Design, Formulation and Evaluation of Transdermal Ketoprfen Gel

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Abstract: The aim of this study was to develop Ketoprofen (KPF) gel for tansdermal delivery that could enhance dissolution and permeability of KPF. 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 *in vitro* release, permeation and viscosity of gel formulae was tested. The results showed that both polymers and permeation enhancers affect release, permeation and rheological properties of KPF gel. Formula containing 5% MC and 5 % Tween80 showed the best in-vitro release (98.22% ±1.18), the best permeation through rat skin (96.39% ±3.23) and the lowest viscosity.

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1. 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 make this challenging. The aim of this study is to enhance the transdermal permeation and therapeutic efficacy of KPF by using different types of gel forming agents as delivery vehicles and using different permeation enhancers.

2. Material and Methods

Material

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. All other chemicals were commercially available products of analytical grade.

Methods

Formulation of KPF gel without permeation enhancers (Table, 1)

2.5% w/w KPF gels were formulated using three different gelling agents; CMC (2 and 4 %), HPMC (2 and 4 %) and MC (5 and 7%). 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 was 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 [(1)].

***In-vitro* release of KPF gels without permeation enhancers**

The dissolution rate studies were performed on the prepared gels enclosed in tea bags [(2)] by USP dissolution tester, apparatus I (basket method). The dissolution medium was 900 ml of phosphate buffer pH 7.4 [(3)] .The stirring speed was 100 rpm, and the temperature was maintained at 37°C ± 0.5°C**.**Samples of 5ml were withdrawn at 15, 30, 45, 60, 90,120, 180, 240, 300 and 360 minutes and replaced with fresh medium. The samples were filtered and analyzed spectrophotometrically.

Formulation of KPF gel with permeation enhancers (Table, 1)

From the previous experiment, polymer concentrations that achieved better drug release were chosen in addition to two different permeation enhancers; Tween 80 (2.5 and 5%) and Oleic acid (5 and 10%). 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 [4] .

In-vitro release of KPF gels with permeation enhancers

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***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]. The same previous technique of in-vitro release was performed.

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 [5].

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): +++ [6].

Homogeneity

It was determined by visual inspection for the appearance of gel and presence of any aggregate [7].

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 [5].

Extrudability

One 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 [6].

pH

Two grams 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 [7].

Drug content

Two hundred mgs of gel was dissolved in 25 ml phosphate buffer (pH 7.4) and shaken for 2 hrs on mechanical shaker in order to get complete solubility of drug [8]. 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 of was determined using the planimeter in order to calculate the hysteresis loop between the upward curve and downward curve of the chosen formulae [8].

3.Results And Discussion

***In- vitro* release of KPF gels without permeation enhancers**

In-vitro release of KPF from the prepared gels decreased as polymer concentration increased (Figure, 1). That may be attributed to higher polymer viscosity, increasing the diffusional resistance [9] and increasing the density of chain structure in gels' microstructure which limits the movement area of drug [10]. These findings are also consistent with **Lauffer (1961)** [11] molecular diffusion theory of polymer gels, which states that the diffusion coefficient of a solute is inversely proportional to the volume fraction occupied by the gel-forming agent.

The *in-vitro* release 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 [12].

KPF gel bases which achieved the highest in-vitro release; MC (5 %), HPMC (2 %) and CMC (2 %) were formulated in addition to two different perm

***In- vitro* release of KPF gels with permeation enhancers**

eation enhancers: Tween 80 (2.5 and 5%) and Oleic acid (5 and 10%) and used in further studies.

As shown in Figure (1), the in-vitro release of KPF increased in the presence of permeation enhancers. That may be attributed to the high concentration gradient (due to solubilized KPF) and changing the gel consistency after addition of permeation enhancers [13]. The *in-vitro* release of KPF was higher in case of Tween 80 than Oleic acid. That may be explained by its higher water solubility which leads to greater enhancement of dissolution rate [14].In addition, as the concentration of permeation enhancers increased, the *in-vitro* release of KPF increased. Among all formulae, F16 achieved the highest *in-vitro* release (98.22%).According to the previous results, KPF gel formulae containing higher permeation enhancer concentrations were chosen for performing the permeation study and compared with those without permeation enhancers.

***In vitro* skin permeation of KPF gels**

As shown in Figure (2), 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 [12]. 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 F16 achieved the highest permeation (96.39%).From the previous results, it was found that both drug release and drug permeation were enhanced by addition of permeation enhancers so, six (6) KPF gel formulae ; F8, F10 ,F12, F14,F16 and F18were chosen for completing the other tests .

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, 2). 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, 3).

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, 4). 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 [12].The viscosities of formulae containing Oleic acid were higher than those containing Tween 80. F16 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).

Conclusion

Formulation of KPF as tansdermal gel with addition of permeation enhancers could assist its dissolution enhancement and thus improve 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 release, in-vitro permeation and rheological properties, F16 (5% MC with 5 % Tween80) formula was the best among the studied formulations.

Table (1): Suggested formulae of KPF gels

F No.	KPF %	CMC %	HPMC %	MC %	Tween 80 %	Oleic acid %	Ethanol (%)	Water(%) to
F1	2.5	2			---	---	30	100
F2	2.5	4			---	---	30	100
F3	2.5		2		---	---	30	100
F4	2.5		4		---	---	30	100
F5	2.5			5	---	---	30	100
F6	2.5			7	---	---	30	100
F7	2.5	2			2.5	---	30	100
F8	2.5	2			5	---	30	100
F9	2.5	2			---	5	30	100
F10	2.5	2			---	10	30	100
F11	2.5		2		2.5	---	30	100
F12	2.5		2		5	---	30	100
F13	2.5		2		---	5	30	100
F14	2.5		2		---	10	30	100
F15	2.5			5	2.5	---	30	100
F16	2.5			5	5	---	30	100
F17	2.5			5	---	5	30	100
F18	2.5			5	---	10	30	100

Table (2): 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
F3	3.11	0.00013	------	418.03	9.96E-7	6.23
F5	3.58	0.00014	------	343.89	1.21E-8	59.03
F8	18.45	0.00074	6.64	29.91	1.39E-5	2.41
F10	9.14	0.00036	3.29	11.26	3.7E-5	0.49
F12	22.80	0.00091	7.36	43.98	9.47E-6	4.81
F14	15.40	0.00062	4.97	28.86	1.44E-5	2.13
F16	23.65	0.00095	6.62	23.30	1.78E-5	2.65
F18	23.39	0.00094	6.55	57.90	7.19 E-6	6.50

Table (3): Evaluation of KPF gel formulae

Formula	Clarity	Homogeneity	spreadability	Extrudability	pH	Drug content
F8	+	good	7.4	82.8	5.54	95.25
F10	++	good	5.9	71.76	5.45	95.08
F12	++	good	7.6	96.52	5.37	95.44
F14	++	good	6.52	80.12	5.3	101.44
F16	+	good	9.38	99.36	5.64	104.9
F18	+	good	8.24	88.32	5.58	101.86

+ Satisfactory, ++ Good

Table (4): 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
F8	5920	100.7	2.8	4.18
F10	6500	210.7	4.6	2.75
F12	5860	224.2	4.2	2.44
F14	6170	409	4	1.93
F16	2290	152.3	3	1.23
F18	4590	105.4	2.1	3.45

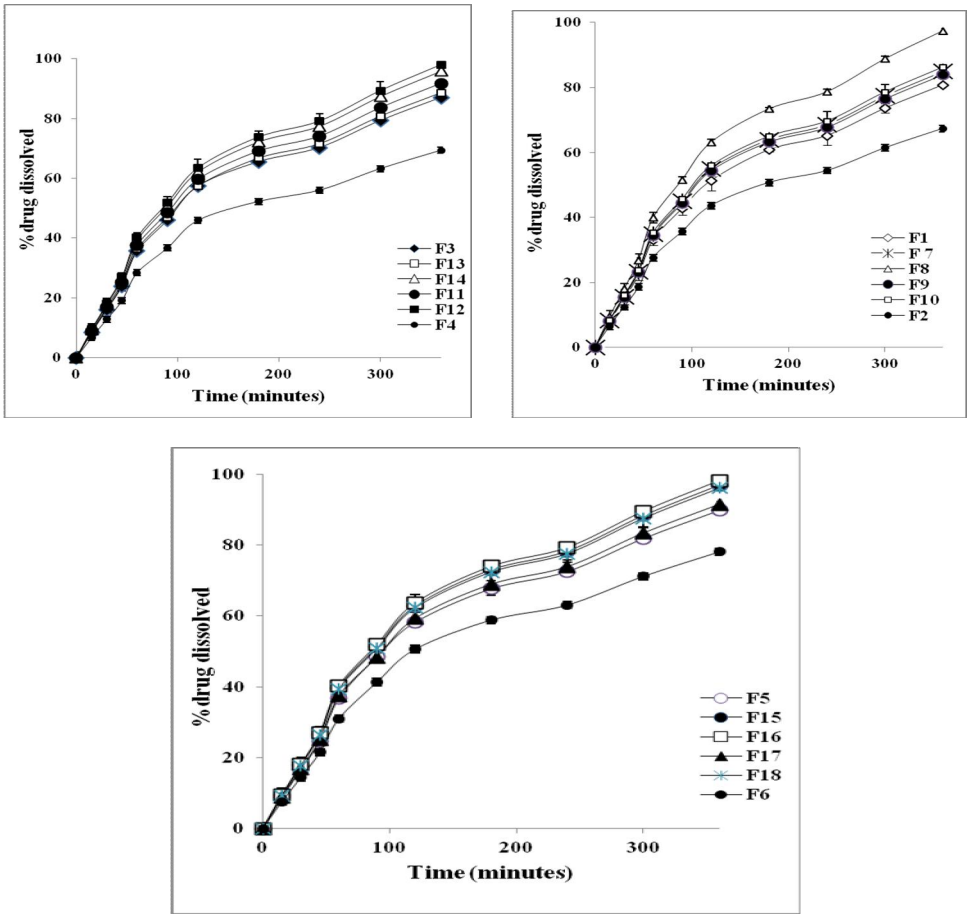
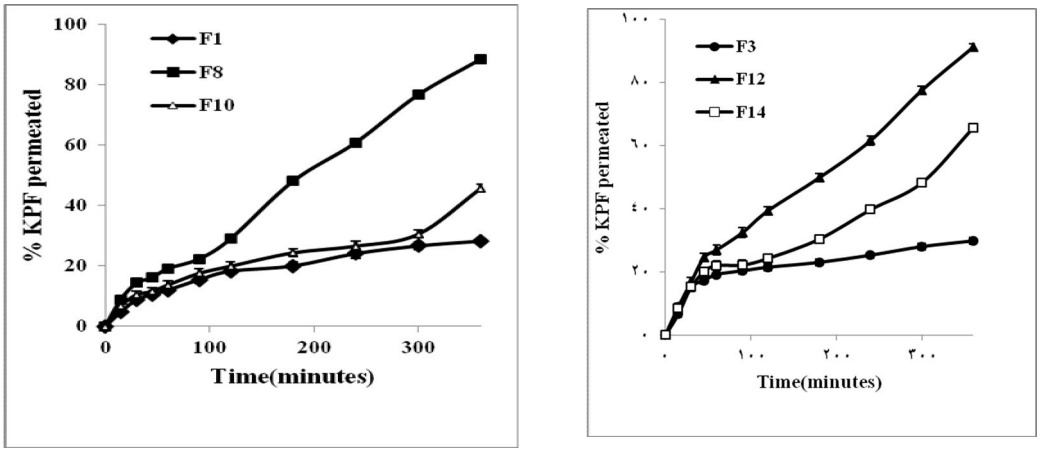


Figure (1): The in-vitro drug release of KPF from a) CMC, b) HPMC and c) MC with and without permeation enhancers



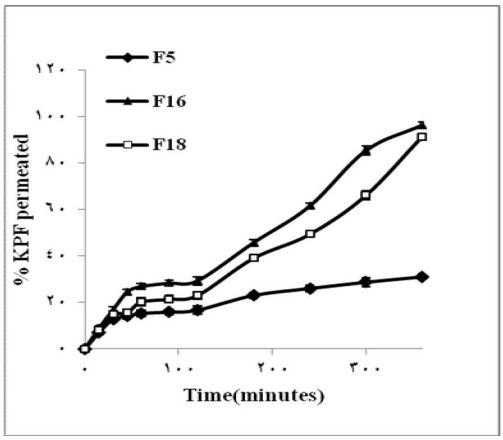


Figure (2): The effect of permeation enhancers on the permeation of KPF from a)2%CMC b) 2%HPMC c) 5%MC

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