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Formulation and evaluation of ciprofloxacin as a topical gel

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الخلاصة:

ان عقار (سايبروفلوكساسين) ، هو مضاد بكتيري يتبع مجموعة الفلوروكوينولون وله طيف واسع من الفعالية ضد الجراثيم السالبة والموجبة لصبغة جرام. تم تصييغ عقار سايبروفلوكساسين ملح الهاديدروكلورايد على شكل هلام موضعي باستخدام قاعدتان مختلفتان ، قاعدة هلام مثيل سيليلوز 5% وقاعدة هلام صوديوم كاربوكسي مثيل سيليلوز 5%. استخدم العقار بتركيز 1% في تحضير كل قاعدة.

تم دراسة تحرر عقار السايبروفلوكساسين ملح الهاديدروكلورايد خارج الجسم الحي من هذه القواعد، بالاضافة الى نفوذية العقار باستخدام مقطع من جلد الفأر درست ايضا .

اوضحت النتائج بان تركيز عقار السايبروفلوكساسين ملح الهاديدروكلورايد المتحرر من قاعدة هلام مثيل سليلوز كان اعلى من قاعدة هلام صوديوم كاربوكس مثيل سيليلوز والنفوذية للعقار من خلال مقطع جلد الفأر كانت اعلى بالنسبة لقاعدة هلام صوديوم كاربوكس مثيل سيليلوز من قاعدة هلام مثيل سيليلوز. وطبقاً لهذه النتائج تم اختيار قاعدة هلام مثيل سيليلوز 5% للدراسات اللاحقة. تم دراسة تأثير مدة الخزن والحرارة على ثبوتية العقار بالاضافة الى الخواص الفيزياوية والاس الهايدروجيني للصيغة المختارة على مدى (45) يوماً. وقد وجد ان تركيز عقار السايبروفلوكساسين ملح الهاديدروكلورايد يقل مع مرور الوقت وارتفاع درجة الحرارة ولم تلاحظ حدوث تغيرات في الخواص الفيزياوية ، عمر العقار في الغلاف للصيغة المختارة لقاعدة الهلام تم حسابه باستخدام طريقة درجات الحرارة العالية وقد وجد انه يساوي (2.5) سنة.

Abstract:

Ciprofloxacin is an antibacterial agent belong to floroquinolones group, it has broad spectrum activity against Gram positive and Gram negaitive bacteria.

Ciprofloxacin – HCl was formulated as a gel dosage form using two different bases, a 5% methylcellulose and 5% sodium croboxy-methyl-cellulose gel base. The concentration of (1% w/w) of the drug in each base was prepared.

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In vitro availability of ciprofloxacin – HCl from these bases was studied, in addition the diffusion of the drug using excised mouse skin technique were also evaluated.

The results indicated that the extent of ciprofloxacin – HCl release was higher from methylcellulose gel base than that from sodium caroboxy-methyl-cellulose gel base. While the data revealed that the diffusion of the ciprofloxacin through the excised mouse skin was higher from sodium croboxy-methyl-cellulose gel base than that from methylcellulose. According to these results, 5% methylcellulose gel base was selected for further studies. The influence of storage time and temperature on the stability of the drug, as well as physical properties and pH, for the selected formula over a period of 45 days was studied. The concentration of ciprofloxacin was found to decrease with time and temperature and no changes in the physical properties were noticed. The shelf life of the drug in the selected gel base was determined using exaggerated temperature techinque and it was equal to 2.5 years.

The overall results of this study suggest that the selected formula could be used in the preparation of ciprofloxacin gel as a topical dosage form to be used in the treatment of some dermatological infections.

Introduction:

Gels are two – component semi – solid systems rich in liquid. Their one characteristic feature is the presence of continuous structure providing solid – like properties. In a typical polar gel, a natural or synthetic polymer builds a three dimensional matrix throughout a hydrophilic liquid [1]. After application, the liquid evaporates leaving the drug entrapped in a thin film of the gel – forming matrix physically covering the skin [2].

Currently the *in vitro* and the *in vivo* dermatological tests show the superiority of the water soluble gels on the corresponding cream and ointment formulations of the same drug such as piroxicam and silver sulfadiazine gels [3, 4]. Generally the gels are easy to apply and evaporation of the water content produces a pleasant cooling effect. The residual film usually adheres well and gives protection but it is easily removed by washing when treatment is completed [5].

The most common gelling agents are alginic acid, bentonite, acacia, carbomer, carboxy methyl cellulose, ethyl cellulose, gelatin, hydroxy ethyl cellulose, hydroxy propyl cellulose, magnesium aluminum silicate, methyl cellulose, poloxamers, polyvinyl alcohol,sodium alginate, tragacanth, and xanthene gum. Although each gelling agent has some unique properties, however there are some generalizations that can be made [6, 7].

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Cellulose derivatives are widely used because they produce neutral gel of very stable viscosity, good résistance to microbial attack, high clarity due to freedom from insoluble impurities and good film strength when dried on the skin[5]. Cellulose may be represented by the formula $[C_6H_7O_2 (OH)_3]_n$ where n may be about 1000. Introduction of the methoxy group (– OCH_3) produce methyl ethers. Four types of methyl cellulose $[C_6H_7O_2 (OH)_2 OCH_3]_n$, are official (Methylcellulose 20 B. P. C, Methylcellulose 450 B. P, Methylcellulose 2500 B. P. C., Methylcellulose 4500 B. P. C.) The numbers after the name indicate the approximate viscosity, in centistokes, of 2 per cent mucilage. The high viscosity grades (2500 and 4500) are used as thickening and dispersing agent. They are white or creamy – white powders that disperse in water, forming viscous solutions. Aqueous suspension neutral to litmus,stable to alkalis and dilute acids [8]. They are non – ionic and, therefore, stable over a wide pH range. Methylcellulose is used in both internal and external preparation; the concentration depends on the viscosity of the polymer but is usually between 0.5 and 2 percent [6]. Methylcellulose is long-chain substituted cellulose that can be used to form gels in concentrations up to about 5% [5].

Carboxymethylcellulose (semi–synthetic): carboxymethyl cellulose differs from methylcellulose in having one of hydrogen atoms of the methyl group replaced by a carboxy group.

Because of the carboxy group, it produces salts and the material available commercially is sodium carboxymethylcellulose (NaCMC) which may be represented by the formula: $[C_6H_{10x}O_5(CH_2.COONa)_x]_n$ where x is the degree of substitution, usually about 0.7. They produce aqueous solutions with viscosity ranging from 6 to 4000 centipoises for 1% solutions. It is more sensitive to pH than methylcellulose, pH outside the range 5 to 10 affect the viscosity of mucilage, while pH below 3 precipitate cellulose glycolic acid [8]. Carboxymethylcellulose in concentrations of 4 to 6 % of the medium viscosity grades can be used to produce gels, glycerin may be added to prevent drying [7].

Ciprofloxacin, its empirical formula is $C_{17}H_{18}FN_3O_3$. HCl. H_2O Fig.(1), like enoxacin, gatifloxacin, levofloxacin, and trovafloxacin, is a fluoroquinolone, Since it contains a fluorine atom at position 6 of the 4 – quinolone nucleus Fluoroquinolones have an expanded spectrum of activity and increased antibacterial potency compared with non fluorinated quinolones (e.g., cinoxacin, nalidixic acid, oxolinic acid) [9]. Ciprofloxacin, like other fluoroquinolones, contains a piperazine group at position 7 of the 4 – quinolone nucleus, which result in antipseudomonal activity. The drug also contains a cyclopropyl group at position1, which enhances antimicrobial activity [10].

Ciprofloxacin inhibits DNA gyrase enzyme of bacteria which is responsible for the continuous introduction of negative supercoils into DNA, so ciprofloxacin is

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considered as bactericidal agent. The concentration needed to inhibit gyrase – mediated DNA super coiling are between (0. 1 – 10 μg/ml) [9].

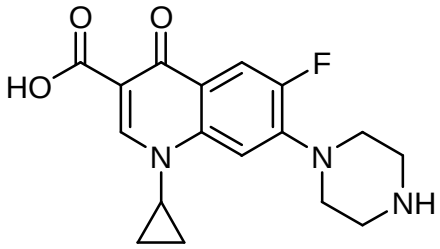

Fig.(1) CIPROFLOXACIN – HCl chemical structure

Ciprofloxacin Hydrochloride contains not less than 98. 0% and not more than 102.0 % of: 1 – cyclopropyl 6 – fluoro – 1, 4 – dihydro – 4 – oxo – 7 – piperazin - 1 – yl quinoline – 3 – carboxylic acid hydrochloride $C_{17}H_{18}FN_3O_3$, HCl, H_2O. Its molecular weight = 385.8 gm [12].

Its antimicrobial spectrum include gram positive aerobic cocci, gram positive aerobic bacilli, gram negative aerobic bacteria (*Helicobacter pylori*), *Neisseria*, *Haemophilus*, *Moraxella catarrhalis*, enterobacteriaceae, *Pseudomonas*, *Vibrio*, anaerobic bacteria, *Mycobacterium*, *Chlamydia* and *Mycoplasma*[10,12].

The present work describes the formulation and evaluation of ciprofloxacin as a topical gel preparation using the fusion method.

Materials and methods:

The materials used in this study were as follows:

Ciprofloxacin–HCl powder (Neuland Laboratories Limited India); benzalkonium chloride (S.D.I); disodium edetate (BDH limited pool, England); methyl cellulose (BDH limited pool England); Na carboxy methyl cellulose (NaCMC) (BDH limited pool England); glycerol (National Factory for Lab chemicals and equipment. Amman Jordan); disodium hydrogen orthophosphate (Merck – Shuchardt, Germany); potassium dihydrogen orthophosphate (Hopkin and Williams Ltd., England); methyl hydroxybenzoate; propyl hydroxybenzoate (S.D.I).

While the instruments used in this study were as follows:

Sensitive balance (Sartorius, Wereke – GMBH, type 2842, Germany); USP dissolution apparatus (Erweka, type DTC, GMBH, Hansen, Stamm, Germany); electrical clipper (Oster, Milwaukee, wis, Model – A_2 patent 2158145, U. S. A.); ovens (Memmert – SP8 100 – Germany); pH meter (Schott – Gerate, type CG820, Germany); ultrasonic shaker (Kerry, Germany); U.V spectrophotometer (Pye – Unicam, SP8 – 100 England); distillator (Gesellschaft fur labortech, Nik m, b, h&Co. type 2016, Germany); flask shaker (Gallenhamp, made in great Britain); water bath (Gallen Kamp); autoclave (Daikyo).

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Preparation of calibration curve of ciprofloxacin HCl in phosphate buffer pH 7.4:

Buffer Solution:

Phosphate buffer solution of pH 7.4 was used to simulate the skin fluids. For the preparation of phosphate buffer solution, two stock solutions were prepared:

* Solution **A** (1/15 molar KH_2PO_4): It was prepared by dissolving 9.08 gm of potassium dihydrogen phosphate in sufficient distilled water to make one liter.
* Solution **B** (1/15 molar $Na_2HPO_{4)}$: This solution was prepared by dissolving 11.87 gm of disodium hydrogen phosphate in sufficient distilled water to make one liter. The buffer solution of pH 7.4 was then prepared by mixing 19.7 ml of solution A with 80.3 ml of solution B [14].

Calibration curve:

Calibration curve of ciprofloxacin HCl in phosphate buffer at pH 7.4 was obtained by preparation of a serial dilutions of ciprofloxacin from a stock solution (1 mg/ml) and the prepared samples were then analyzed spectrophotometically at its λ_{max} (278 nm). The absorbance was plotted versus concentration.

Preparation of Bases:

The general method employed for the preparation of the gel bases was the fusion method [13]**.** After cooling to room temperature, the drug was then incorporated by trituration using a slab and spatula. The quantities of ingredients were taken on weight / weight basis. The procedure for the preparation of each base was a follows:

* Soduim Carboxy methyl cellulose gel

Na carboxy methyl cellulose (NaCMC)	5 gm
Glycerol	15 gm
Methyl hydroxybenzoate	0. 1gm
Purified water to	100 gm

The preservative methyl hydroxybenzoate was dissolved in water using heat, the solution was left to cool and 40 ml. of it was transferred to a beaker, and then warmed to about 70°C with vigorously stirring using an electric stirrer. The NaCMC was mixed with glycerin in a glass mortar and the mixture was poured in small amounts with stirring until a clear gel was formed [15].

* Methylcellulose gel (MC):

A 5% (w/v) polymer powder was dissolved in hot distilled water containing the stabilizer and preservative. The solution of ciprofloxacin HCl was added with gentle mixing [16].

The concentration of ciprofloxacin gel:

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1% concentration of ciprofloxacin which is above the minimum inhibitory concentration (MIC 0.1 %) was chosen and on the bases of previous work of ciprofloxacin HCl ointment base [17].

Formula	Drug gm	BAC 1%w/v	Methyl hydroxyl-benzoate	Disodium EDTA	MC	NaCMC	Glycerin	Final volume with H_2O
A	1	1ml		0. 1gm	5gm			100 gm
B	1		0. 1gm	0. 1gm		5gm	15gm	100 gm

Table-1: the prepared formulas of ciprofloxacin – HCl gel

***In vitro* ciprofloxacin release test:**

A small funnel with a diameter of 2.3 cm was modified in order to be filled with 5 grams of each gel base which contains 1% w/w of ciprofloxacin HCl. The mouth of the funnel was covered with filter paper, and was secured in place with a rubber band. The dialysis cell was inverted and immersed up to 0. 5 cm in 500 ml of phosphate buffer pH7.4 contained in the flask of the dissolution apparatus (collecting medium)[18].

The flask was partially immersed in a large water bath at a constant temperature of 37°C inside the dissolution apparatus. The stirrer was immersed in the collecting medium and the stirring rate was maintained at 100 r. p. m. [18].

The net release of ciprofloxacin HCl was followed by monitoring the receiver medium concentration for 6 hours, Five milliliters samples where withdrawn with a pipette fitted with a filter from the collecting medium after 0. 5, 1, 2, 3, 4, 5 and 6 hours and replaced with an equal volume of fresh buffer of pH 7. 4 at 37°C [19].

The samples where then analyzed spectrophotometrically for there drug content at its λ_{max} (278 nm).

***In vitro* diffusion of ciprofloxacin HCl through skin membrane:**

Preparation of the diffusion membrane:

The preparation of mouse skin was carried out according to the method of Skelly and co–workers [20, 21, 22]. The skin was excised from the abdominal area, defatted by wiping with a cotton tip soaked in ether to remove the subcutaneous fat and scraping the dermal side to remove the muscle and blood vessels, then kept in a phosphate buffer pH 7.4 for about 1 hour in a water bath at 37°C to allow any water

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soluble U.V absorbing materials to leach out. The skin was either used immediately or frozen until ready for use [20].

A 5gm of each gel base containing 1 %(w/w) ciprofloxacin was applied on the epidermal surface of mouse skin. The skin was stretched over the mouth of the test tube with a diameter 1.4 cm and ligated with a cotton thread. The diffusion cell was then inverted and immersed in 500 ml of phosphate buffer pH 7.4 contained in a flask of the dissolution apparatus [23].

The system was maintained at 37°C and the buffer solution was stirred at 100 r.p.m. during the 6 hours of incubation; samples of 5 ml were piped from the collecting medium after (0.5, 1, 2, 3, 4, 5 and 6) hours replaced each time with equal volume of freshly prepared phosphate buffer pH 7.4 at 37°C. Samples were then analyzed spectrophotometrically for their drug content at its λ_{max} (278nm) [23].

Preservative Efficacy:

Challenge test was done for the selected formula to determine the preservative efficacy of Benzalkonium chloride solution B. P. C 0.01 per cent v/v. The test was applied as follows [24, 25]:

1 - Organisms used:
   Candida albicans, Staphylococcus aureus, Escherichia Coli and Pseudomonas aeruginosa.
2 - Inoculum:
   ml /20 ml, 100, 000 to 1000, 000 cell /ml.
3 - Sampling:
   At 7, 14, 21 and 28 days following inoculation.
4 - Effectiveness:
   The vegetative cell must not be more than 0. 1% of the initial concentration by day 14, the concentration of viable yeast and mold must be at or below their initial concentrations after 14 days.

The concentration of each test organism must remain at or below their levels after 28 days. The culture media that were used are nutrient broth, nutrient agar, and plate count agar.

Stability Study:

The stability studies were carried out using the gel base that provided the best release during the release and diffusion experiments.

Effect of storage time and temperature on degradation of ciprofloxacin and determination of expiration date of ciprofloxacin gel:

The prepared gel was divided into three groups all of them were filled in collapsible tubes. Each group consist of three tubes of ciprofloxacin – HCl gel (1% w/w) were kept in ovens at 40°C, 50°C and 60°C [26].

Ciprofloxacin concentration in the stored gels was checked every 15 days for 45 days. This was done by dissolving 1gm of the gel in 100ml methanol then 30

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minutes in flask shaker, then the solution was filtered and 5ml of the filtrate was taken and diluted to 100 ml with D. W, then analyzed spectrophotometrically at 278 nm.

A standard solution of ciprofloxacin HCl prepared by dissolving 100mg of ciprofloxacin HCl powder in 100 ml D. W, then 10ml of this solution was taken and completed the volume to 100ml D. W then 5 ml of this solution was taken and added to it 5 ml methanol and complete the volume to 100 ml D. W, then analyzed spectrophotometrically at 278 nm.

pH of the gel:

The pH of the gel was measured using pH meter at time intervals of 1st day, 15, 30 and 45 days by taking 2gm of the gel and shaking up with 10ml of D. W, then the pH of the mixture was measured.

Physical properties:

The physical properties (colour, odour) of the selected formula of ciprofloxacin gel were observed over the storage period 45 days.

Statistical Analysis:

Results were presented as mean ± SD for the ciprofloxacin–HCl gel (1%) and its placebo treated lesions. T test was done to compare between 2 variables at ($p < 0.05$) was considered to be significant.

Results and Discussion:

Calibration curve

Figure (2) shows the calibration curve of ciprofloxacin – HCl in phosphate buffer (pH 7.4). A straight line was obtained by plotting the concentration of ciprofloxacin – HCl (µg/ml) versus absorbance. This indicates that the calibration curve of the drug obeys Beer's law within the range of concentration used.

Release and diffusion of ciprofloxacin – HCl from different gel bases:

Figures (3) and (4) show the release of the ciprofloxacin – HCl from 2 different semi–solid bases containing 1% w/w ciprofloxacin– HCl. The result indicates that large difference existed in the extent of release of ciprofloxacin – HCl from the MC gel bases as compared to the NaCMC gel base. The release of ciprofloxacin from MC base was higher from that of CMC gel base. The difference in the release profiles of the MC gel base with the NaCMC gel base was statistically significant at ($p < 0.05$).

A general rule in the semi – solid formulation is that, if the drug is held firmly by the vehicle the rate of release is slow [3].

The release of ciprofloxacin HCl from NaCMC gel is slower than that of MC gel may be due to the higher solubility of ciprofloxacin HCl in NaCMC gel, in addition to the highest viscosity of NaCMC gel it self.

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The measurement of drug release from gel bases is useful in detecting the possible interaction between the drug and the vehicle which may influence the drug absorption through the skin, i.e, the release of drugs from gels may be influenced by the type and composition of the base [27].

Figure (5, 6) shows the variation in the diffusion of ciprofloxacin – HCl through the mouse skin. The NaCMC gel base was found to allow the highest permeation of ciprofloxacin – HCl through the skin after 6 hours. The difference in the diffusion profiles of the NaCMC gel base and the MC gel base was statistically significant ($P < 0.05$) as shown in figures (5, 6).

The order of the diffusion of ciprofloxacin – HCl from these bases was: NaCMC base > MC base. The above data indicate that the diffusion of ciprofloxacin – HCl from a semi – solid base through mouse skin can be altered by modifying the composition of the vehicle. This could be explained as the interaction between the Na^+ from NaCMC molecules and Cl^- from salt of ciprofloxacin resulting in liberating free ciprofloxacin – base (more lipophilic) which diffused through the mouse skin easily, and/or may be due to higher viscosity of NaCMC gel which ensure close contact (increase contact time) with the mouse skin, thus facilitating penetration of ciprofloxacin – HCl.

It was found that the percentage of release of Ciprofloxacin – HCl gel was higher than the percentage diffused through mouse skin, this may be due to the fact that the skin acts as a barrier which decrease the amount of drug diffused in addition to physicochemical properties of the drug.

Since the drug have a partition coefficient of 8/2 = 4 (w/o) which indicates that it is hydrophilic more than lipophilic in nature and it can not cross skin barrier. So the prepared ciprofloxacin – HCl gel exerts its effect locally more than systemically, which leads to increase in its effectiveness in treatment of skin pathological conditions locally.

Since the methylcellulose gel base gave the highest release and lowest diffusion than NaCMC gel base, so the prepared gel of ciprofloxacin – HCl utilizing MC gel base is more reliable for pharmaceutical and clinical point of view (for further studies).

Stability study:

Effect of storage time and temperature on the stability of ciprofloxacin in methylcellulose gel base and determination of shelf life of the selected gel:

The stability of ciprofloxacin – HCl in methylcellulose gel base was studied at various temperature 40°C, 50°C and 60°C for 45 days.

At temperature 40°C, 50°C and 60°C a gradual decrease in the amount of ciprofloxacin – HCL was noticed ($p < 0.05$) with the increase in storage time and temperature.

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The degradation of ciprofloxacin–HCl concentration follow first– order kinetics, since straight lines were obtained from the plot of logarithm of % remaining of ciprofloxacin versus time fig.(7).

The degradation rate constant (K) at 40, 50 and 60 °C were calculated from the slopes of the lines as shown in Table (2).

From the "Arrhenius Plot" it is possible to estimate the shelf life of ciprofloxacin – HCl gel by plotting log K versus 1/T fig.(8), on which the degradation rate constant at 25 °C was obtained from the extrapolation of the resulting straight line to 25 °C. the slop of the line, T being the absolute temperature [28].

The shelf – life indicates the time for the extent of degradation of 10% of ciprofloxacin – HCl gel, therefore, t 10% value represents the stability of the drug [29].

Temperature °C	1/T x 10^{-3}	K x 10^{-3} (day^{-1})	Log K
40	3.195	0.251	- 3.6
50	3.095	0.398	- 3.4
60	3.003	0.645	- 3.19
25	3.35	0.112	- 3.95

Table-2: The effect of temperature on the rate of degradation of ciprofloxacin HCl gel

The calculated degradation rate constant (K) at 25°C was equal to ($0.112*10^{-3}$).

Since the degradation of the drug follows first-order kinetics, therefore, the expiration date can be calculated using the following equation:

$t_{10\%}$ = 0. 104 /$K_{25°C}$

= 2.5 years.

Effect of storage time and temperature on the physical properties of the selected gel:

In collapsible tubes there were no change in color and odor after 45 days of storage, which indicates the physical stability of the selected formula in the storage tubes at all temperatures of the study (40, 50 and 60°C).

No significant changes were observed in the pH of the stored gel (around 4.7), indicating that the storage time and temperature had no effect on the pH.

Preservative Efficacy:

The result of preservative efficacy test indicates that the preservatives used were very effective and they caused 100% reduction in the growth of all tested

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microorganisms after 7days, 14 days, and 28 days of the inoculation which fits the U.S.P. requirements.

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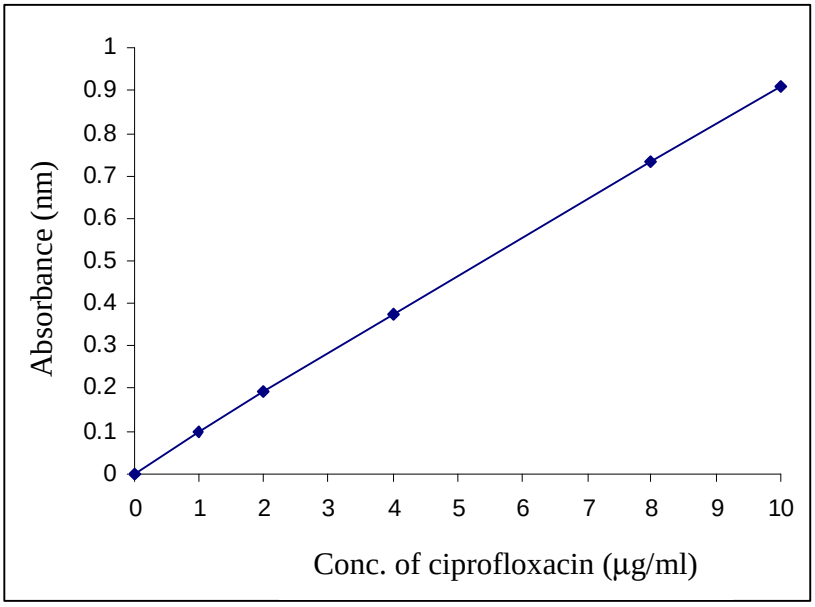

Fig. 2: Standard curve of Ciprofloxacin - HCl in phosphate buffer solution (pH 7.4)

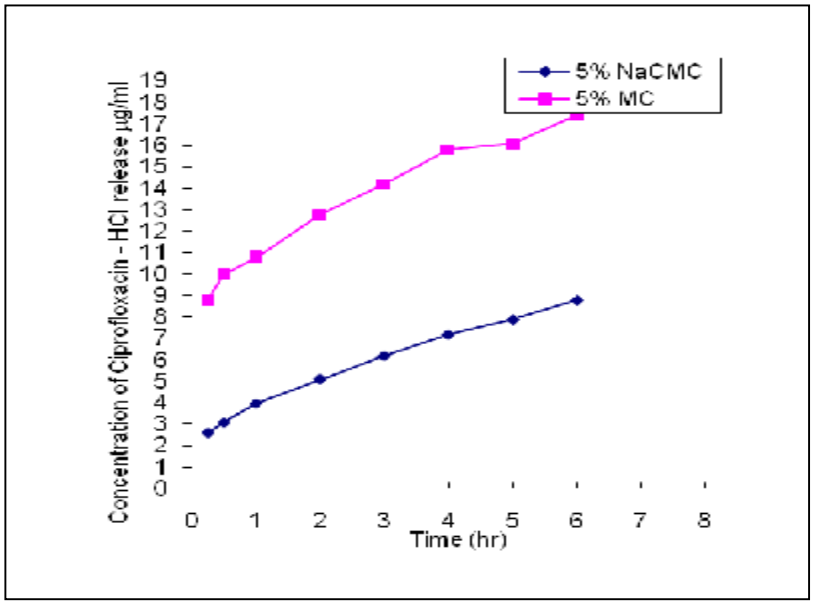

Fig. 3: Effect of different gel bases on the release of ciprofloxacin - HCl 1% w/w

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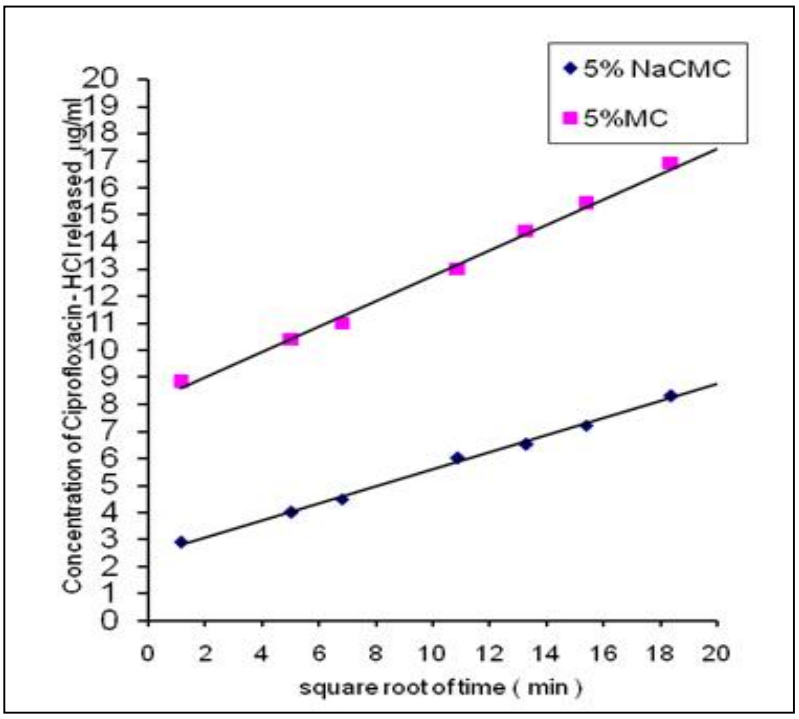

Fig. 4: Effect of different gel bases on the release of ciprofloxacin 1% w/w.

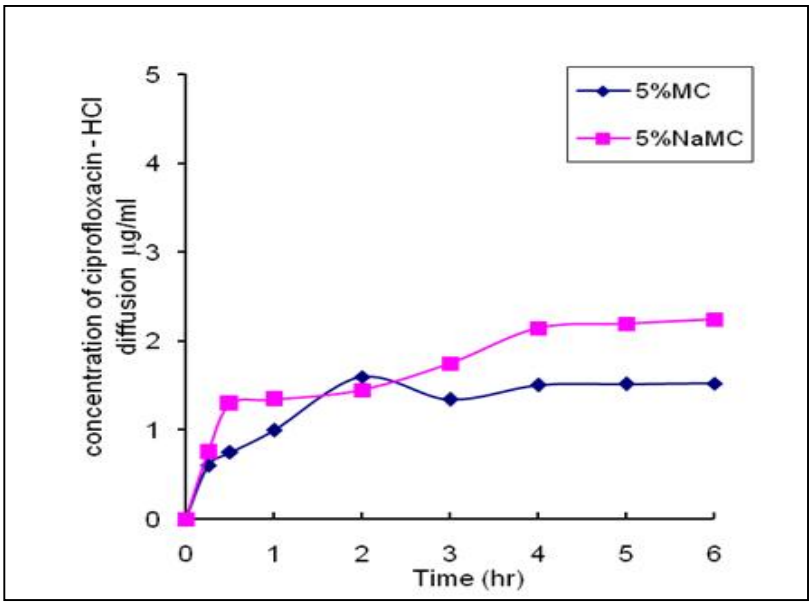

Fig. 5: Effect of different bases on the diffusion of ciprofloxacin 1%w/w

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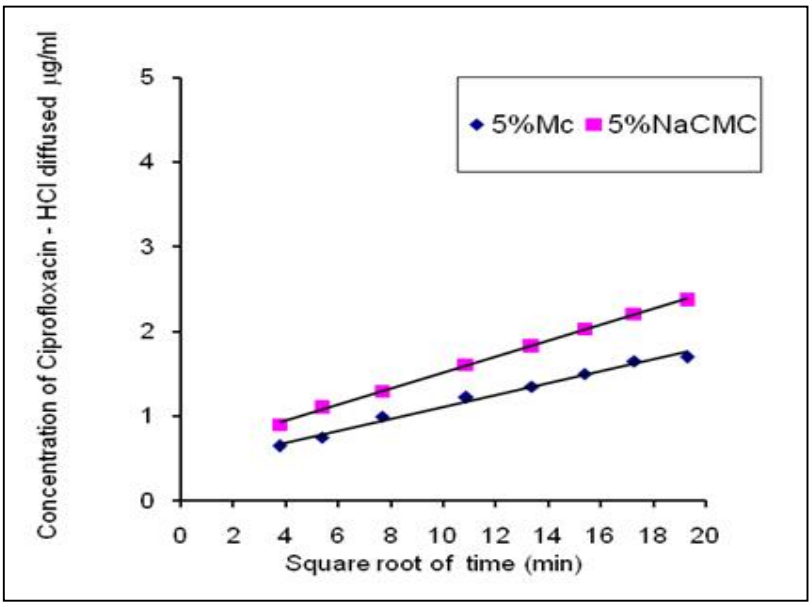

Fig (6) Effect of different gel bases on the diffusion of ciprofloxacin 1% w/w

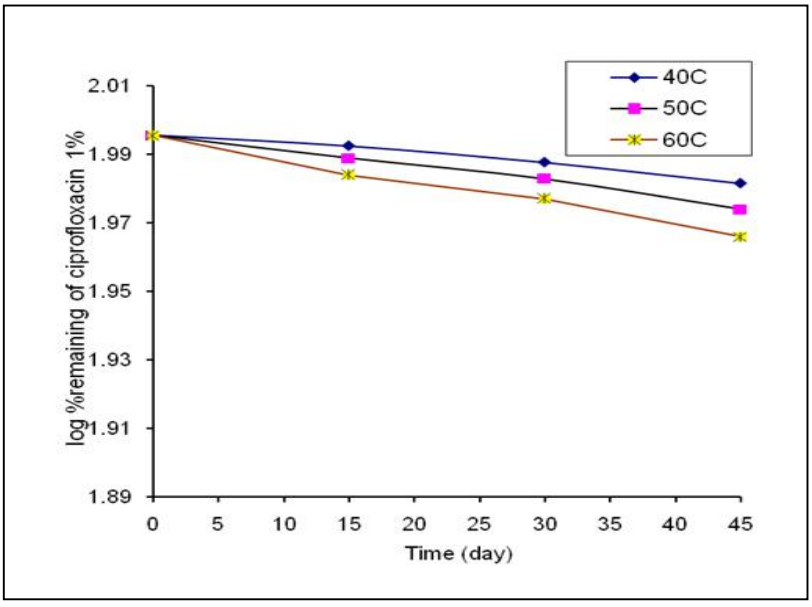

Fig (7) Degradation curve of ciprofloxacin-HCl at 40°C, 50°C, and 60°C for MC formula

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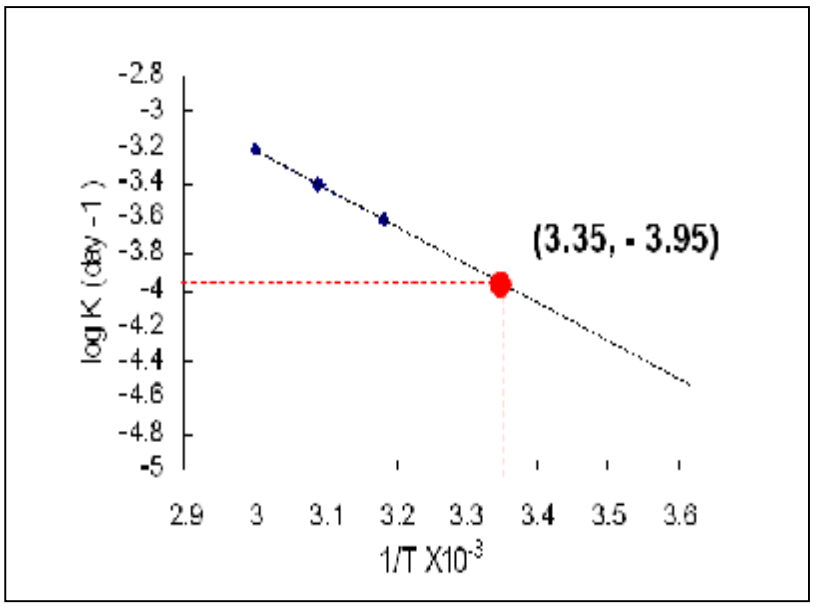

Fig (8) Arrhenius plot for expiration date estimation of1% Ciprofloxacin HCl gel