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Topical Formulation and in-Vitro Assessment of Moxifloxacin Hydrochloride Emulgel

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Abstract

Moxifloxacin HCL (MOXF HCL) was formulated as an emulgel dosage form in eight formulas using five main gel bases, carboxymethyl cellulose, hydroxypropyl methylcellulose, sodium alginate, sodium carboxy methyl cellulose, and a combination of hydroxypropyl methylcellulose and sodium alginate. The study revealed that the best emulgel base with accepted physical properties was CMC 2 %(w/w) in combined span 20 and tween 20 as surfactants compared with other cellulose derivative polymers, which gave us 97.85% of drug release. In contrast, HPMC gave us 76.5%, NaCMC gave us 57.83%, and Sod. Alginate gave us 64.92%, and HPMC/sod.alginate gave us 67.64%. Moreover, the Moxifloxacin HCL release from the selected formula in phosphate buffer pH 5.5 was increased as a result of growing surfactants used while increasing the liquid paraffin as an oil phase resulted in a decrease of drug release. On the other hand, the kinetic analysis of the amount of drug release from all Emulgel bases used showed mostly obeyed the Higuchi model.

Keywords:

MOXF HCL, Emulgel, Cellulose derivative polymers

Water-in-oil or oil-in-water emulsions are called "Emulgel" , that have been combined with a gelling agent to form a gel; they gave numerous essential benefits to combat numerous issues related to drugs; the dispersion may either be oil in water (o/w) emulsions which are particularly beneficial for general cosmetic usage and as water-washable medication bases or water in oil (w/o) emulsions which are used more often to treat dry skin and provide emollient treatments. Emulgel as a topical administration method lengthens the drug's mean resident time and contact time at the applied location. topical drug delivery systems, in general; easy, painless and straightforward to be terminating any unfavorable or undesirable repercussions occurs.

For hydrophobic or water-insoluble medicines, emulsified gel provides a stable formulation and a superior delivery system, emulsified gels are based on the two formulations emulsion and gel. [(1)] MOXF HCL is the fourth generation of quinolones used as anti-bacterial and anti-infective agents; is a slightly yellow to-yellow crystalline powder, soluble in water, Ethanol, 2-propanol, and acetone, higher solubility observed in phosphate buffers, and it has a half-life of about 12 hours. The chemical name is 1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7- [(4aS, 7aS)-octahedron-6H-pyrrolyl [3, 4-b] pyridin-6-yl]-4-oxo-3 quinoline carboxylic acid ($C_{21}H_{24}FN_3O_4 \cdot HCl$). M.Wt=437.89, M.P. = 238- 242ºC, PK_a=2 l, Fig. (1) demonstrated the chemical make-up of moxifloxacin HCL. [(2)]

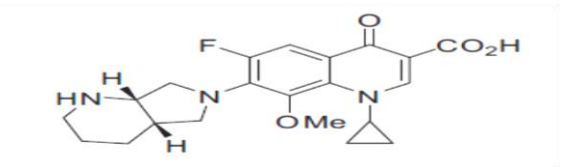

Figure (1): The chemical makeup of Moxifloxacin

HCL (3)

Materials and Methods

Chemicals and drugs

MOXF HCL powder supplied by MSN pharma chem Pvt. Ltd. factory; India, Hydroxy propyl methyl cellulose, Methylparaben, Propyl paraben, Propylene glycol, Citric acid obtained from Samarra drug industry; Iraq, Carboxy methyl cellulose supplied by Goodrich; USA, Sodium alginate provided from Hopkin and Williams Ltd, Chadwell, Essex; England, Sodium Carboxy methyl cellulose,

Monobasic sodium phosphate obtained from BDH chemicals Ltd, Poole, England, Tween 20 Span 20, Germany's Riedel-De Haen AG Seelze provides Ethanol; liquid paraffin, which is provided by Merk-Schuncherdt; Hannover, Millipore filter paper0.45µm from Viking; London, Dibasic sodium phosphate supplied from Fluka AG, Puriss.p.a.; Switzerland.

Preparation of Emulgel Formulas

the practice of 8 MOXF HCL formulas Emulgel is created by gently swirling the resulting emulsions and gel in a (1:1) ratio until they are homogeneous ; as shown in Table (1).The general method for preparation of an emulsion, by first preparation of the phase of oil by dissolving 1.66g of span20 in 5%w/w liquid paraffin, secondly by dissolving the aqueous phase of 0.34g of tween20 in 50 %(w/w) purified water, then we dissolve 2 %(w/w) of MOXF HCL in 2.5g ethanol. At the same time, 0.15g of methylparaben and 0.05g of propyl paraben dissolved in 5g of propylene glycol, mixing both of them with the aqueous phase; after that, both the oily phase and aqueous phase were warmed independently to (70-80℃). The aqueous phase in addition to the oil phase with constant stirring at 500rpm until it has reached room temperature. After this, the emulgel was prepared. The amount of gel that is mixed with emulsion for preparation of jellified emulsion also depends on the type of polymer used, but the amount of purified water that used in gel preparation of different polymers is constant not more than 50%(w/w) of distilled water. [4, 5]

Table 1. Composition of MOXF HCL Emulgel.

Substance	F1	F2	F3	F4	F5	F6	F7	F8
MOXF HCL (gm)	2	2	2	2	2	2	2	2
HPMC (gm)	3.5	3.5	-	-	-	-	-	-
Sod. alginate (gm)	-	4	-	-	-	-	-	-
CMC (gm)	-	-	-	2	2	2	2	-
NACMC (mg)	-	-	2.5	-	-	-	-	-
Span 20 (ml)	5	5	5	5	5	7.5	7.5	5
Tween 20 (ml)	1.66	1.66	1.66	1.66	3.32	1.66	3.32	1.66

Determination of physical properties

Determination of λ max and Calibration curve

Ten milligrams of MOXF HCL were dissolved in 100 ml distilled water and buffer (phosphate buffer pH 5.5), scanned spectrophotometrically from 200-400 nm, and record the result. The Curve of calibration of moxifloxacin HCL in phosphate buffer at pH 5.5; it was acquired by preparing serial dilutions of MOXF HCL from the stock solution (100µg /ml) from this stock solution aliquots of 1, 2,3,4,5 and 6ml were withdrawn and analyzed spectrophotometrically at its λ_{max}296nm the absorbance of the solution was shown in relation to concentrations.

Solid system characterization

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of the MOXF HCL Emulgel samples were compared with the standard FTIR spectra of the pure drug, IR spectroscopy was carried out to ensure the compatibility between the drug and polymers inside the emulsified gel, and each formula powder was ground, combined with potassium bromide and formed into discs by pressing. The discs were analyzed by FTIR spectroscopy from 2000-4000cm^{-1}

Determination of pH

The pH value is one of the crucial parameters in topical preparations because of the critical effect of pH on the solubility and stability of formulations, the topical emulgel should have a pH range of 5 to 7.4 so there is no irritation to the patient skin upon administration of the formulation. The PH of the Emulgel was premeditated by shaking 1 gm of Emulgel with 100 ml purified water; then, the PH value was established by blending 100 ml of purified water with one gram of Emulgel, and then the PH value was obtained. [6]

Rheological studies

The viscosity of prepared formulations is an essential factor in determining the residence time of the drug on the skin; programs were obtained at 37°C using a brook field viscometer, and the prepared formulas were sheared with Spindale 61 over the range of speed setting from 1 to 10 rpm with 30 seconds between each pair of subsequent speeds, followed by declining order. [7]

Dissolution studies

In vitro dissolution study of MOXF HCL from different formulations was studied by putting a 0.45µm Millipore filter paper in the bottom of the dissolution apparatus basket; after that, we filled the basket with 3 gm of each formula, then closed the basket with its cover then immersed to about 0.5 cm of the surface of phosphate buffer pH 5.5 in a jar of dissolution apparatus with stirring rate of 50 rpm, the study was carried out at 37±0.5°C, samples of 10 ml were withdrawn by pipette after a fixed time intervals and replaced with an equal amount of fresh buffer, the samples were then analyzed spectrophotometrically at λ_{max} 296nm. [8]

Effect of different types of polymers on the release of MOXF HCL in pH 5.5 at 37 °C in phosphate buffer

The best formula set according to the type of polymer has used different polymers (NaCMC, HPMC, Sod. alginate, CMC, HPMC/Sod. Alginate) as gelling bases in preparation of emulgel and compared its effect on the drug release process.

Impact of utilizing various concentrations of emulsifying agents upon releasing of MOXF HCL in pH 5.5 at 37 °C in phosphate buffer

For the selected base, the results of increasing the amount of Span20, tween20 from 2% to 4% (w/w) by using CMC as a gelling base for the preparation of Emulgel and comparing its drug release with CMC Emulgel drug release to select the best amount of emulsifying agent for the preparation of perfect Emulgel formula.

Impact of utilizing various concentrations of oil phase upon releasing of MOXF HCL in phosphate buffer pH 5.5 at 37°C

For a selected base, the change in the concentration from 5% to 7% (w/w) of liquid paraffin with using CMC as a gelling base for the preparation of emulgel and comparing it with CMC Emulgel to see the best drug release.

Statistical analysis

One-way analysis of variance (ANOVA) was performed to compare the outcomes of the various emulgel formulations under study, and the level of significance was chosen at α-0.05, and ($P<0.05$) was considered to be statistically significant. [9]

Preparation of Emulgel Formulas

Preparation of emulsion

The general method for preparation of an emulsion [4] is first the oil phase trial through dissolution 1.66g of span20 in 5%w/w liquid paraffin; secondly, the preparation of the aqueous phase by dissolving 0.34g of tween20 in 50 %(w/w) purified water. Then we dissolved 2 % (w/w) of MOXF HCL in 2.5g ethanol, while 0.15g of methylparaben and 0.05g of propyl paraben in were dissolved 5g of propylene glycol. Both together; blended with the aqueous phase. After that, both the oily and aqueous phases were warmed independently to (70-80°C), then the aqueous phase was added to the oil phase along with constant stirring at 500rpm until room temperature has been reached. [5]

Preparation of gel

The amount of gel mixed with emulsion for preparation of jellified emulsion also depends on the type of polymer used. Still, the amount of purified water used in gel preparation of different polymers is constant, at most 50%(w/w) of distilled water.

Sodium Carboxymethyl cellulose (NaCMC) Emulgel

The gel of NaCMC was prepared by dispersing 2.5%(w/w) in 50%(w/w) of heated purified water, and After being cooled to room temperature, the dispersion was left overnight. [10]

Hydroxy propyl methyl cellulose (HPMC) Emulgel

The gel had been made by dispersing 3.5%(w/w) of HPMC in50%(w/w) of hot water (80°C). The dispersion was mixed until cooling at room temperature. After that, the prepared HPMC gel was mixed with formerly prepared emulsion. [11]

Sodium Alginate (Sod. Alginate) Emulgel

This gel was arranged by dispersing 4 %(w/w) of Sod. Alginate in 50 %(w/w) purified water with heating to (60°C) while stirring, then left overnight for complete swelling and dissolving of polymer in the system. After that, we mixed the prepared Sod. Alginate gel was mixed with previously prepared emulsion. [13]

Sodium alginate and Hydroxy propyl methyl cellulose Emulgel

This gel was made by distributing 3.5 %(w/w) HPMC with 4 % (w/w) Sod. Alginate in 50% (w/w) heated purified water with stirring until cooling, then the prepared gel was kept at (4°C) for the following 24 hours as complete swelling of polymers and uniformity of the system. [12]

Carboxymethyl cellulose (CMC) Emulgel

The gel was prepared by dispersion of CMC 2 %(w/w) in purified water with continuous stirring, then left overnight for homogenization of the system at room temperature, after that the prepared CMC gel was mixed with previously prepared emulsion by a 1:1 ratio to get the desired Emulgel. [13]

Results and Discussion

λmax of MOXF HCL and Calibration curve

The λ max for MOXF HCL; was found to be 295 nm, near the reported value of Clarke s and pharmacopeia value, which was set up to be 296 nm. [14] Figure (2) demonstrates the calibration curve for moxifloxacin HCL in phosphate buffer pH 5.5 at 296 nm, a straight line was obtained by plotting the absorbance versus concentration with a correlation coefficient (r) of 0.999 and Consequently, the calibration curve is true if the medicine complies beers law within the range of concentration used.

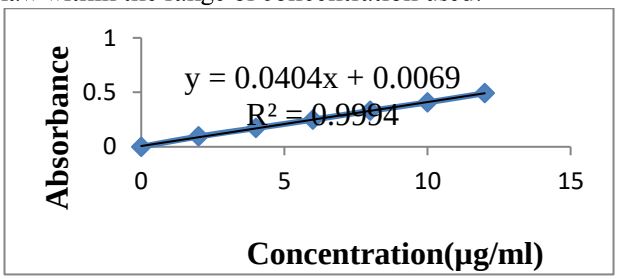

Figure (2) Calibration curve of MOXF HCL in phosphate buffer pH 5.5 at 37°C.

Infrared Spectrum

FTIR of pure MOXF HCL sample was measured and compared with infrared spectra of the prepared physical mixture from MOXF HCL and NaCMC, CMC, HPMC, HPMC/Sod. Alginate and Sod. Alginate polymers are shown in figures (3, 4, 5, 6, 7, and 8) respectively, indicating that MOXF HCL does not interact with polymers when compared to a pure drug's infrared spectrum. as fundamental functional group frequencies were present. The characteristic range of MOXF HCL was characterized by the following bands: [15]

- 1037 F stretching of F-C group
- 1708 C=O stretching of the carbonyl group.
- 3370 N-H stretching of the secondary amine group.
- 3528 O-H stretching of a carboxyl group.

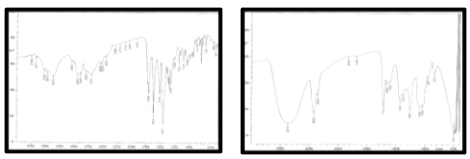

Figure (3) Pure MOXF HCL's IR spectra. Figure (4) MOXF HCL physical mixture with NaCMC.

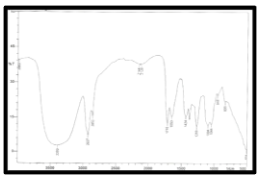

Figure (5) IR spectra of physical mixture HCL and HPMC

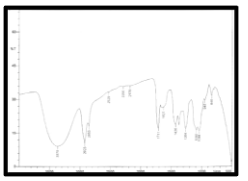

Figure (6) IR spectra of physical mixture of MOXF of MOXF HCL and CMC

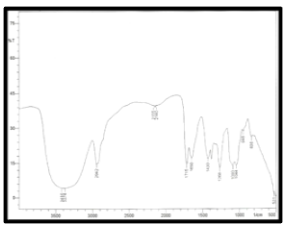

Figure (7) Physical mixture's Infrared spectrum of MOXF HCL and Sod. Alginate

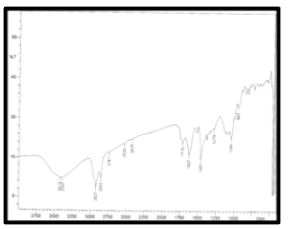

Figure (8) IR spectra of physical mixture of MOXF HCL and HPMC/Sod. Alginate.

Estimation of physical properties of different formulas

As an accepted physical appearance of most formulas of MOXF HCL Emulgel, as shown in Table (2). demonstrates the pH and the viscosity of the prepared formulas, the result revealed that most of the procedures are within the accepted limit of gel-pH preparation, that is, one can conclude no other skin irritation results from pH changes on the skin during application. It was obs that as the concentration of polymer changed, its viscosity changed too. Also, as the consistency of the prepared formula increased, the drug release decreased because the same amount of polymer of higher viscosity induced greater chain entanglement than a polymer of low density. [16]

Effect of different Emulgel based on the release of MOXF HCL

The result showed that the MOXF HCL release from CMC2 % (w/w) Emulgel was higher compared with other formulas in a rank CMC 2%(w/w) > 3.5%(w/w) HPMC > 3.4%/4%(w/w) HPMC/Sod. alginate > 4 %(w/w) Sod. alginate > 2.5 %(w/w) NaCMC. This outcome could be referred to; as the effect of hygroscopicity of cellulose derivatives, which affects water entrapment in the cross-linking gel of 2.5% (w/w) NaCMC, more than that of 2%CMC since this amount of water may hinder other water molecules from diffusing inside Emulgel structure. Then less drug release from NaCMC 2.5%(w/w) compared with CMC 2%(w/w); this result is inconsistent with the result obtained by Magdy I.M.et.al[17] when chlorphenamine Emulgel formulated using cellulose derivative polymers. According to the above results, CMC 2 %(w/w) Emulgel can be used as a selected formula for further parameters that affect the study, as observed in the table 3 and figure (9)

Table 2. Some Physical Properties of Different Emulgel Formulas

formulas	pH	Viscosity	
		1rpm min (poises)	10rpm max (poises)
NaCMC2.5%(W/W)	6.6	870.43	244.4
Sod.alginate4%(W/W)	6.7	840.44	214.5
HPMC3.5%(W/W)	5.9	93.576	38.57
HPMC/Sod.Alginate3.5%/4 %(w/w)	6.8	200.52	82.65
CMC2%(W/W)	7.1	83.543	28.57

Table 3. Effect of Different Bases on Release Rate Constant (K) of MOXF HCL 2 %(w/w) in Phosphate Buffer pH 5.5 at Temperature 37℃.

Type of Base	%of drug release after 3 hours	K (mg)/ ml.min	Correlation coefficient (r2)
2%(w/w) CMC	89.69	0.572	0.995
3.5%(W/W) HPMC	76.5	0.592	0.988
3.5%/4% (w/w) HPMC/Sod. Alginate	67.64	0.490	0.944
4%(W/W) Sod. Alginate	64.92	0.473	0.942
2.5%(W/W) NaCMC	57.83	0.362	0.903

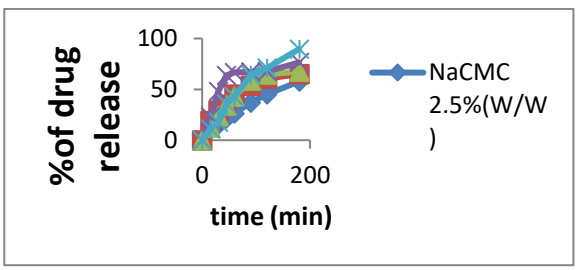

Figure (9) Effect of polymer bases type upon releasing of MOXF HCL 2 %(W/W) in pH 5.5 and

temperature 37℃.

Impact of utilizing various concentrations of emulsifying agents upon releasing of MOXF HCL from selected formula (CMC Emulgel)

The effect of the addition of Span20 and Tween20 as emulsifying agents to produce an Emulgel structure is shown in table 4 and figure (10). It saw the concentration was raised of emulsifying agent from 2 %(w/w) to 4 %(w/w) using CMC as a gel base led to a significant (P<0.05) augmentation in the amount of MOXF HCL released in a medium for disintegration, this increase was found to be from 89.69% to 97.85%, which " may be used to describe the capacity of these emulsifying agents to reduce the interfacial tension between oily and aqueous layer in the dispersion medium, indicating an increase the water-loving nature of emulgel which then improves penetration of dissolution medium into the emulgel structure and then increasing the quantity of moxifloxacin HCL release" this release was inconsistent with that outcome produced by Wan L. et al [18]

Effect of oil phase concentration on MOXF HCL release

Enhanced liquid paraffin from 5%(w/w) to 7.5%(w/w), as shown in table (5)and figure (11), the result revealed a significant(P<0.05) decrease in the amount of MOXF HCL release from CMC as a gel base, the results explained " based on the idea that medicines have an escape propensity, the assumption was increasing the thermodynamic activity which can be described in words of relative medication solubility lead increase the release of drugs from the vehicle.

The same effect was obtained by Ban NB et al [19] who proved that the increase liquid paraffin led to retardation of chloramphenicol freedom from its Emulgel formulation, on other hand increase the emulsifying agent concentration Span20 and Tween20 from 2%to 4% (w/w) with increasing the concentration of liquid paraffin from 5% to 7.5%(w/w) resulted in a significant increase in the release of Moxifloxacin HCL from CMC as a gel base" ; table (6). The same result was obtained when tween 20 was used as a surfactant in the protection of recombinant human growth hormone protection against the agitation process. (20)

Table 4. Effect of Different Concentrations of Emulsifying Agents on The Rate Constant (K) of MOXF HCL 2%(w/w) Release from Selected Formula CMC Emulgel in Phosphate Buffer pH 5.5 at Temperature 37℃.

Surfactant concentration	%of drug Release after 3 hours	K(mg)/ ml. min	Correlation Coefficient (r2)
2%(w/w) 0.34%(w/w) tween20 1.66%(w/w) span20	89.69%	0.572	0.995
4%(w/w) 0.68%(w/w) tween20 3.32%(w/w) span20	97.85%	0.735	0.998

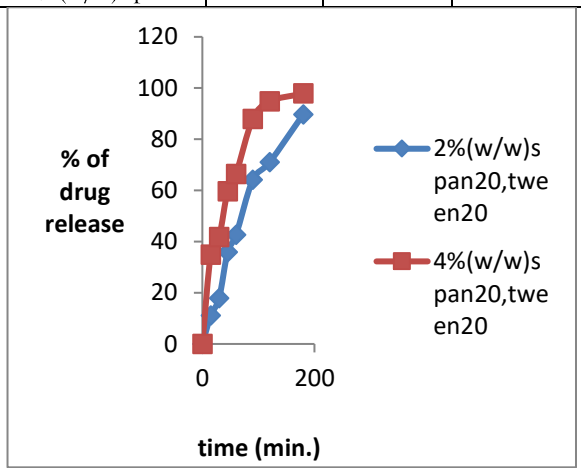

Figure (10) Effect of different concentrations of emulsifying agents on the release of MOXF HCL 2%(w/w) from selected formula CMC Emulgel in phosphate buffer pH 5.5 at temperature 37℃.

Table 5. Effect of Different Concentrations of Oil Phase on The Release of MOXF HCL 2 %(w/w) From Selected Formula (CMC Emulgel) in Phosphate Buffer pH 5.5 at temperature 37℃.

Liquid paraffin concentration	% of drug release after 3 hours	K (mg)/ ml. min	Correlation coefficient (r2)
7.5% (w/w) with 2%(w/w) Span20 and Tween20	36.21%	0.226	0.918
7.5%(w/w) with 4%(w/w) Sapn20 and Tween22	39.80%	0.295	0.943

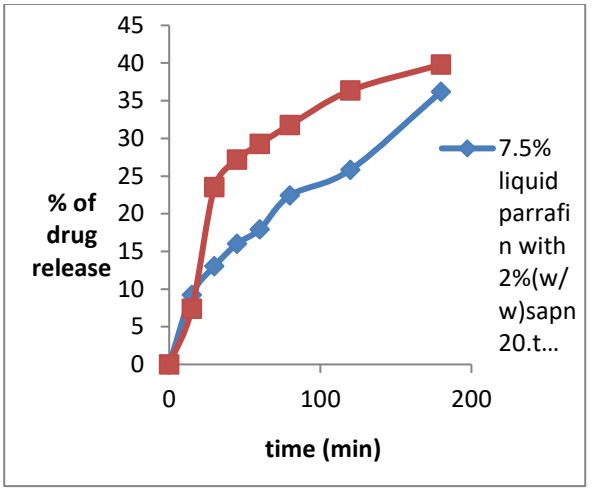

Figure (11) Effect of different concentrations of oil phase on the release of MOXF HCL 2 % (w/w) release from the selected formula (CMC Emulgel) in phosphate buffer pH 5.5 at 37°C.

Table 6. Effect of Different Concentrations of Oil Phase on The Release of MOXF HCL 2%(w/w) From Selected Formula (CMC Emulgel) with Different Concentrations of Surfactant in Phosphate Buffer pH 5.5 at 37°C.Temperature.

Liquid paraffin concentration	% of drug release after 3 hours	K(mg)/ ml. min	Correlation coefficient (r^2)
7.5% (w/w) with 2%(w/w) Span20and Tween20	36.21%	0.226	0.918
5%(w/w) with 2%(w/w) Span20and Tween20	89.69%	0.572	0.995
7.5%(w/w) with 4%(w/w) Sapn20 and Tween20	39.80%	0.295	0.943
5%(w/w) with 4%(w/w) Sapn20 and Tween20	97.85%	0.735	0.998

Kinetic of MOXF HCL release from different Emulgel bases:

The analysis of drug release kinetic from different emulgel bases using different Emulgel in the formulas illustrated in table (7), an empirical formula has been used substantiated by fitting the amount of moxifloxacin HCL released as a function of the square root of time takes over, which provide straight line given for diffusion process, the result indicated that linear relationship was obtained as the quantity of moxifloxacin HCL released (m) was plotted versus square root of time ($t^{1/2}$) and the slop which represent the rate constant (K) for diffusion. As previously mentioned, the drug release followed Higuchi linear expression as all Emulgel had given almost linear relationship when a drug release load was plotted with the square root of time, the data fitted to various kinetic models, and it was noted that the best formula provides Higuchi –model.[21]

Table 7. The Kinetic Analysis of MOXF HCL Release from Different Gel Bases According to First Order, Zero Order Kinetic, and Higuchi model.

Type of Gel Base	Higuchi	Zero-order	First order	
	K (mg)/ (min)1/2	Correlation coefficient (r2)	Correlation coefficient (r2)	Correlation coefficient (r2)
2%(w/w) CMC	0.810	0.997	0.995	0.970
3.5%(W/W) HPMC	0.642	0.978	0.988	0.768
3.5%/4% (w/w) HPMC/Sod. Alginate	0.651	0.985	0.944	0.954
4%(W/W) Sod. Alginate	0.618	0.981	0.941	0.974
2.5%(W/W) NaCMC	0.544	0.998	0.903	0.997

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