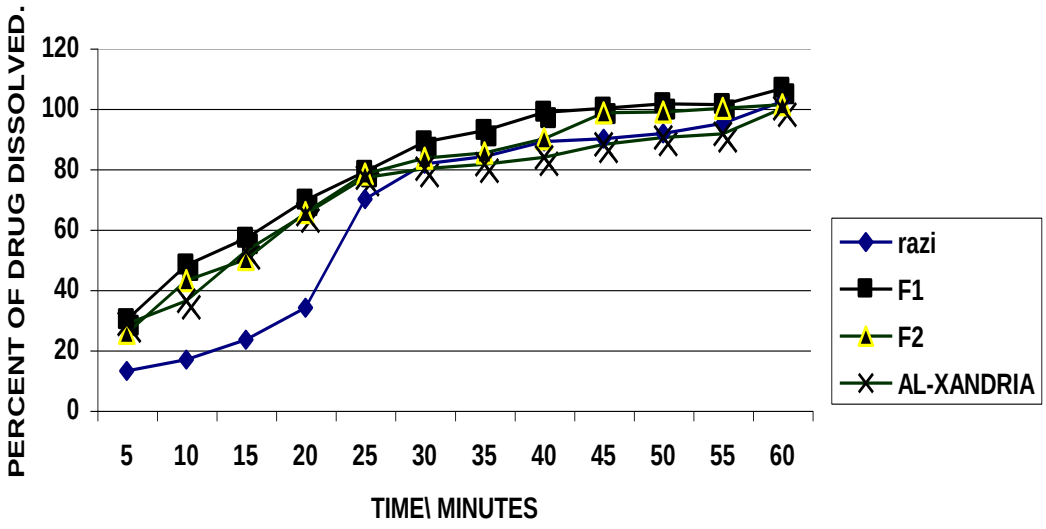


FIG 4 . DISSOLUTION STUDY FOR FORMULA 1&2 IN COMPARISON WITH REFERENCE FORMULAS IN BUFFER PH 4 (TOLERANCE NOT LESS THAN 80% IN 30 MIN.).

Effect of temperature : The stability of the selected formula F1 was studied at different temperatures 25ºC, 40ºC, 50ºC&70ºC.for six months. The degradation of Norfloxacin follows first order reaction, since non linear line was obtained with zero order reaction when the logarithm of percent remaining of Norfloxacin was plotted versus time .The degradation rate constant (K) can be calculated from the slope of the line.

$$\text{Log } Ct = \text{Log}C_0 \_\text{--}\_ K_{f\,/\,2.303}$$

Kf= SLOPE X 2.303 first order $t\,90\% = \frac{0.105}{Kf}$

The expiration date was calculated at 25ºC, 40ºC, 50ºC, & 70ºC from slopes and Kf, found to be equal to 7.3 years, 4.7 years, 2.4 years & 4 months respectively. Results are shown in Table 4,5,6 & FIG 5 .

Table 4 . Percents concentrations of norfloxacin 400 mg tablets (formula 1) at different times .

TEMPERATURE.	% CONCENTRATIONS \ DAYS					
C°	0	30	60	90	120	180
25	100.3	100.0	99.90	99.75	99.65	99.58
40	100.3	99.95	99.70	99.50	99.30	99.20
50	100.3	99.88	99.84	99.41	98.30	97.50
70	100.3	99.0	96.0	93.0	89.50	88.0

Table 5 . Log of percents remaining of norfloxacin 400 mg tablets (formula1) .

TEMPERATURE.	TME\MONTHS					
C°	0	1	2	3	4	6
25	2.001301	2.000282	1.999565	1.998913	1.998477	1.998172
40	2.001301	1.999783	1.998695	1.997823	1.996919	1.996512
50	2.001301	1.999479	1.997736	1.99503	1.992554	1.989005
70	2.001301	1.999544	1.982271	1.951823	1.951823	1.944483

Table 6 . Expiration date of norfloxacin 400mg (formula1) according to first order kinetc .

TEMPERATURE. C°	SLOPES	K1	MONTHS	YEARS
25	-0.000520087	0.001198	87.64608	7.30384
40	-0.000801392	0.001846	56.87974	4.739978
50	-0.002114021	0.003533	29.71978	2.476649
70	-0.01074	0.02473422	4.2451	0.35376

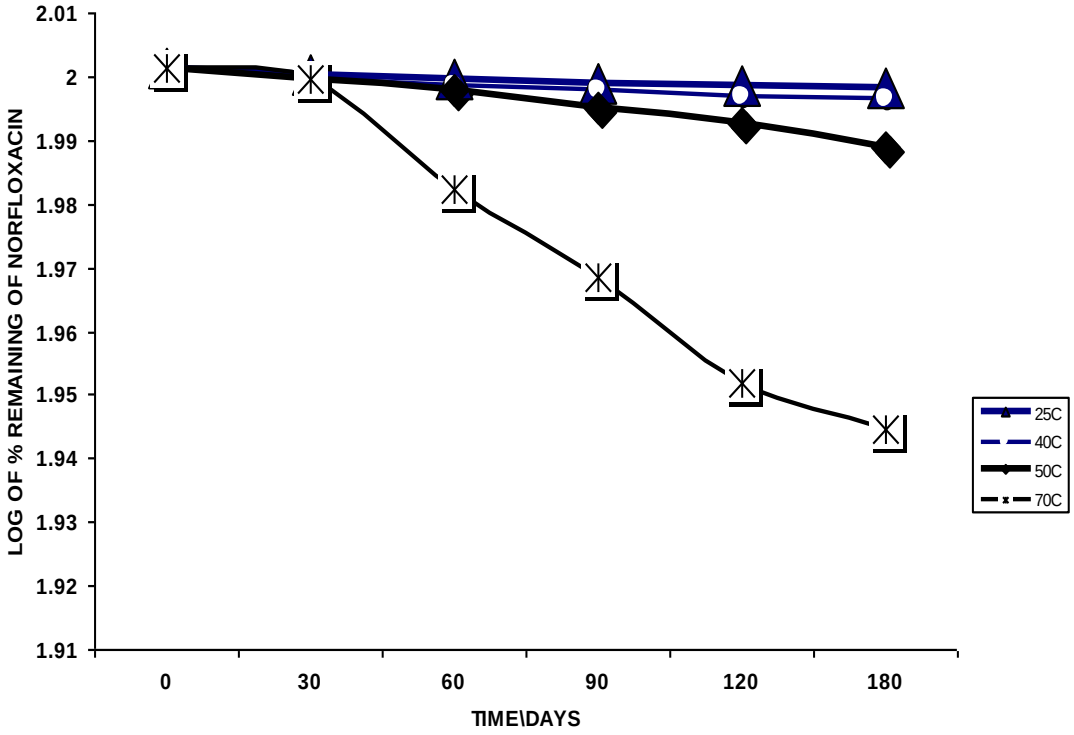


FIG 5 . DEGRADATION CURVES OF NORFLOXACIN 400MG TABLETS FORMULA (1) AT DIFFERENT TEMPERATURES 25C,40C, 50C, 70C. USING THE FIRST ORDER KINETICS(LOG Y=ax+b)

CONCLUSIONS :

One can conclude that:

1. The best binder and diluent that can be used are the 10% P.V.P w\v in alcohol and lactose since they are available, compressible and compatible, P.V.P as a binder was more stable than paste starch.
2. Formula 1 was chosen as the best satisfactory in comparison with the others, and with the reference formulas of Noroxacine&Neofloxin.
3. Starch was chosen with, carboxymethyl cellulose, since they had shown good physical parameters.
4. Sodium starch glycolate was the most satisfactory disintegrating agent.
5. Formula 1 was chosen for stability study.
6. Expiration date was found to be equal to 7.3 years at 25C.
7. The selected formula 1 Norfloxacin 400mg tablets may be manufactured in Iraq and used instead of that of other companies.

Further studies :

1- Bioequivalence study of Norfloxacin in normal & healthy person should be carried.
2-Kinetics of Norfloxacin should be studied in patients with varying degree of renal insufficiency.
3-Formulation of a newly developed floroquinolone, Ex: Gemifloxacin & Trovafloxacin.[29,31]

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