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Research Article

FORMULATION AND EVALUATION OF DIFFEREFNT TRANSDERMAL DRUG DELIVERY SYSTEMS OF KETOPRFEN

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ABSTRACT

Objective: The aim of this study was to develop Ketoprofen (KPF) gel for tansdermal delivery that could enhance permeability of KPF and to study the change in permeation of transdermal gel after formulating KPF as niosomes and solid dispersions.

Methods: KPF gels were prepared using Carboxy methyl cellulose (CMC), hydroxyl propyl methyl cellulose (HPMC) and methyl cellulose (MC) with and without permeation enhancers (Tween 80 and Oleic acid). The effect of the employed gel bases and permeation enhancers on the permeation and viscosity of gel formulae was tested. The best formula was formulated as niosomal and solid dispersion gels. The effect of drug modification on the properties of KPF gel was examined.

Results: The results showed that both polymers and permeation enhancers affect permeation and rheological properties of KPF gel. Formula containing 5% MC and 5 % Tween80 showed the best permeation through rat skin (96.39% ±3.23) and the lowest viscosity. The permeation from the niosomal gel was highly prolonged when compared to conventional gel (F8).On the other hand, it was enhanced from the solid dispersion gel.

Conclusion: Drug modification affects the behavior of KPF transdermal gel

Keywords*:* Ketoprofen, Transdermal, Permeation, Methyl cellulose, Tween80

INTRODUCTION

The transdermal route has many advantages for the administration of drugs. The stratum corneum (SC), forms a strong barrier to most exogenous substances including drugs due to its multilayered structure .One approach for drug delivery through skin is to reversibly reduce the barrier function of skin with penetration enhancers [1].

KPF is an NSAID with analgesic and antipyretic properties, but it may cause adverse effects such as irritation and ulceration of the gastro-intestinal (GI) mucosa. Administration via the dermal route can bypass these disadvantages and may maintain relatively consistent plasma levels for long term therapy from a single dose [2]. KPF is practically insoluble in water [3] and the barrier function of the skin limits its formulation as a transdermal dosage form and makes this challenging. Solid dispersion is an effective technique which can easily enhance the dissolution rate of drugs [4].Niosomes are capable of forming vesicles which entrap drug increasing the contact time with the applied tissue [5]. The aim of this study is to enhance the transdermal permeation and therapeutic efficacy of KPF by using different types of gel forming agents & permeation enhancers and to study the effect of drug modification (as niosomes& solid dispersion) on gel behavior.

MATERIALS AND METHODS

Materials

KPF was purchased From Sigma Company (Cairo, Egypt),HPMC, Alpha Chemica, Mumbai, India, MC, Oxford company, Hartlepool, United Kingdom,CMC, Oxford company, Hartlepool, United Kingdom,Tween 80,Oxford company, Hartlepool, United Kingdom, Oleic acid, PureLab, Madison, USA, Sodium dihydrogen phosphate and disodium hydrogen phosphate, PureLab , Madison ,USA. Sodium hydroxide, PureLab, Madison, USA.. Span 60, Kermel Company, Tianjin, China. Chlorofrm, Alpha Chemica, Mumbai, India. Cholesterol, Laboratory Rasayan , Mumbai, India.PVPK-90, Mumbai, India. Chitosan, Oxford Company, Hartlepool, United Kingdom. HP-β-CD (MW 1380), kindly donated by Medical Union Pharmaceuticals, Abu-Sultan, Ismailia, Egypt. All other chemicals were commercially available products of analytical grade.

Equipment

USP Dissolution Tester, six cups model, Apparatus II, Erweka Apparatebau GmbH, Germany, Shimadzu UV spectrophotometer (2401/PC), Japan, Brookfield R/S +RHEOMETER, Rotary Viscometer, Brookfield Engineering Laboratories, Inc. (USA), Magnetic stirrer with hot plate (Brandstead /Thermolyne, 50/60HZ, 220-240 volts, Dubuque /Iowa 52001 U.S.A), pH meter, JENWAY Designed and manufactured in the EU by Barloworld Scientific Ltd, Dunnlow, Essex, CM6 3LB, England, Digital Planimeter , KP-92n, Swastik Scientific Company, Mumbai, Maharashtra, India, Buchi rotavapor R-3000, BUCHI Labortechnik AG in Flawil, Switzerland,Sonicator, Hielscher Ultrasonics, Germany, Centrifuge, Biofuge, primo Heraeus (Germany).

Methods

Formulation of KPF transdermal gel

2.5% w/w KPF gels were formulated using three different gelling agents; CMC (2 %), HPMC (2 %) and MC (5 %) in addition to two different permeation enhancers; Tween 80 (5%) and Oleic acid (10%). The weighed amount of polymer powder (MC and CMC) was sprinkled gently in boiling distilled water and stirred magnetically at a high speed. In case of HPMC, the same method was used but using a portion of hot water at 80°C and the remaining amount of water was added on cold after formation of thin hazy dispersion. KPF and permeation enhancers were dissolved in ethanol (30%w/w) and added to the dispersion of polymer with stirring to get a homogeneous dispersion of drug in the gel [6].

In-vitro permeation of KPF gels

In vitro permeation was determined by a modified USP XXVII dissolution apparatus I using, modified Franz diffusion cell; a cylindrical tube (2.5 cm in diameter and 6 cm in length). Accurately weighed 1gm gel was spread uniformly on the epidermal surface of excised rat abdominal skin which was stretched over the lower open end of the tube with SC side facing upwards and the dermal side facing downwards into the receptor compartment [1]. The dissolution medium was 300 ml of phosphate buffer pH 7.4. The stirring speed was 100 rpm, and the temperature was maintained at 37°C ± 0.5°C [3]. Samples of 5ml were withdrawn at 15, 30, 45, 60, 90,120, 180, 240, and 300 and 360 minutes, filtered and analyzed spectrophotometrically. Kinetic treatment of the obtained data was carried out.

The average cumulative amount of KPF permeated per unit surface area (µg/cm^2) was plotted as a function of time. The drug flux at steady state (JSS) was calculated from the slope of the straight line. Permeability coefficient (KP) was calculated using the following equations: KP = JSS/Co (where Co is the initial concentration of the drug) .Enhancement ratio (Er) was calculated as follows: Er = JSS of formulation/JSS of control. D (diffusion coefficient, cm^2/min) was calculated as follows: D = h^2/6 Lt: where h is the thickness of the skin in cm and Lt the Lag time in minutes [7].

Evaluation of Gels

Clarity

It was determined by visual inspection under black and white background and it was graded as follows: turbid: +, clear: ++, very clear (glassy): +++ [8].

Homogeneity

It was determined by visual inspection for the appearance of gel and presence of any aggregates [9].

Spreadability

A spreadability test was conducted by pressing 0.5 g of gel between two glass slides and leaving it for about 5 min. until no more spreading was expected. The diameter of the formed circle was measured and used as comparative values for spreadability [7].

Extrudability

1 gm of gel was filled in clean collapsible tube; 0.25 gm weight was placed on the free end of the tube and was just touched for 30 second. Amount of gel extruded was noted [8].

pH

2grams of gel was dispersed uniformly in 20 ml of distilled water using magnetic stirrer for 2 hrs. The pH of dispersion was measured by using digital pH meter [9].

Drug content

200 mg of gel was dissolved in 25 ml phosphate buffer (pH 7.4) and shaken for 2 hr on mechanical shaker in order to get complete solubility of drug [10]. Then, samples were analyzed spectrophotometrically

Rheological properties determination

The viscosity was determined using Brookfield R/S+RHEOMETER using spindle CC 14. The measurement was started at 1 rpm; the speed was gradually increased till reached 200 rpm, the speed was then reduced gradually until reaching the starting rpm. Measurement of thixotropic behavior was determined using the planimeter in order to calculate the hysteresis loop between the upward curve and downward curve of the chosen formulae [10].

Formulation of solid dispersion incorporated gel

The required amount of KPF and carrier in 1:4 ratios were mixed using geometric dilution method and kneaded with sufficient volume of methanol with continuous stirring to obtain thin paste (kneading method). The samples were dried at 45° for 24 hrs. The dried mass was pulverized , passed through sieve no. 60 and stored in desiccator until used for further studies [11]. Weight of solid dispersion equivalent to 2.5% KPF was dispersed in ethanol (30%w/w) and added to the dispersion of polymer with stirring to get a homogeneous dispersion of drug in the gel.

Formulation of niosomal gel

The surfactant, cholesterol and drug were weighed separately and dissolved in chloroform till complete dissolution. The organic mixture was completely evaporated by a rotary flash evaporator at 60^{o}C at 180 rpm to form a thin film on the wall of the flask (thin film hydration method). It was hydrated using distilled water for 1 hour with rotation. Then the niosomal dispersion was collected, cooled in an ice bath and sonicated for three minutes at 150V.Weight of niosomal dispersion equivalent to 2.5% KPF was added to the dispersion of polymer with stirring to get a homogeneous dispersion of drug in the gel [12].

Effect of drug modification on gel behavior

The effect of drug modification on the permeation, gel properties and rheological behavior of KPF was examined in solid dispersion and niosomal gels as described before.

Microscopic evaluation of gel formulae

Internal structure of niosomal and solid dispersion gels was compared with the chosen gel by observation under light microscope. 1 gm of chosen gel was spread uniformly on glass slide and observed under light microscope [13].

RESULTS AND DISCUSSION

In vitro skin permeation of KPF gels

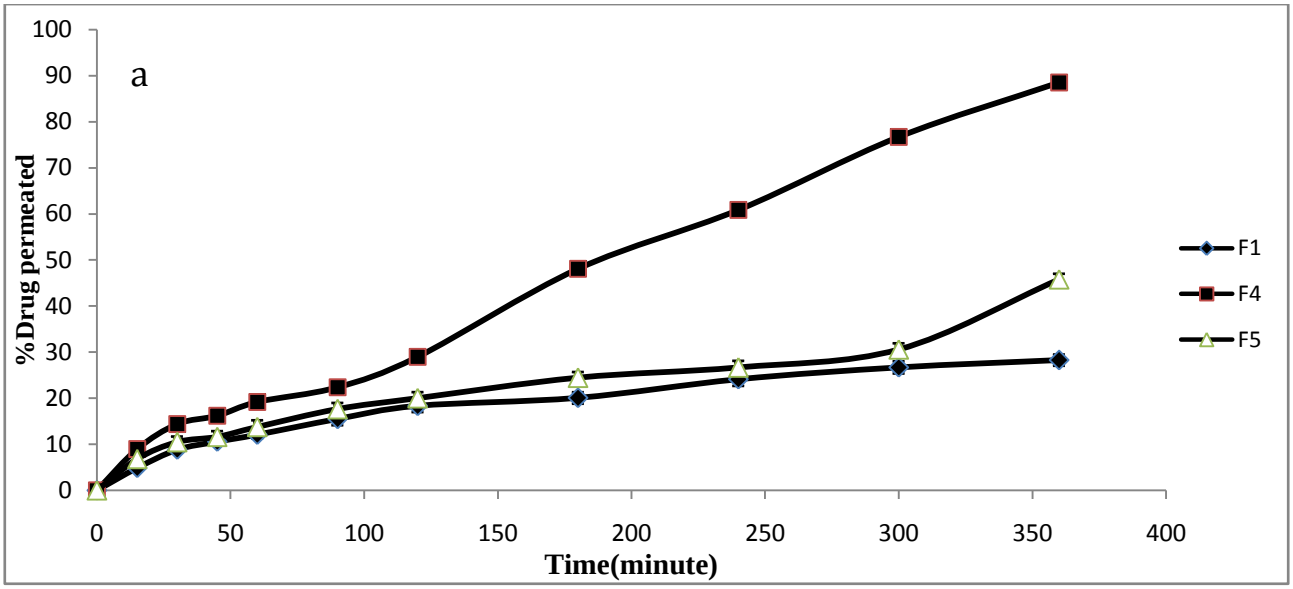
Prepared gel formulae are described in Table (1).As shown in Figure (1), the permeation of KPF from MC gel bases was higher than that from CMC and HPMC polymers. These differences may be attributed to the variation in shape and dimension of the crystallites of the solid fraction [14]. The permeation rate of KPF increased in presence of permeation enhancers. Enhancement of skin permeation by Tween 80 may be attributed to creation of a network within skin proteins which disrupts the lipid bilayer, enhancement of diffusion rate because of the hydrophilicity of Tween 80 and the polar nature of the receiver compartment as well and also may be due to decreasing of the gel viscosity [15].Enhancement of skin permeation by Oleic acid may be attributed to its cis double bond at C9, which causes a kink in the alkyl chain and disrupts the skin lipids [16].

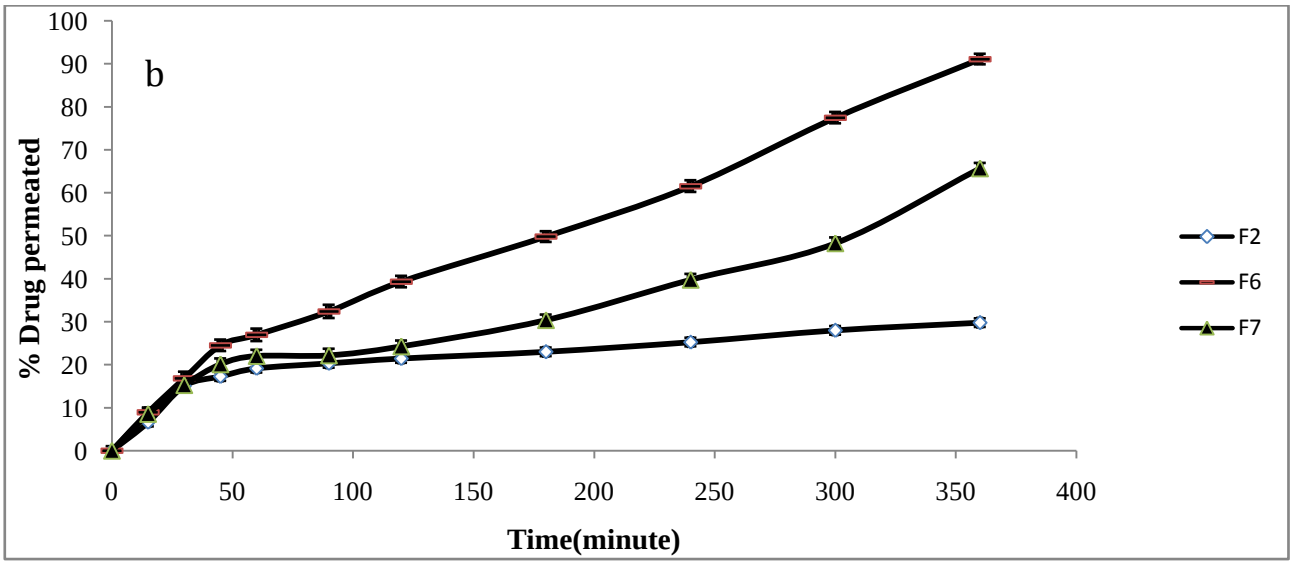
KPF gel formulae containing Tween 80 showed an increase in the permeation rate compared to that containing Oleic acid which may be due to its higher water solubility [15].

Among all formulae F8 achieved the highest permeation (96.39%).From the previous results, it was found that drug permeation was enhanced by addition of permeation enhancers so, KPF gel formulae containing permeation enhancers were chosen for completing the other tests.

Table 1: Suggested formulae of KPF gels

Formula	KPF %	CMC %	HPMC %	MC %	Tween 80 %	Oleic acid %	Ethanol (%)	Water (%) to
F1	2.5	2			---	---	30	100
F2	2.5		2		---	---	30	100
F3	2.5			5	---	---	30	100
F4	2.5	2			5	---	30	100
F5	2.5	2			---	10	30	100
F6	2.5		2		5	---	30	100
F7	2.5		2		---	10	30	100
F8	2.5			5	5	---	30	100
F9	2.5			5	---	10	30	100





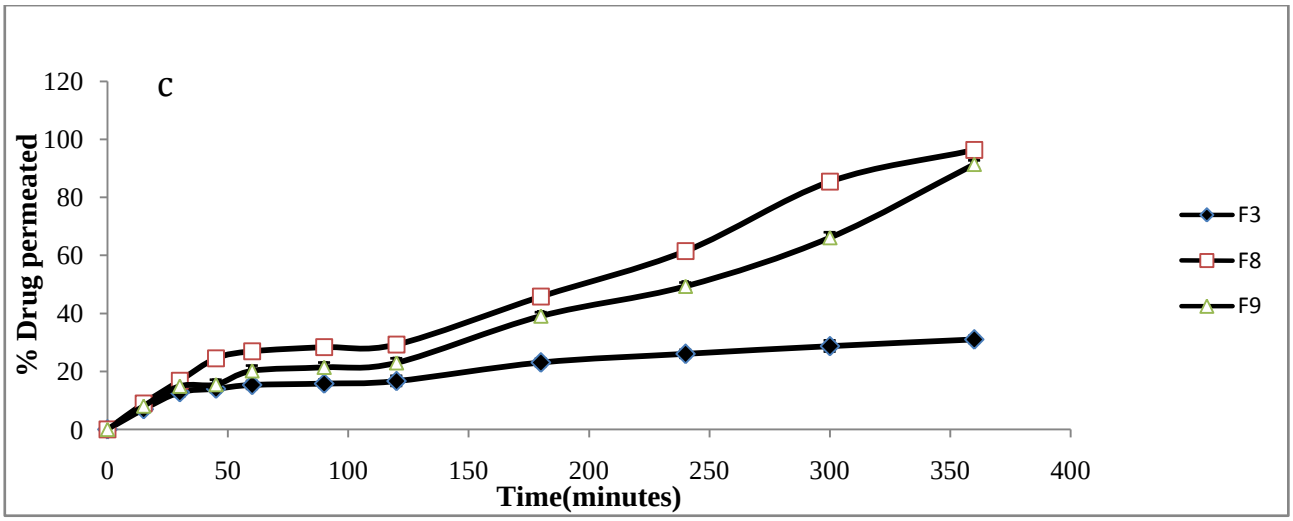


Fig. 1: The effect of permeation enhancers on the permeation of KPF from a)2%CMC b) 2%HPMC c) 5%MC

Kinetic treatment

The permeation of the prepared KPF formulae doesn't obey the same kinetic order. Formulae containing KPF without permeation enhancers (F1, F2and F3) followed the Higuchi's diffusion model. Formulae containing KPF with permeation enhancers (F4, F5, F6, F7, F8 and F9) followed the zero order model as shown in Table 2 according to correlation coefficient values which ensure constant and uniform release [17].

Table 2: The calculated correlation coefficients for the permeation of KPF gels

KPF	Correlation Coefficients (r)		
Formula	Zero-order	First-order	Higuchi's diffusion model
F1	0.968	0.976	0.995
F2	0.896	0.916	0.944
F3	0.974	0.981	0.986
F4	0.997	0.965	0.975
F5	0.972	0.958	0.959
F6	0.984	0.907	0.950
F7	0.976	0.949	0.951
F8	0.987	0.912	0.962
F9	0.981	0.886	0.943

Permeation data analysis

The flux, steady state flux and permeability coefficient of KPF from MC gel bases were higher than those from CMC and HPMC polymers. In addition, they are higher in presence of permeation enhancers. They are higher in case of Tween 80 than Oleic acid, Table (3). No direct correlation was observed between the lag time and the apparent flux released.

Evaluation of Gels

All the prepared gel formulae are of smooth and homogenous appearance. They have good spreadability and extrudability values. The pH values were found to be in the range of (5.3-5.64) which is within the required physiological range, i.e., pH 4-7 units and was considered to be safe and non-irritant for transdermal application. Drug content was found to be in the range of (95.08- 104.9%) which shows a good content uniformity, Table 4.

Rheological properties of gel formulae

All the rheological data of the different gels were fitting to the power's law with (R^2) values ranged between (0.959- 0.997).The minimum viscosities were in the range (100.7 – 409) cPs, while the maximum viscosities were in the range (2290– 6500) cPs, Table 5. The maximum viscosities of MC gel bases were lower than that of other tested cellulose derivatives .This may be attributed to variation in shape and dimensions of crystallites of different polymers [14].The viscosities of formulae containing Oleic acid were higher than those containing Tween 80. F8 was the lowest formula in viscosity. Thixotropic behavior ranged between (2.1 Cm^2 -4.6 Cm^2). The pseudoplastic behavior is evidenced by that the flow curves approach the origin with no yield values and N value is higher than1, it ranged between (1.23-4.18). Among all formulae F8 achieved the best results; therefore it was chosen for completing the other tests.

Table 3: Permeation parameters of KPF from prepared gels

Formula	Steady state flux Jss ($\mu g\ cm^{-2}\ min^{-1}$)	Permeability coefficient ($Cm\ min^{-1}$)	Enhancement factor	Lag time (min)	Diffusion coefficient ($Cm^2\ min^{-1}$)	Partition coefficient
F1	2.78	0.00011	------	464.58	8.96E-7	6.2
F2	3.11	0.00013	------	418.03	9.96E-7	6.23
F3	3.58	0.00014	------	343.89	1.21E-8	59.03
F4	18.45	0.00074	6.64	29.91	1.39E-5	2.41
F5	9.14	0.00036	3.29	11.26	3.7E-5	0.49
F6	22.80	0.00091	7.36	43.98	9.47E-6	4.81
F7	15.40	0.00062	4.97	28.86	1.44E-5	2.13
F8	23.65	0.00095	6.62	23.30	1.78E-5	2.65
F9	23.39	0.00094	6.55	57.90	7.19 E-6	6.50

Table 4: Evaluation of KPF gel formulae

Formula	Clarity	Homogeneity	spreadability	Extrudability	pH	Drug content
F4	+	good	7.4	82.8	5.54	95.25
F5	++	good	5.9	71.76	5.45	95.08
F6	++	good	7.6	96.52	5.37	95.44
F7	++	good	6.52	80.12	5.3	101.44
F8	+	good	9.38	99.36	5.64	104.9
F9	+	good	8.24	88.32	5.58	101.86

+ Satisfactory, ++ Good

Table 5: Data of viscosity, thixtropic behavior and Farrow's constant of KPF formulae

Formula	Max. viscosity (CP)	Min. viscosity (CP)	Thixtropic behavior (Cm^2)	Farrow's constant
F4	5920	100.7	2.8	**4.18**
F5	6500	210.7	4.6	**2.75**
F6	5860	224.2	4.2	**2.44**
F7	6170	409	4	**1.93**
F8	2290	152.3	3	**1.23**
F9	**4590**	**105.4**	**2.1**	**3.45**

Permeation of solid dispersion incorporated gels

The permeation of solid dispersion incorporated gels was in the range (97.22-98.53%) after 6 hrs which is higher than F8 which showed 96.39% drug permeated. The in-vitro drug permeation was increased in the manner of: F8 < chitosan < PVP < HPβCD. That may be attributed to higher solubility, enhanced permeation of solid dispersion as compared to pure KPF [18]. Higher permeation from HPβCD may be due to its higher solubilizing

effect [19] and its action as permeation enhancer by transferring the drug from the solution towards lipophilic surface of biological membrane [18] , Figure (4).

Permeation of niosomal gels

The permeation of niosomal gels was in the range (36.51-54.76%) after 6 hrs which is lower than F8 which showed 96.39% drug permeated which may be due to controlled drug release due to the entrapment of drug in vesicles [20]. In-vitro permeation of KPF from the prepared gels decreased as surfactant concentration increased which may be due to higher entrapment efficiency [21], Figure (2).Prepared gel formulae are listed in Tables 6 & 7.

Table 6: Suggested formulae of solid dispersion incorporated gels

Formula	Polymer	Drug-Polymer Ratio
SD1	Chitosan	1:4
SD2	PVP	1:4
SD3	HPβCD	1:4

Table 7: Suggested formulae of niosomal gels

Formula	Drug-Span60–Cholesterol Ratio
NS1	1:0.5:1
NS2	1:1:1
NS3	1:2:1

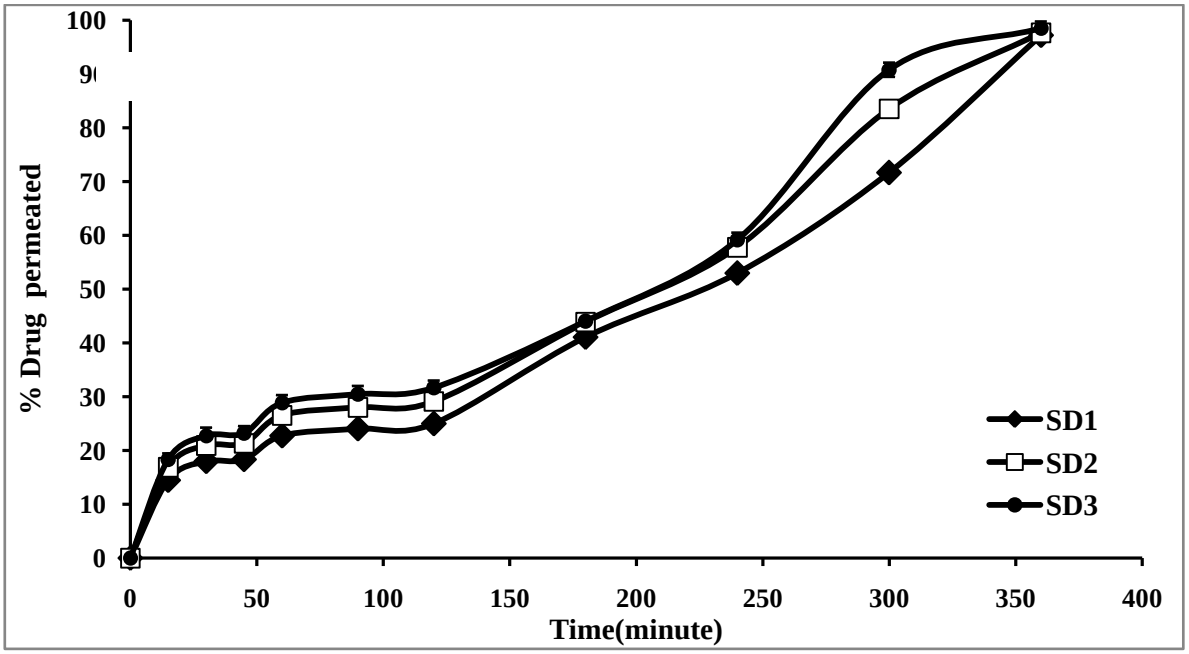


Fig. 2A: The in-vitro permeation of KPF from solid dispersion incorporated gels

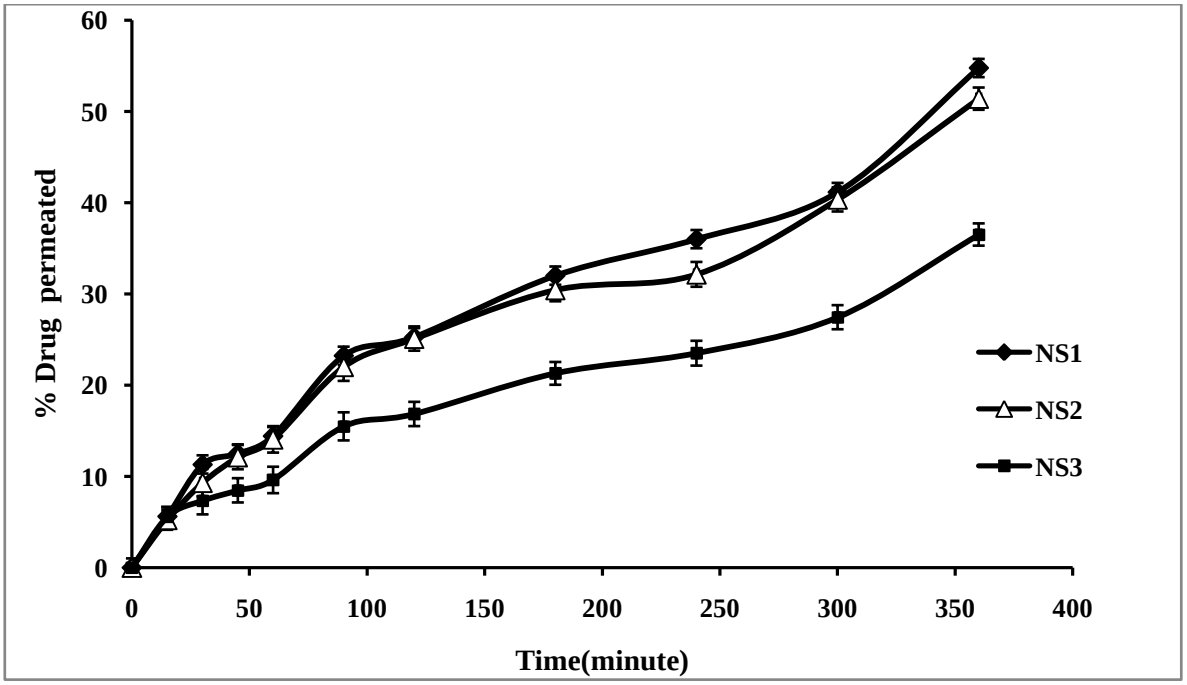


Fig. 2B: The in-vitro permeation of KPF from niosomal gels

Kinetic treatment

All the studied formulae followed zero order kinetics as shown in table (8) according to correlation coefficient values which ensure constant and uniform release [17].

Table 8: The calculated correlation coefficients for the permeation of KPF solid dispersion and niosomal gels

Formula	Correlation Coefficients (r)		
	Zero-order	First-order	Higuchi's diffusion model
SD1	0.976	0.835	0.930
SD2	0.981	0.873	0.939
SD3	0.976	0.879	0.935
NS1	0.977	0.956	0.937
NS2	0.988	0.972	0.962
NS3	0.986	0.985	0.981

Permeation data analysis

KPF solid dispersion gel formulae can be arranged in a descending order according to the flux of KPF (µg/cm^2 /min) after six hours as follows: SD3 (13996.41) > SD2(13870.44) > SD1(13810.19). In case of niosomal gels:NS1(7778.11)>NS2(7301.14)>NS3(5185.41), Table (9).

The flux, steady state flux and permeability coefficient of KPF from solid dispersion gel formulae were higher than those from conventional gel (F8). That may be explained due to decreasing particle size of drug, increasing wettability and preventing the aggregation of drug by carriers leading to higher permeation rate [18].On the other hand, these parameters in niosomal gels are lower than those from conventional gel (F8). That may be attributed to slower drug release and higher drug entrapment [20].

Evaluation of KPF solid dispersion and niosomal gels

All the prepared gel formulae were of smooth and homogenous appearance and showed good extrudability and spreadability. Spreadability and extrudability values were higher than conventional gel (F8) in niosomal gels and lower than conventional gel (F8) in solid dispersion gels. That may be related to consistency of these formulae. pH of all formulations lies in the normal pH range of the skin [9].The drug content was in agreement with USP specifications indicating content uniformity [3].All results are summarized in Table (10).

Table 9: Permeation parameters of KPF solid dispersion and niosomal gels

Formula	Steady state flux Jss (µg cm^{-2} min^{-1})	Permeability coefficient (Cm min^{-1})	Enhancement factor	Lag time (min)	Diffusion coefficient (Cm^2 min^{-1})	Partition coefficient
SD1	25.71	0.00103	7.19	66.70	6.25E-6	8.23
SD2	26.11	0.00104	7.31	54.88	7.59E-6	6.88
SD3	26.24	0.00105	7.35	45.09	9.24E-6	5.68
NS1	9.88	0.00039	2.77	64.82	6.43E-6	3.07
NS2	9.56	0.00038	2.68	55.58	7.50E-6	2.55
NS3	6.67	0.00027	1.87	58.74	7.09E-6	1.88

Table 10: Evaluation of KPF solid dispersion and niosomal gels

Formula	Clarity	Homogeneity	Spreadability	Extrudability	pH	Drug content
SD1	+	good	7.72	86.1	5.44	96.25
SD2	++	good	7.93	88.35	5.35	97.08
SD3	++	good	8.47	92.62	5.47	95.24
NS1	+	good	9.49	99.38	5.62	100.04
NS2	++	good	9.74	99.46	5.74	98.33
NS3	++	good	10.22	99.52	5.89	95.88

+ Satisfactory, ++ Good

Rheological properties of KPF solid dispersion and niosomal gels

For solid dispersion gels, the minimum viscosities were in the range (139.7- 233) cPs, while the maximum viscosities of them were in the range (1788.49– 3677.7) cPs .These values were greater than conventional gel. That may be attributed to addition of carriers [18]. For niosomal gels, the minimum viscosities were in the range (93.8-146.14) cPs, while the maximum viscosities of them were in the range (1788.49– 2114) cPs. These values are lower than conventional gel. That may be attributed to decreasing the viscosity of gel in the presence of niosomes.

Thixotropic behavior of solid dispersion gels ranged between (3.9-4.35). While, that of niosomal gels ranged between (3.35-4.4).

Like conventional gel, solid dispersion gels and niosomal gels showed pseudoplastic behavior which is evidenced by that N value is higher than1.N values ranged between (1.75- 2.30). In addition, pseudoplastic behavior is evidenced by decreasing viscosity with increasing shear rate (shear thinning) and an increase in the shear stress with increasing the speed [10]. Different parameters of rheological behavior are expressed in Table (11).

Table 11: Data of viscosity, thixtropic behavior and Farrow's constant of KPF solid dispersion and niosomal gels

Formula	Max. Viscosity (CP)	Min. Viscosity (CP)	Thixtropic behaviour (Cm^2)	Farrow's constant
SD1	3677.7	233	4.35	**2.01**
SD2	3214	139.7	3.9	**2.15**
SD3	2840	230.4	4.3	**1.75**
NS1	1788.49	146.14	3.9	**2.22**
NS2	1955.15	122.39	3.35	**2.08**
NS3	**2114**	**93.80**	**4.4**	**2.30**

Microscopic evaluation

Most of the vesicles of niosomal gels were found to be spherical in shape. Solid dispersion gels exhibited uniform drug distribution within carrier, Figure (3).

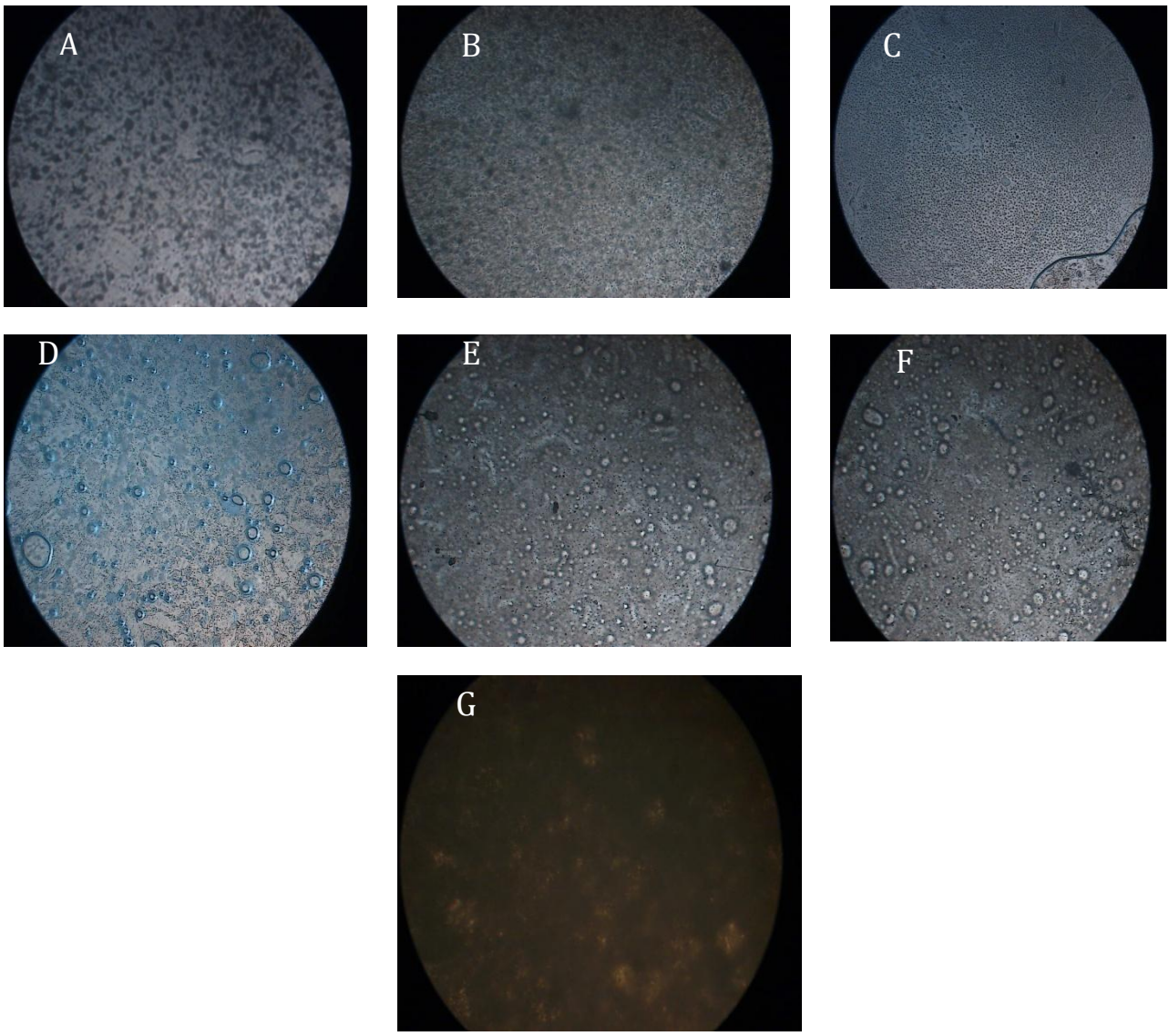


Fig. 3: Microscopic evaluation of A) SD1 B) SD2 C) SD3 D) NS1 E) NS2 F) NS3 G) Conventional gel (F8)

CONCLUSION

Formulation of KPF as tansdermal gel with addition of permeation enhancers could assist its skin permeability. All the studied gels are of acceptable physical properties and drug content. They exhibited pseudoplastic flow with thixotropic behavior. Considering in-vitro permeation and rheological properties, F8 (5% MC with 5 % Tween80) formula was the best among the studied formulations which was chosen to be formulated as solid dispersion and niosomal gels. Formulation of KPF as solid dispersion and niosomal gels changed the permeation profile and the rheological behavior of conventional gel. The diffusion of KPF gel was improved by solid dispersion, while controlled and prolonged drug release was obtained by niosomal preparations. The viscosity of gel increased with solid dispersion gels and decreased with niosomal gels.

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