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FORMULATION AND EVALUATION OF GATIFLOXACIN TOPICAL SEMISOLID DOSAGE FORMS

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ABSTRACT

The aim of this work is to formulate Gatifloxacin in different semisolid preparations including gels and emulgels of good rheological and release properties. All formulations contained 0.1w/w% Gatifloxacin(GF) concentration. Results showed that all semisolid formulations depicted acceptable physical properties, all gel and emulgel formulations followed non Newtonian, pseudoplastic flow,All formulations depicted thixotropic behavior with varying recovery rate.Polymers and formulations of lower viscosities achieved rapid recovery.Sodium carboxy methylcellulose(SCMC) gel(2w/w%)showed the most rapid recovery compared to other gel and emulgel formulations, Polymer concentration highly affected the degree of shear rate and shear stress. It was found that $F_{Eg}7$ depicted the highest drug release and permeation compared to the other emulgel formulations .Therefore it is the most suitable formulation for topical formulation.

KEYWORDS: Gatifloxacin, Gel, Emulgel, Polymers.

INTRODUCTION

Gatifloxacin is a member of the fluoroquinolone antibiotic family. It is approved for treatment of bacterial conjunctivitis caused by a broad range of microorganisms.[1] As with other members of this group it functions by inhibiting the bacterial enzymes DNA gyrase and topoisomerase IV. This design for fourth generation fluroquinolones theoretically enables them to reduce the opportunity for microbial resistance to the antibiotic.

Topical drug delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders (e.g. acne) or the cutaneous manifestations of a

general disease (e.g. psoriasis) with the intent of confining the pharmacological or other effect of the drug to the surface of the skin or within the skin. Topical activities may or may not require intra-cutaneous penetration or deposition[2]Topical drug delivery systems include a large variety of pharmaceutical dosage forms like semisolidsTopical preparations are used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membranes. The main advantage of topical delivery system is to bypass first pass metabolism. Avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time are other advantage of topical preparations.[3,4] Semi-solid formulation in all their diversity dominate the system for topical delivery, but foams, spray, medicated powders, solution, and even medicated adhesive systems are in use. The topical drug delivery system is generally used where the other systems of drug administration fail or it is mainly used in pain management, contraception, and urinary incontinence.

MATERIALS AND METHODS

Materials

Gatifloxacin (Sigma Chemical Company,USA); Carbopol 934P (Goorich Co, USA); Hydroxypropyl methylcellulose(HPMC)(50,100 and 4000 cps) , Methycellulose(L 0512 ;450 cps); Sodium Carboxymethylcellulose (high,medium and low viscosities(Sigma Chemical Company,USA); Triethanolamine ;Sodium hydrogen phosphate ; Potassium dihydrogen phosphate;Propylene glycol; Tween 20 ; Span 20 ; Liquid paraffin;Methy and Propyl parabens(kindly supplied from El-Nasr Pharmaceutical Chemicals Co.,Egypt);Cellulose membrane(Thomas Co,Philadelphia,USA). All reagents and solvents used were of analytical grades.

Method

Formulation and Preparation of Semisolids

All formulations contained 0.1w/w% GF concentration.

Preparation of GF Gel Using Cellulose Derivatives

All the cellulose derivatives were used in concentrations of 2,6 and 10w/w%. Hydrophilic cellulose derivative gel base was taken in a 100-ml beaker and wetted by water for 24 h.[5] GF was dissolved in some water and this solution was added little by little to the wetted gel base and mixed well using magnetic stirrer. Prepared formulations are given in Table1.

Table.1.Composition of the Formulations(w/w%)

Formulation	HPMC	HPMC	HPMC	SCMC	SCMC	SCMC	MC	MC	MC	GF
F_g1	2									0.1
F_g2		6								0.1
F_g3			10							0.1
F_g4				2						0.1
F_g5					6					0.1
F_g6						10				0.1
F_g7							2			0.1
F_g8								6		0.1
F_g9									10	0.1

HPMC:hydroxypropyl methylcellulose ; SCMC:sodium carboxymethyl cellulose ; MC: methylcellulose

Preparation of GF Emulgel

Gatifloxacin emulgel was prepared by the method reported [6] with minor modification. The Gel in formulations were prepared by dispersing Carbopol 934 in purified water with constant stirring at a moderate speed in purified water with constant stirring at a moderate speed then the pH was adjusted to 6 to 6.5 using Tri Ethanol Amine (TEA).The oil phase of the emulsion were prepared by dissolving Span 20 in light liquid paraffin while the aqueous phase was prepared by dissolving Tween 20 in purified water and propylene glycol .Gatafloxacin was dissolved in ethanol and both solutions was mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70° to 80°C; then the oily phase were added to the aqueous phase with continuous stirring until cooled to room temperature. Gel and emulsion were mixed in a ratio of 1:1 to obtain the emulgel.

Experimental design

Eight GF emulgel formulations (Table.2) were prepared according to a 2^3 factorial design employing the qualitative factors and levels shown in table 2 and table 3.

Table.2. Factor and Level for the 2^3 Factorial Designs

Factors	Levels
(A) Gelling agent type	+0.6 % - 0.3 %
B) Liquid paraffin concentration	+7.5% -5%
(C) Emulsifying agent concentration	+2.5% - 1.5%

Table.3. Various composition of Basic GF Emulgel formulation

Formula	Gelling Agents(%) (Carbopol 934)	Emulsifying Agents(%) Tween-20 and Span-20	Liquid Paraffin(%)
$F_{Eg}1$	0.6	1.5	5
$F_{Eg}2$			7.5
$F_{Eg}3$		2.5	5
$F_{Eg}4$			7.5
$F_{Eg}5$	0.3	1.5	5
$F_{Eg}6$			7.5
$F_{Eg}7$		2.5	5
$F_{Eg}8$			7.5

High concentration represents a high level(+) and low concentration represents a low level(-)

Table.4.Various composition of GF Emulgel formulation

Ingredients(%w/w)	$F_{Eg}1$	$F_{Eg}2$	$F_{Em}3$	$F_{Eg}4$	$F_{Eg}5$	$F_{Eg}6$	$F_{Eg}7$	$F_{Eg}8$
GF	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Carbopol 934	0.6	0.6	0.6	0.6	0.3	0.3	0.3	0.3
Liquid paraffin	5	7.5	5	7.5	5	7.5	5	7.5
Tween-20	1.5	1.5	2.5	2.5	1.5	1.5	2.5	2.5
Span-20	1.5	1.5	2.5	2.5	1.5	1.5	2.5	2.5
Propylene glycol	5	5	5	5	5	5	5	5
Ethanol	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Methy paraben	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Propyl paraben	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005
Purified water(q.s)	100	100	100	100	100	100	100	100

Evaluation and Characterization of GF Semisolids

Physical Properties

All formulations are examined for appearance. color, homogeneity, oily feel , odor water dilution ,clarity ,odor,oily feel , homogeneity.

Gelling Capacity

The gelling capacity of the prepared formulations of both gels and emulgels were determined by placing a drop of the formulation in a vial containing 2ml of freshly prepared simulated tear fluid and visually observed . The time taken for gelling was noted.[7]

Extrudability Study

The extudability test was carried out using hardness tester. A 15 gm of tested formulation was filled in aluminium tube. The plunger was adjusted to hold the tube properly. 1kg/cm^2 was applied for 30 second . The quantity of semisolid extruded was weighed . The procedure was repeated at 3 equidistance places of the tube.[8]The extrudability was then calculated by using the following formula.[9]

Extrudability = Applied weight to extrude gel from tube (in gm) / Area (in cm^2)

Ex–vivo Bioadhesive Strength

The two pans of physical balance were removed.Right side pan was replaced with a 100 ml beaker and on the left side, a glass slide was hanged. For balancing the assembly,a weight of 20 g was hanged on the left side. Another glass slide was placed below the hanged slide. Portions of hairless fresh rat skin were attached with both slides. One gram of gel was placed between two rat skin faces. Little pressure was applied to form bioadhesion bond, and then slowly water was added on right side beaker, till the gel was separated from one face of rat skin attached. Volume of water added was converted to mass.This gave the bioadhesive strength of gel in grams.[10]

Swelling Index

Swelling of the polymer depends on the concentration of the polymer, ionic strength and the presence of water. To determine the swelling index of prepared topical gel, 1 gm of gel was taken on porous aluminum foil and then placed separately in a 50 ml beaker containing 10 ml 0.1 N NaOH. Then samples were removed from beakers at different time intervals and put it on dry place for some time after it reweighed. Swelling index was calculated as follows [11].

Swelling Index (SW) % = [(Wt – Wo) / Wo] × 100.

Where, (SW) % = Equilibrium percent swelling, Wt = Weight of swollen gel after time t, Wo = Original weight of gel at zero time.

pH measurements[12]

The pH of various gel formulations was determined by using digital pH meter.1 g of gel was dissolved in 100 mL freshly prepared distilled water and stored for two hours. The measurement of pH of each formulation was done in triplicate and average values were calculated.

Drug Content[13, 14]

A specific quantity (1 g) of developed gel or emulgel was taken and dissolved in 100mL of phosphate buffer of pH 5.4. The volumetric flask containing gel or emulgel solution was shaken for 2 h on mechanical shaker in order to get complete solubility of drug. The solution was filtered through 0.45 µm membrane filter and estimated spectrophotometrically at 285 nm using phosphate buffer (pH 5.4) as blank. Ointment bases , oleaginous , absorption and emulsion bases were dissolved in ether whereas water soluble base were dissolved in water.

Rheology Study[15]

The formulations were poured into the sample adaptor of the Brookfield DV-E rheomoter and angular velocity was increased gradually from 1 to 40 rpm using spindle no. 4. The hierarchy of angular velocity was reversed and the average dial reading multiplied by spindle constant(20) give viscosity. The temperature was maintained within 37 ± 0.1°C.

In-vitro Rlease Study of Gatifloxacin from Different Semisolid Formulations

Modified USP Dissolution Apparatus II (the paddle method) was used.Three grams of the base containing 3 mg GF was spread over the surface of a watch glass of a 8 cm diameter and covered with equally sized wire screen. The watch glass-base and screen were held together by three equally spaced binder clips.[16 17]

The assembly was placed at the bottom of USP dissolution tester vessel containing 300 ml of phosphate buffer at pH 5.4, adjusted to a temperature of 37±0.5^{o}C. Release was carried out in aforementioned apparatus at a paddle speed of 50±2rpm. At predetermined time intervals, an aliquot of 5ml of the dissolution medium was withdrawn, filtered and measured spectrophotometry at λ_{max} 285 nm. The experiment was repeated in triplicate.

In-vitro Drug Diffusion Study

Formulations chosen to undergo diffusion test through cellulose membrane those depicted the highest drug release.

Release of Gatifloxacin from selected formulations was studied employing the permeation apparatus designed as described. A glass cylinder with cross sectional area of 7.5 cm^2 was used as permeation cell. A cellulose membrane(0.01 cm thickness,soaked in buffer solution for 24 hours before use) was fixed to one end of the cylinder with the aid of an adhesive to result as a permeation cell. 3 gm of medicated gel and/or emulgel was taken in the cell (donor

compartment) and cell was immersed in a beaker containing 300 ml of pH5.4 phosphate buffer as receptor compartment. The entire surface of the cell was in contact with the receptor compartment which was agitated using magnetic stirrer and a temperature of 37±1°C was maintained. Samples (5 ml) of the receptor compartment were taken at 1hr interval of time over a period 10 hours with same amount replaced. The sample was analyzed for Gatifloxacin at 285 nm against blank using UV Spectroscopy. Amount of Gatifloxacin released at various time intervals was calculated using equation of linear regression analysis.

The permeation parameters of Gatifloxacin (Permeability coefficient [P(cm.hr^{-1})], partition coefficient [K(mg.hr$^{-1/2}$], diffusion coefficient [D(cm.hr$^{-1/2}$)], Apparent steady state flux [Jss(mg.cm^{-2}.hr^{-1}], enhancing factor [Fen], lag time [tL(hrs], relative permeation rate [RPR]) were calculated from the penetration data.

Plotting the cumulative amount permeated versus time,

and the slope represents [Jss]

$P = Jss / C_o$ C_o: is the initial concentration in a donor compartment (3mg drug present in 3g formulation)

Plotting amount permeated versus square root of time(Higuchi model)

[D] was calculated from the slope obtained according to

the following equation

$D = (slope / 2 Co)2 . \pi$

[K] was calculated from P and D using the penetration barrier L with known thickness of semipermeable membrane (0.01 cm) from equation :

$K = P. L / D$

[tL] was calculated from equation : $tL = L^2 / 6 D$

[Fen] = Cumulative amount permeated from formula /Amount permeated from control

[RPR]= P of the formula / P of the control.

Statistical Analysis

All data were represented as mean ± SD (n = 3). Statistical comparisons were made using Student's t – test.

RESULTS AND DISCUSSION

Physical Evaluation

Table.5. depicts the organoleptic properties of different GF semisolid formulations**.** All formulations were evaluated for their homogeneity,appearance color, oily feel , odor and water dilution.All these properties are inhereted in the ingredients of the semisolid formulations.

Table. 5.Organoleptic Properties of Different GF SemisolidFormulations

Formulation	Homogeneity	appearance	Color	Odor	Oily feel	Water dil.
F_g1	****	**HighlyViscous,translucent**	**Faint yellow**	+	**0**	+
F_g2	****	**HighlyViscous,translucent**	**Faint yellow**	+	**0**	+
F_g3	****	**Viscous,translucent**	**Faint yellow**	+	**0**	+
F_g4	****	**HighlyViscous,translucent**	**Faint yellow**	+	**0**	+
F_g5	****	**HighlyViscous,translucent**	**Faint yellow**	+	**0**	+
F_g6	****	**Viscous,translucent**	**Faint yellow**	+	**0**	+
F_g7	****	**HighlyViscous,translucent**	**Faint yellow**	+	**0**	+
F_g8	****	**Viscous,translucent**	**Faint yellow**	+	**0**	+
F_g9	****	**Viscous,translucent**	**Faint yellow**	+	**0**	+
$F_{Eg}1$	****	**HighlyViscous,translucent**	**Faint yellowish green**	++	**0**	+
$F_{Eg}2$	****	**HighlyViscous,translucent**	**Faint yellowish green**	++	**0**	+
$F_{Eg}3$	****	**HighlyViscous,translucent**	**Faint yellowish green**	++	**0**	+
$F_{Eg}4$	****	**HighlyViscous,translucent**	**Faint yellowish green**	++	**0**	+
$F_{Eg}5$	****	**HighlyViscous,translucent**	**Faint yellowish green**	++	**0**	+
$F_{Eg}6$	****	**HighlyViscous,translucent**	**Faint yellowish green**	++	**0**	+
$F_{Eg}7$	****	**HighlyViscous,translucent**	**Faint yellowish green**	++	**0**	+
$F_{Eg}8$	****	**HighlyViscous,translucent**	**Faint yellowish green**	++	**0**	+

****** means excellent ; *** means very good ; ** means good**

0:unavailable ; (+):moderate ; (++):good ; (+++):best

Drug Content, Spreadability study, Extrudability study and Bioadhesive strength measurement of Semi-solid Formulations.

Table.6.Illustrates drug content,spreadability, extrudability and bioadhesive of gel and emulgel formulations strength. Mostly $F_{Eg}7$ as compared to other gel , emulgel formulations depicted the greatest values of spredability , extudability and lowest bioadhesive strength.

Table.6.Drug Content, Spreadability study, Extrudability study and Bioadhesive strength measurement of Topical Gel

Formulation	Drug Content(%w/v)	Spreadability(cm) average±S.D.	Extrudability (gm./cm^2)	Bioadhesive strength (gms)
F_g1	88.7	1.1±013	6.5±0.11	62.9
F_g2	86.4	1.3±0.22	6.8±0.21	64.4
F_g3	93.5	0.9±0.06	5.5±0.23	73.5
F_g4	94.6	2.9±0.61	12.20±0.35	33.5
F_g5	82.7	2.4±0.04	11.90±0.24	35.6
F_g6	88.2	2.1±0.31	11.30±0.32	41.2
F_g7	95.3	2.0±0.36	12.0±0.41	42.5
F_g8	84.9	1.7±0.90	10.90±0.25	45.6
F_g9	96.8	1.6±0.25	9.90±0.44	51.3
$F_{Eg}1$	89.66	1.8±0.01	7.60±0.26	67.8
$F_{Eg}2$	99.1	1.9±0.07	8.10±0.02	68.4
$F_{Eg}3$	100	2.0±0.36	7.30±0.06	69.5
$F_{Eg}4$	86.7	2.2±0.44	8.10±0.04	71.6
$F_{Eg}5$	91.8	1.8±0.03	10.50±0.19	50.4
$F_{Eg}6$	94.3	2.4±0.60	10.90±0.33	52.3
$F_{Eg}7$	96.1	3.3±0.09	12.50±0.24	32.6
$F_{Eg}8$	98.7	2.9±0.05	12.10±0.04	38.2

Swelling Index Study of Different semisolid Formulations

Figures(1,2)depicted the effect of time on Swelling Index of different polymers used in the preparation of different formulations of gels and emulgels From these data we found that, emulgel formulations had greater percent swelling Index than gel formulations. $F_{Eg}1$ revealed the greatest Swelling Index as compared to other formulations. Whereas gels prepared with HPMC depicted the lowest Swelling Indices. The Swelling Index depends on polymer concentration , degree of cross-linking , amount of water.

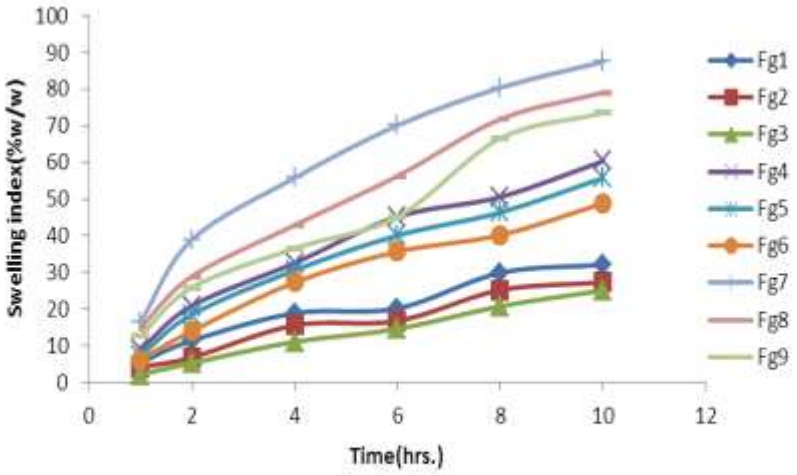

Fig.1.Swelling Index Pattern of Different Gel Formulations.

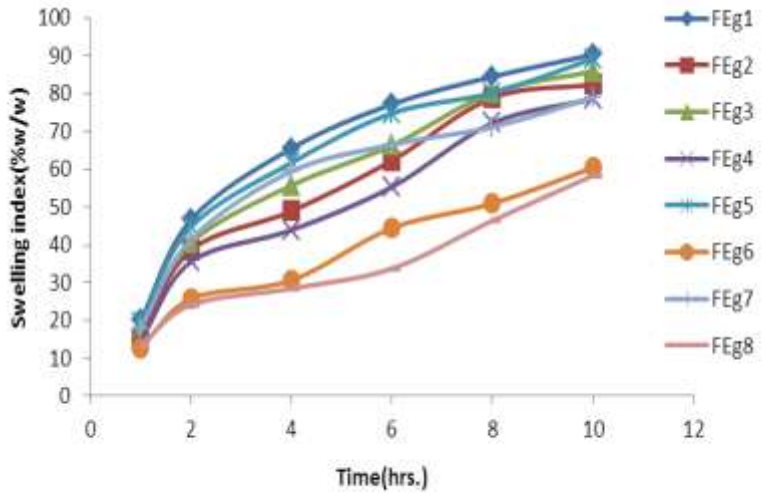

Fig.2. Swelling Index Pattern of Different Emulgel Formulations.

pH Measurement and Gelling Capacity of Different Formulations of Gel and Emulgel Formulations.

Table.7.illustrates pH values and gelling properties of different gel and emulgel formulations.

Table.7.pH Values and Gelling Capacity of Different Formulations of Gel and Emulgel

Formulation	pH	Gelling capacity
F_g1	7.2	++
F_g2	6.8	++
F_g3	6.9	++
F_g4	8.6	+
F_g5	8.1	+
F_g6	8.0	+
F_g7	7.6	+
F_g8	6.1	+
F_g9	5.8	+

$F_{Eg}1$	6.3	++
$F_{Eg}2$	6.2	++
$F_{Eg}3$	6.5	++
$F_{Eg}4$	6.7	++
$F_{Eg}5$	6.1	++
$F_{Eg}6$	6.6	++
$F_{Eg}7$	6.9	++
$F_{Eg}8$	6.3	++

+ : Gellation after few miutes ; ++ Gellation immediately

Rheology study

Viscosities (in poise) of Gatifloxacin gel and emulgel formulations at low and high rates of shear are illustrated in tables(8 and 9) .The consistency depends on the ratio of solid fraction, which produces structure, to liquid fraction. The difference in the type of the gelling agents result changes in structure consistency.[18]The viscosity of the gel and emulgel formulations generally reflects its consistency .Carbopol 934– based formulations ($F_{Eg}1$ - $F_{Eg}8$) possessed considerably higher viscosities than hydroxylpropylmethyl cellulose, sodium carboxymethylcellulose and methylcellulose –based formulations (F_g1 - F_g9). This effect may be attributed to the higher hygroscopicity of cellulose derivatives as compared to carbopol 934 .So that , the type and the concentration of the base used play an important role in the topical preparation design since it affects the viscosity of the gel and emulgel. Meanwhile incorporation of emulsifying agent and liquid paraffin in emulgel formulations made carbopol 934 gave marked effect on the consistency of the resulted base as a viscous or softy cream emulgel.[19] Formulations ($F_{Eg}1$- $F_{Eg}4$) depicted higher viscosities than formulations($F_{Eg}5$- $F_{Eg}8$). This is due to the high concentration of carbopol 934 in the former formulations.Formulations($F_{Eg}3$ and $F_{Eg}4$) showed higher viscosities than formulations($F_{Eg}1$ and $F_{Eg}2$) . This is because $F_{Eg}3$ and $F_{Eg}4$ included higher concentration of emulsifying agents(2.5w/w%).Formulation $F_{Eg}6$ depicted the lowest viscosity as compared with all emulgel formulations. This is due to the low polymer and high liquid paraffin concentrations. Emulgel formulations were ranked according to their viscosities in a descending order as follow.

$F_{Eg}3$> $F_{Eg}4$> $F_{Eg}1$> $F_{Eg}2$> $F_{Eg}7$> $F_{Eg}8$> $F_{Eg}5$> $F_{Eg}6$

It was seen that an increase in concentration of emulsifying agents (tween 20 and span 20) , from 1.5 w/w % to 2.5 w/w% , led to an increase in the viscosity of carbopol 934 – based formulations ($F_{Eg}3$, $F_{Eg}4$, $F_{Eg}7$ and $F_{Eg}8$) as compared with ($F_{Eg}1$, $F_{Eg}2$, $F_{Eg}5$ and $F_{Eg}6$) ,

respectively , at both low and high rate of shear. On the other hand rising liquid paraffin content from 5 to 7.5w/w% for formulations ($F_{Eg}2$, $F_{Eg}4$, $F_{Eg}6$) reduced the viscosity as compared with formulations ($F_{Eg}1$, $F_{Eg}5$). These results may be attributed to the ability of liquid paraffin to contribute in a formulation of emulsion with water[20], that make the utilization of span 20 and tween 20 as a surfactants is possible.All the prepared emulgel formulations exhibited a shear thinning behaviour since the viscosity (the reciprocal of slope) decreased with increasing the shear rate.

As the shear stress is increased , the normally disarranged molecules of the gelling material are caused to align their long axes in the direction of flow. Such orientation reduces the internal resistance of the material and hence decreases the viscosity.[21] Rheograms showed that Gatifloxacin gel and emulgel formulations possessed pseudoplastic flow with thixotropic behaviour, where the down curve was displaced with regard to the up curve, showing at any rate of shear on the down curve a lower shear stress than it had on the up curve; a hysteresis loop was formed between the two curves. Thixotropy, or time-dependent flow , occurs because the gel requires a finite time to rebuild its original structure that breaks down during continuous shear measurements.[22] It is noteworthy that thixotropy is a desirable characteristic in pharmaceutical preparations in order to deliver an initially thick product as a thinner, easily spreadable material. These findings are in agreement with Gatifloxacin emulgel using carbopol 934 or carbopol 940,HPMC, SCMC and MC as gelling agents.[23] It was noticed that polymers and formulations of lower viscosities achieved rapid recoveries from shear rate and hence lower thixotropic behavior than those of higher viscosities.

Table.8.Rheological Parameters of Different Gel Formulations

Formulation	Viscosity(cp) at a low shear rate	Viscosity(cp) at a high shear rate	Coefficient of determination(r^2)	Flow index	Consistency index(m)	Rheologicl behavior	Flow property
F_g1(2w/w% HPMC)	5821	4897.79	0.998	0.95	6025.6	Non-Newtonian	Pseudo-plastic
F_g2(6w/w% HPMC)	8317.6	7079	0.980	0.90	10568.2	Non-Newtonian	Pseudo-plastic
F_g3(10w/w% HPMC)	11220	8912.5	0.992	0.85	15995.6	Non-Newtonian	Pseudo-plastic
F_g4(2w/w% SCMC)	79.4	19.7	0.980	0.48	243.2	Non-Newtonian	Pseudo-plastic
F_g5(6w/w% SCMC)	300	69.1	0.957	0.55	1122	Non-Newtonian	Pseudo-plastic
F_g6(10w/w% SCMC)	428	156	0.949	0.45	1774.2	Non-Newtonian	Pseudo-plastic

F_g7(2w/w% MC)	1584.9	540	0.998	0.69	3133.3	Non-Newtonian	Pseudo-plastic
F_g8(6w/w% MC)	2511.9	380	0.967	0.30	22750.9	Non-Newtonian	Pseudo-plastic
F_g9(10w/w% MC)	2280	631.0	0.799	0.3	16982.4	Non-Newtonian	Pseudo-plastic

Table.9.Rheological Parameters of Different Gel Formulations

Formulation	Viscosity(cp) at a low shear rate	Viscosity(cp) at a high shear rate	Coefficient of determination(r^2)	Flow index	Consistency index(m)	Rheologicl behavior	Flow property
F_{Eg}1	19952.6	7150	0.991	0.36	58076.4	Non-Newtonian	Pseudo-plastic
F_{Eg}2	15848.9	10000	0.997	0.64	35892.2	Non-Newtonian	Pseudo-plastic
F_{Eg}3	41403.12	6344.9	0.990	0.64	623734.8	Non-Newtonian	Pseudo-plastic
F_{Eg}4	30831.9	6220.5	0.606	0.34	33573.8	Non-Newtonian	Pseudo-plastic
F_{Eg}5	12589.3	1995.3	0.982	0.35	73451.4	Non-Newtonian	Pseudo-plastic
F_{Eg}6	12302.7	398	0.992	0.04	117219.5	Non-Newtonian	Pseudo-plastic
F_{Eg}7	13489	2754	0.980	0.16	134896	Non-Newtonian	Pseudo-plastic
F_{Eg}8	13350	10000	0.998	0. 90	16557.7	Non-Newtonian	Pseudo-plastic

In-vitro Release Studies of Semisolids

Release Study from Gel Formulations

GF release from the different gel formulations was represented graphically in figures(3-5).GF released from the formulations decreased as the polymer concentration increased. It is possible that at the higher polymer concentrations the drug is trapped in smaller polymers and it is structured by its close proximity to that polymer molecules. This increases the release resistance by more than expected. Also, the density of chain structure which has been observed in gels' microstructure increases at the higher polymer concentration and this limits the drug movement area.[24] The ability of a hydrogel system to serve as a reservoir for drug delivery is influenced by the macro and microrheological properties of the matrix. Viscosity is the most widely utilized reference for the characterization of polymer structure, although it is not sufficiently comprehensive for the full determination of hydrogel strength . Viscosity is negatively related to release of active substance from formulation and its penetration through the diffusion barriers. This decrease in the release could be attributed to increased

microviscosity of the gel by increasing polymer concentration. Thus, both high concentration of polymer and high viscosity complete each other in decreasing the release of active substance release from the formulation[25] The better release of the drug from all gel base formulations can be observed and ranked in the following descending order.

2w/w % SCMC > 6% w/w % SCMC > 2w/w% HPMC > 2 w/w % MC > 10w/w% SCMC > 6w/w % MC > 10w/w % MC > 6 w/w % HPMC > 10 w/w % HPMC . Where the amounts of the drug released after 3 hours were 100w/w% , 91.34 w/w % , 87.6 w/w % , 86.3 w/w %, 81.7 w/w % , 74.9 w/w % , 71.3 w/w % , 55.9 w/w % and 45.68 w/w % respectively.

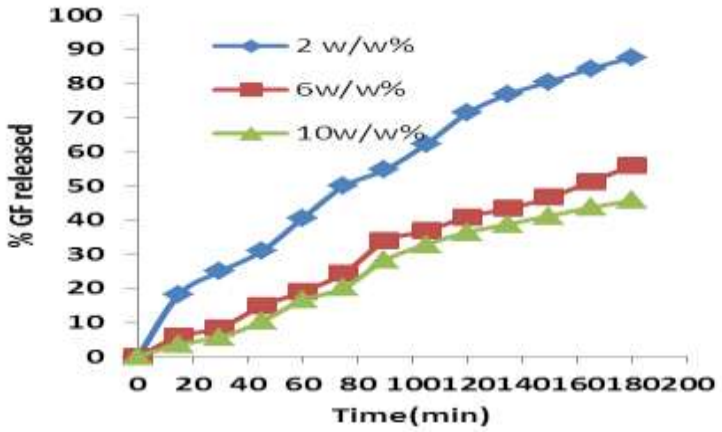

Fig.3.Release Pattern of Gatifloxacin from Different Concentrations of HPMC in Phosphate Buffer pH 5.4 at 37±0.5°C.

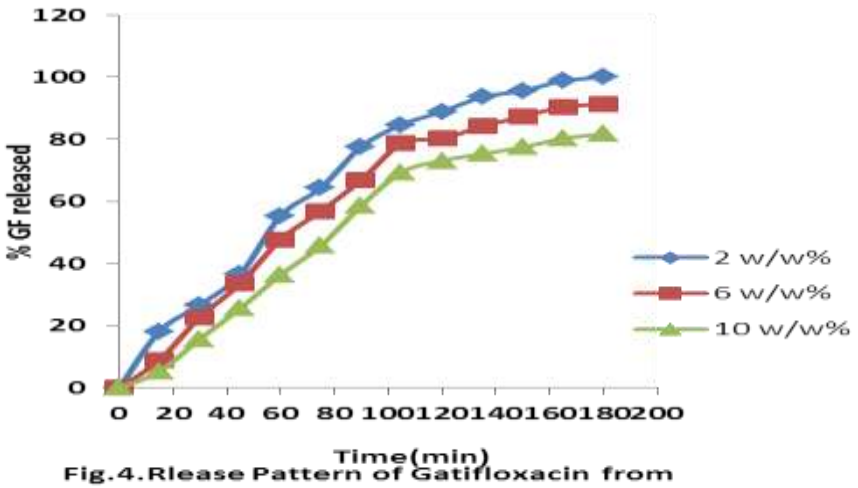

Fig.4.Rlease Pattern of Gatifloxacin from Different Concentrations of SCMC in Phosphate Buffer pH 5.4 at Temperature 37±0.5oC

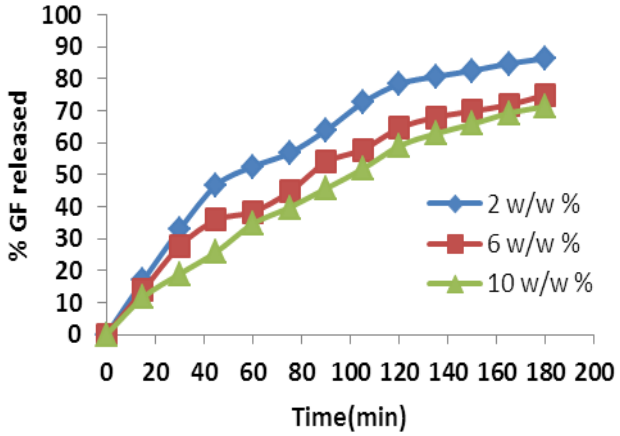

Fig.5. Release Pattern of Gatifloxacin from Different Concentrations of MC in Phosphate Buffer pH 5.4 at 37±0.5oC.

Release Study from Emulgel Formulations

In vitro release patterns of Gatifloxacin from its various emulgel formulations were represented graphically in Figure 6. The high release rate of the drug from formulations $F_{Eg}7$, $F_{Eg}8$, $F_{Eg}5$ and $F_{Eg}6$ compared to $F_{Eg}1$- $F_{Eg}4$.can be observed . This may be due to the low polymer concentration (0.3w/w%). Formulation $F_{Eg}7$ depicted the highest drug release compared to other formulations. This is due to low polymer concentration(0.3w/w%) , low concentration of liquid paraffin(5w/w%) and high concentration of emulsifiers(2.5w/w%). It was seen that increasing the concentration of emulsifying agent from 1.5 % to 2.5w/w% led to significant ($p<0.05$) increase in the amount of Gatifloxacin released in dissolution medium ,.This effect may be referred to the ability of these emulsifying agents to lower the interfacial tension between oily and aqueous layers in the dispersion medium (Higuchi,1982), indicating an increase in the hydrophilicity of emulgel which in turn increase penetration of dissolution medium into the emulgel structure.Formulation $F_{Eg}2$ depicted the lowest drug release compared to other formulation. This is due to the high polymer concentration(0.6w/w%) which increases the viscosity, low emulsifiers concentrations(1.5w/w%) and high liquid paraffin concentration(7.5w/w%). The effect of paraffin concentration on the release of Gatifloxacin from carbopol 934 emulgel .Increasing the liquid Paraffin concentration from 5 w/w% to 7.5 w/w% in carbopol , led to significant decrease ($p <0.05$) in the amount of gatifloxacin released compared to other formulations.This result may be explained according to the concept of escaping tendency of drugs[26],it was supposed that increasing the thermodynamic activity which can be expressed in terms of relative solubility of drug lead to enhance the releasing of drugs from vehicle.The

same effect was proved that the increased liquid paraffin led to retardation of Gatifloxacin release from its emulgel formulation.The release of GF from emulgel formulations can be ranked in the following descending order: $F_{Eg}7$ > : $F_{Eg}8$> : $F_{Eg}5$ > : $F_{Eg}6$ > : $F_{Eg}3$> : $F_{Eg}4$ > : $F_{Eg}1$> $F_{Eg}2$, where the amounts of the drug released after 3 hours were 89.5±0.14%, 86.2±0.35%, 84.5±0.22%, 81.3±0.36%,78.1±0.11%, 74.4±0.22%, 70.8±0.42% and 68.1±0.46%, respectively.

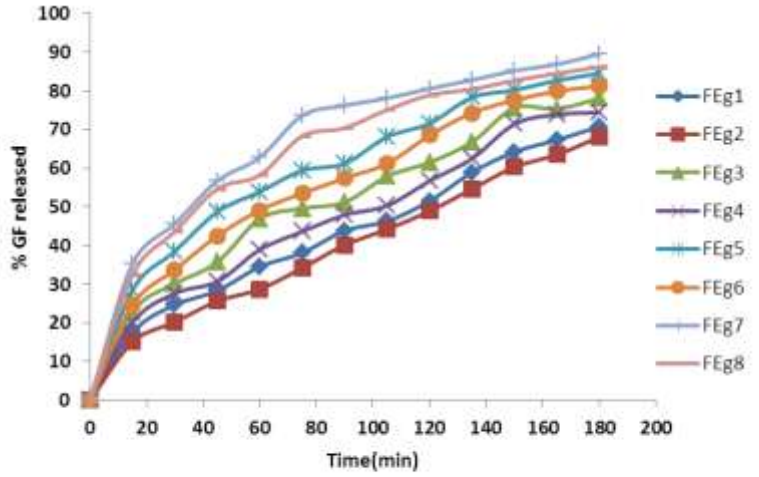

Fig.6.Rlease Pattern of Gamifloxacin from Different Emulgel Formulations in Phosphate Buffer(pH 5.4) at 37±0.5°C

In-vitro Drug Permeation Study

The results showed that the formulation used was able to release the drug Figure7. With the exception of F_g1 there is no significant difference in the amounts of GF permeated through cellulose membrane after 9 hrs. Marketed sample depicted a comparable result with all formulations with the of F_g1. The ranking order of drug permeated in a descending order after 9 hrs was as follow.

$F_{Eg}7$> M> F_g4> > F_g7> F_g1.

$F_{Eg}7$ depicted a comparative permeation with marketed sample added to its excellent physical properties.Therefore,it represented the formulation of choice.

Tables(10 and 11) illustrate the Permeation Parameters of Gatifloxacin from the selected formulations across Semi-permeable membrane.It appears that for all prepared formulations; the amount permeated after 9hrs was higher compared to F_g1 which depicted the lowest Jss(0.024µg/cm^{2}hr). All formulations with the exception of F_g1 depicted comparative

permeation Parameters. This reflects their abilities in permeation of the semipermeable membrane.

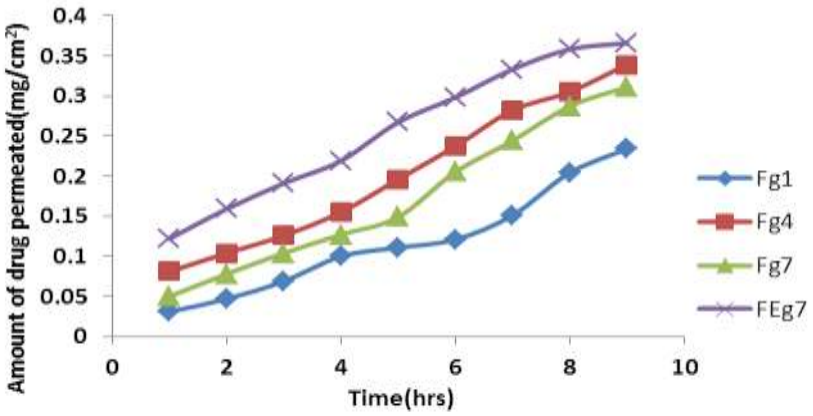

Fig.7.Permeation Pattern of Gatifloxacin in Selected Formulations through Cellulose Membrane in Phosphate Buffer(pH 5.4) at 37±0.5°C

Table.10.Kinetic Analysis of the Diffusion Data of Gatifloxacin from the Selected Formulations.

Formula	Order of release	Slope(Jss)(mg.cm^{-2}.hr^{-1})	Y-intercept	P(cm.hr^{-1})	RPR	Fen
F_g1	Zero	0.024	-0.003	0.008	0.72	0.678
F_g4	Zero	0.033	0.033	0.011	1.00	0.983
F_g7	Zero	0.033	0.003	0.011	1.00	0.901
$F_{Eg}7$	Zero	0.032	0.95	0.0106	0.96	1.061

Jss: Apparent steady state flux ; P : Permeation coefficient ; RPR : Relative permeation rate ; Fen : Enhancing factor.

Table.11.Kinetic Analysis of the Diffusion Data of Gatifloxacin from the Selected Formulations Formulations(Higuchi)

Formula	Order of release	Slope(mg.cm^{-2}.hr$^{-1/2}$)	Y-intercept	D(cm.hr$^{-1/2}$)	K(10^{-3}) (mg.hr$^{-1/2}$)	tl(10^{-3}) (hr)
F_g1	Diffusion	0.097	-0.090	0.100	0. 80	0.167
F_g4	Diffusion	0.135	0.087	0.140	0.785	0.119
F_g7	Diffusion	0.135	-0.117	0.140	0.785	0.119
$F_{Eg}7$	Diffusion	0.131	-0.025	0.136	0.779	0.123

D : Diffusion coefficient ; Tl : Lag time

Statistical Study

Tables(12,13) illustrate the student's t-test which showed the statistical analysis of different formulations of gel and emulgel

Table.12.Statistical Release Analysis Between F_g4 and other Gel Formulations

Formulation	Mean	Pooled variance	T stat.	D.F	P
F_g1	63.4	722.4951117	1.206324482	22	0.240505288
F_g2	50.9	574.4705936	3.91409217	22	0.000743516
F_g3	48.5	546.2375117	4.521579513	22	0.000168742
F_g5	66.2	831.8257269	0.646810233	22	0.524446374
F_g6	61.9	799.1954845	1.412692764	22	0.17173748
F_g7	66.5	680.3826288	0.673784354	22	0.507466401
F_g8	60.9	623.5899348	1.794889064	22	0.086424255
F_g9	58.2	637.910039	2.299226022	22	0.031359956

Table.13.Statistical Release Analysis Between $F_{Eg}7$ and other Emulgel Formulations

Formulation	Mean	Pooled variance	T stat.	D.F	P
$F_{Eg}1$	58.3	303.965303	3.599036374	22	0.00159518
$F_{Eg}2$	56.5	305.2177273	4.087043943	22	0.000487775
$F_{Eg}3$	62.7	318.3276894	2.307613489	22	0.030808411
$F_{Eg}4$	60.5	321.4993939	2.905259767	22	0.008205711
$F_{Eg}5$	66.5	313.2658712	1.126762543	22	0.271983528
$F_{Eg}6$	64.9	324.7666667	1.694494832	22	0.104282341
$F_{Eg}8$	69.5	299.8822348	0.446743477	22	0.659427082

CONCLUSION

All formulations with the exception of F_g1 depicted comparative permeation Parameters. This reflects their abilities in permeation of a semipermeable membrane which simulates the skin. $F_{Eg}7$ represented the formula of choice as the best formulation for topical application.

REFERENCES

1. Hosaka M, Yasue T, Fukuda H, Tomizawa H, et al. In vitro and in vivo antibacterial activities of AM-1155, a new 6-Fluoro-8-Methoxy. Quinolone., 1992; 36: 2108–17.
2. Gordon LF General Introduction and Conceptual Differentiation of Topical and Transdermal Drug Delivery Systems. In: Shah VP, Maibach HI, editors. Topical Drug Bioavailability, Bioequivalence and Penetration. 1st ed. Springer US., 1993; 369-391.
3. Bhasha SA, Khalid SA, Duraivel S, Bhowmik D, Kumar KS. Recent Trends in Usage of Polymers in the Formulation of Dermatological Gels. Ind J Res Pharmacy Biotech., 2013; 1(2): 161-168.
4. Sharma S, Pawar S, Jain UK. Development and Evaluation of Topical Gel of Curcumin from Different Combination of Polymers Formulation and Evaluation of Herbal Gel. Int J Pharm Pharm Sci., 2012; 4(4): 452-456.

5. Wu P, Huang Y, Fang J, Tsai Y, Percutaneous absorption of captopril from hydrophilic cellulose derivativesthrough excised rabbit skin and human skin, Drug. Dev. Ind. Pharm., 1998; 24: 179-182.
6. Mohamed MI. Optimization of Chlorphenesin emulgel formulation. Aaps., 2004; 6: 1-7.
7. Mohan EC,Kandukuri JM,Allenkiv.Preparation and evaluation of in-situ gels for ocular drug delivery . J.Pharm. Res., 2009; 6: 1089-1094.
8. Gallagher S , Trottet L , Heard C ; Ketoprofen release from permeation across and rheology of simple gel formulation that stimulate increasing dryness ; International journal of pharmaceutics., 2003;268:37-45.
9. Rathore RPS, Nema RK, Formulation and evaluation of topical gels of Ketoprofen, Asian. J. Pharm. Clinical. Res., 2008; 1: 12 – 16.
10. Navya M, Hemat K S Y , Hemanth K S , Toshi C K , Snkeerth K N.Design and evaluation of a lyophilized liposomal gel of an antiviral drug for intravaginal delivery., 2014; 131(2): 1-9.
11. Mishra DN, Gilhotra RM, Design and characterization of bioadhesive in – situ gelling ocular insert of gatifloxacin sesquihydrate, Daru., 2008; 16: 1 – 8.
12. Gupta V.Formulation and evaluation of naproxen gel containing tulsi oil as penetration enhancer. Int J Pharm Clin Res., 2009; 1(3): 153-155.
13. Patel J, Patel B, Banwait H, Parmar K, Patel M. Formulation And Evaluation of Topical Aceclofenac Gel Using Different Gelling Agent. Int J Drug Dev Res., 2011; 3(3): 9275-9344.
14. Setty CM, Babubhai SR, Pathan IB. Development of Valdecoxib Topical Gels: Effect of Formulation Variables on the Release of Valdecoxib. Int J Pharm Pharm Sci., 2010; *5*(10): 70-73.
15. Kavitha K; Rajas NJ. International Journal of PharmTech Research, 2011; 3(2): 702.
16. Jones D S. , Woolfson A.D. , Brown A.F. , Coulter W.A., mclelland C. and Irwin C.R.; Design characterization and preliminary clinical evaluation of a novel mucoadhesive topical formulation containing Tetracycline for treatment of periodontal disease,J.Cont. Rel., 2000; 67: 357-368.
17. El-Nabrawy M.A. , Nesseem D.I. and Sleem A.A ; Delivery and analgesic activity of Tramadol from semi-solid (topical) and solid (rectal)dosage forms; Bull.Fac.Pharm.Cairo Univ., 2003; 41(2).
18. Danester Q., Evone S G., Formulation and characterization of nystatin gel.PRHSJ. March., 2008; 27(1): p.61-67.

19. Ban N B., Cleland J L., Yang J., Manning M.C.Tween protects recombinanthuman growth hormone against agitation induced damage via hydrophobic interactions, J. Pharm.Sci., 1998; 87: 1554-1559.
20. Eros I., Ugri-Hunyadvari H.,Investigation of the rheologicalcharacteristic of ointment gels containing emulsifier and emulsion type ointments, Cosmetics and Toiletries., 1979; 94: 67-70.
21. Yehia I.K.,AnInvestigation release and rheological properties of miconazole nitrate from emulgel. Iraqi J. Pharm. Sci., 2009; 18(2): 26-31
22. Sheikh N., Faiyaz S., Sushma T., JavedA. Formulation development and optimization using nanoemulsion technique: a technical note, AASP Pharm.Sci.Tech. 2007;8 (2), article 28.
23. Abd El-Bary A, Shalaby S, Abd El-Aal S.Formulation and stability of chloramphenicol gel and emulgel. Bull Fac Pharm., 2001; 39: 89-99.
24. Wang Y Y, Hong C T, Chiu W T, Fang J Y, In vitro and in vivo evaluations of topically applied capsaicin and nonivamidefrom hydrogels, Int. J. Pharm. 2001;224 : 89-104.
25. Welin-Berger K, Neelissen JAM and Bergenståhl B .The effect ofrheological behaviour of a topical anaesthetic formulation on the release and permeation rates of the active compound. Eur. J. Pharm. Sci., 2001; 13: 309-318.
26. Raghavan S.L., Trividic A., Davis A.F.,Hadgraft J., Effect of cellulose polymer on supersaturation and in vitro membrane transport of hydrocortisone acetate,International Journal of Pharmaceutics., 2000; 193: 231-237.