

## Effect of Drug modification on properties of Ketoprofen Transdermal Gel

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### Abstract

The aim of this study was to develop Ketoprofen (KPF) gel for transdermal delivery that could enhance dissolution and permeability of KPF and to study the change in release and permeation of transdermal gel after formulating KPF as niosomes and solid dispersions. 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 polymers and permeation enhancers on the in vitro release and permeation 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. The results showed that both polymers and permeation enhancers affect release and permeation of KPF transdermal gel. The release and permeation from the niosomal gel were highly prolonged when compared to conventional gel. On the other hand, they were enhanced from the solid dispersion gel.

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### Key words:

KPF, transdermal, gel, niosomes, solid dispersion

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### 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<sup>(1)</sup>.

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 <sup>(1)</sup>. Solid dispersion is an effective technique which can easily enhance the dissolution rate of drugs <sup>(2)</sup>.

Niosomes are capable of forming vesicles which entrap drug increasing the contact time with the applied tissue <sup>(3)</sup>.

The aim of this study is to enhance the transdermal permeation of KPF by using 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 Chemical, 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 20, Kermel company,Tianjin, China. Span 60,Kermel company,Tianjin, China. Chlorofrm, Alpha Chemical, 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.

### Methods

#### Formulation of KPF gel without permeation enhancers

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 <sup>(1)</sup>, Table (1).

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

The dissolution rate studies were performed on the prepared gels enclosed in tea bags <sup>(4)</sup> by USP dissolution tester, apparatus I (basket method). The dissolution medium was 900 ml of phosphate buffer pH 7.4 <sup>(5)</sup>.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

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 <sup>(6)</sup> , Table (1).

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

As described before

#### In-vitro permeation of KPF gels

In vitro permeation was determined by a modified USP XXVII dissolution apparatus I using 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 <sup>(1)</sup>.

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 (5,7).

The same previous technique of in-vitro release was used.

**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	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

**Formulation of solid dispersion incorporated gel**

The required amount of KPF and carrier in 1:2 & 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 and passed through sieve no. 60 and stored in desiccator until used for further studies (8),Table (2).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.

**Table 2:** Suggested formulae of solid dispersion incorporated gels

Formula	Polymer	Drug-Polymer Ratio
SD1	Chitosan	1:2
SD2	Chitosan	1:4
SD3	PVP	1:2
SD4	PVP	1:4
SD5	HPβCD	1:2
SD6	HPβCD	1:4

**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°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, Table (3).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 (9).

**Table 3:** Suggested formulae of niosomal gels

Formula	Surfactant	Drug-Surfactant-Cholesterol Ratio
NS1	Span 60	1:0.5:1
NS2	Span 60	1:1:1
NS3	Span 60	1:2:1
NS4	Span 20	1:0.5:1
NS5	Span 20	1:1:1
NS6	Span 20	1:2:1

**Effect of drug modification on gel behavior**

The effect of drug modification on the in-vitro release and permeation profiles 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 solid dispersion gel was spread uniformly on glass slide and observed under light microscope <sup>(10)</sup>.

**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 <sup>(11, 12)</sup>. These findings are also consistent with (Lauffer, 1961) <sup>(13)</sup> 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.

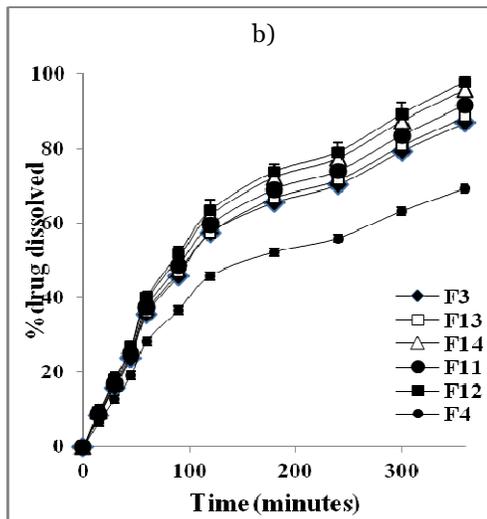
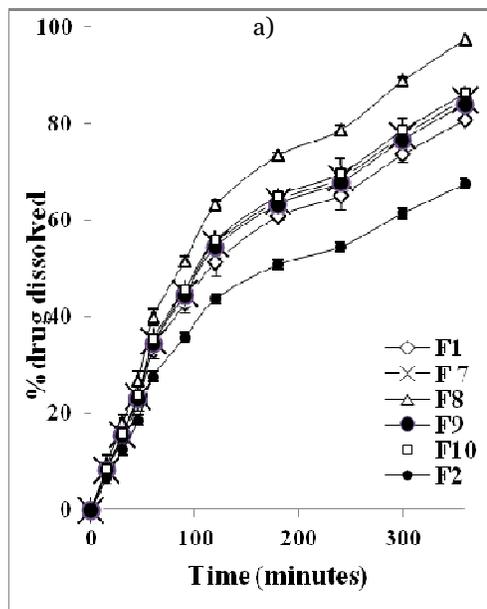
The in-vitro release of KPF from MC gel bases was higher than that from CMC and HPMC polymers. These differences may be attributed to the variation in shape and dimension of the crystallites of the solid fraction <sup>(14)</sup>.

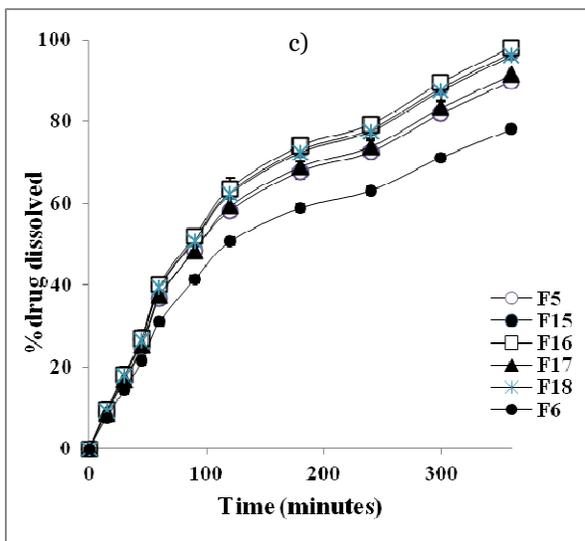
KPF gel bases which achieved the highest in-vitro release; MC (5 %), HPMC (2 %) and CMC (2 %) were formulated in addition to two different permeation enhancers: Tween 80 (2.5 and 5%) and Oleic acid (5 and 10%) and used in further studies.

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

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 <sup>(15)</sup>. 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 <sup>(16)</sup>. 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.





**Figure 1:** The in-vitro drug release of KPF from a) CMC, b)HPMC and c)MC with and 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 (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 (17). 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 (18). 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 (17).

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

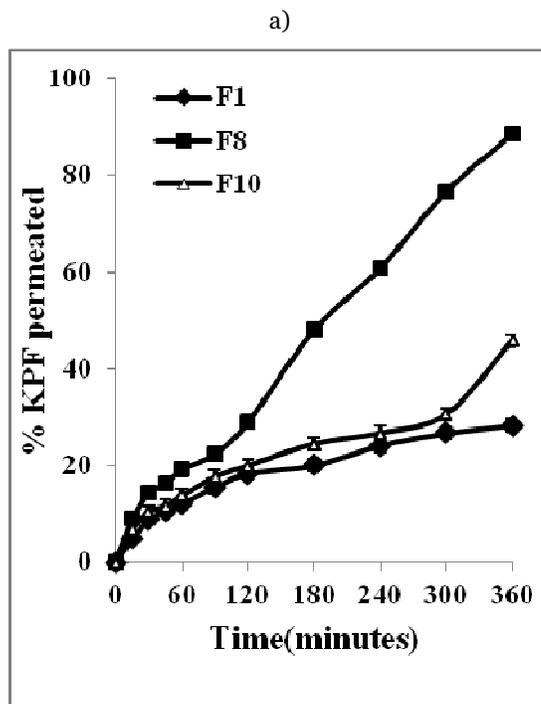
permeation enhancers so, six (6) KPF gel formulae ; F8, F10 ,F12, F14,F16 and F18 were chosen for completing the other tests .

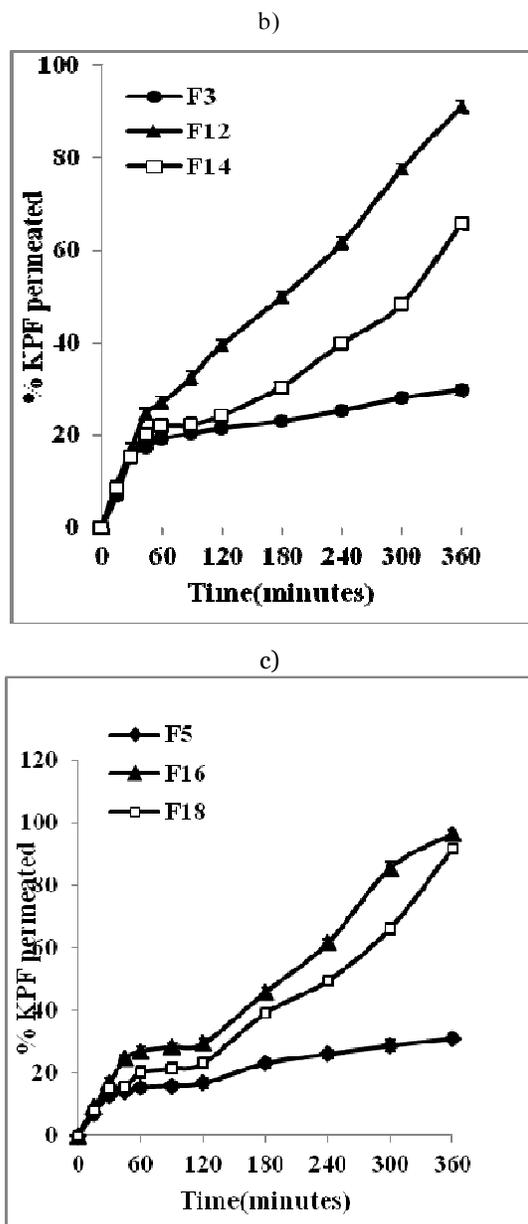
**In- vitro release of solid dispersion incorporated gels**

The dissolution of solid dispersion incorporated gels was in the range (98.41-99.75%) after 6 hrs which is higher than F16 which showed 98.22% of drug release. The in-vitro drug release was increased in the manner of F16 < chitosan < PVP < HPBCD, Figure (3).

That may be attributed to higher solubility of KPF incorporated in solid dispersion as compared to pure KPF(19). Higher release from HPBCD may be due to its ability to solubilize lipophilic entities through molecular encapsulation and formation of water-soluble aggregates which are able to solubilize lipophilic drugs through micelle-like structures (20).

In-vitro release of KPF from the prepared gels increased as carrier concentration increased. That may be attributed to higher solubilization of drug (19). Therefore; higher carrier concentrations (SD2, SD4 and SD6) were used for further studies.



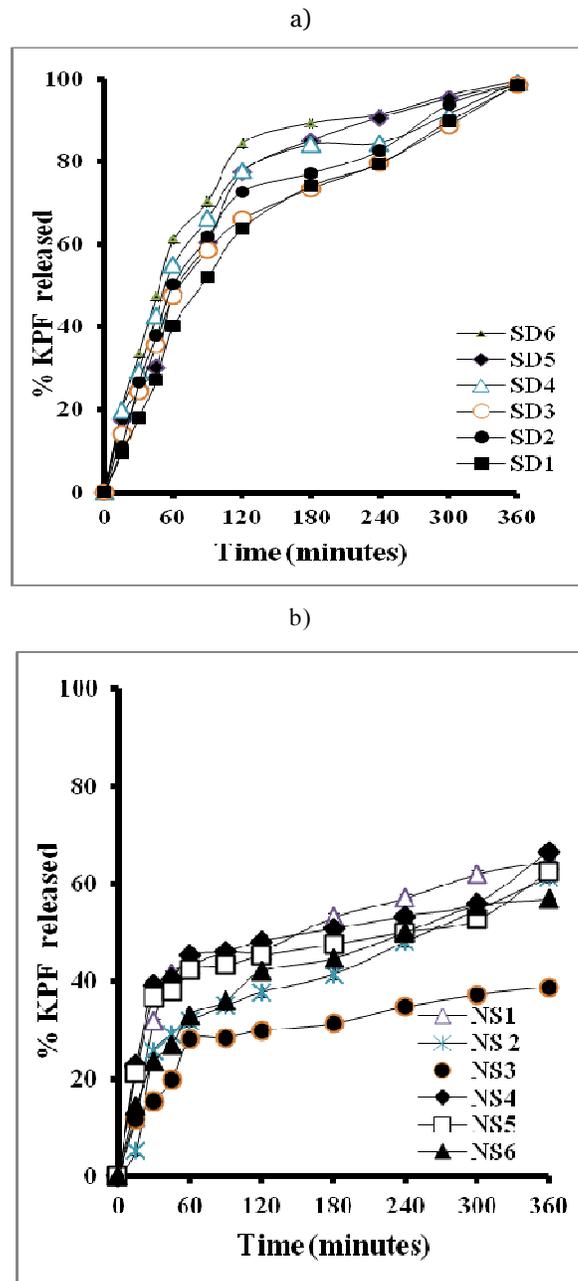


**Figure 2:** The effect of permeation enhancers on the permeation of KPF from a) 2%CMC b) 2%HPMC c) 5%MC

**In- vitro release of niosomal gels**

The dissolution of niosomal gels was in the range (38.84-66.53%) after 6 hrs which is lower than F16 which showed 98.22% of drug release, Figure (3). The highest retardation of drug release was observed with span 60 as compared to span 20. This could be due to the its larger alkyl chain length, lower HLB and higher phase transition temperature (50 °C) that lead to higher entrapment efficiency<sup>(21)</sup>.

In-vitro release decreased as surfactant concentration increased which may be due to higher entrapment efficiency with higher surfactant concentration <sup>(21)</sup>. Therefore, KPF niosomal gels which achieved the highest drug retardation; NS1, NS2 and NS3 were used for permeation study.



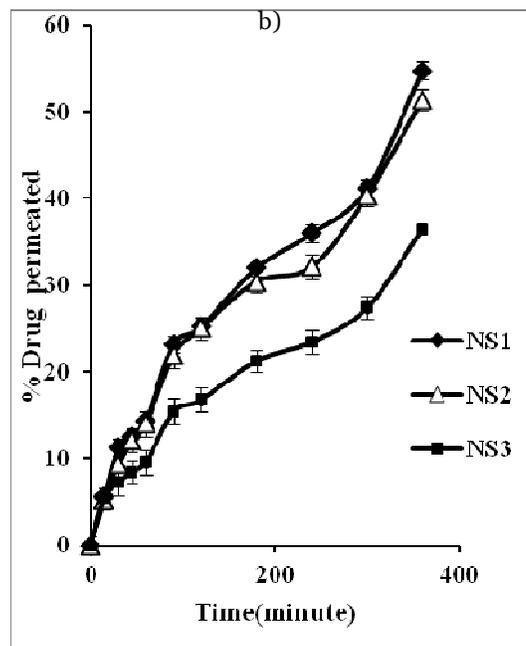
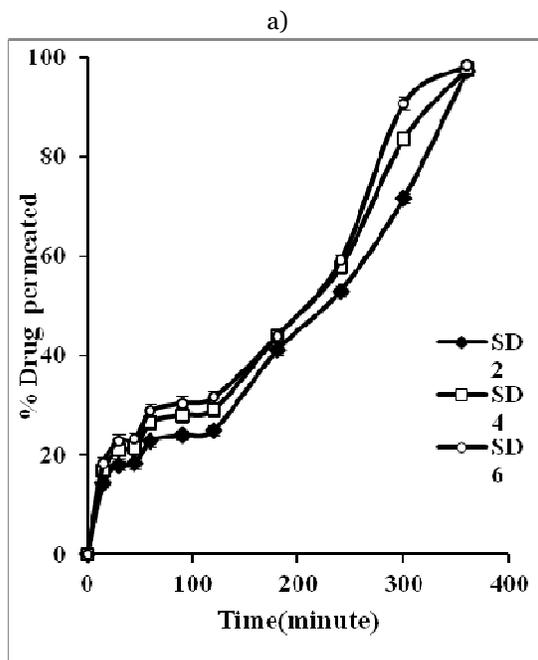
**Figure (3):** The in-vitro drug release of KPF from a) solid dispersion incorporated gels and b) niosomal gels

**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 F16 which showed 96.39% drug permeated. The in-vitro drug permeation was increased in the manner of: F16 < chitosan < PVP < HPβCD. That may be attributed to higher solubility, enhanced permeation of solid dispersion as compared to pure KPF (19). Higher permeation from HPBCD may be due to its higher solubilizing effect (20) and its action as permeation enhancer by transferring the drug from the solution towards lipophilic surface of biological membrane (19), Figure (4).

**Permeation of niosomal gels**

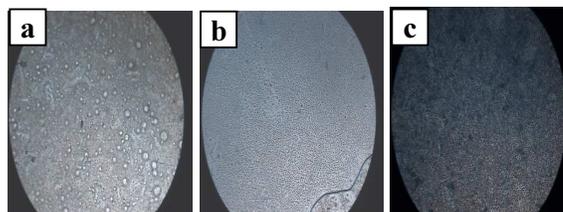
The permeation of niosomal gels was in the range (36.51-54.76%) after 6 hrs which is lower than F16 which showed 96.39% drug permeated which may be due to controlled drug release due to the entrapment of drug in vesicles (21). In-vitro permeation of KPF from the prepared gels decreased as surfactant concentration increased which may be due to higher entrapment efficiency (21), Figure (4).



**Figure 4:** The in-vitro permeation of KPF from a) solid dispersion incorporated gels and b) niosomal gels

**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 (5).



**Figure 5:** Microscopic evaluation of niosomal gel (a), solid dispersion gel (b) and (c) F16

**CONCLUSION**

Formulation of KPF as transdermal gel with addition of permeation enhancers could assist its dissolution enhancement and thus improve its skin permeability. Considering in vitro release and in-vitro permeation, F16 (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. The in vitro release and diffusion of KPF gel was greatly improved by solid dispersion, while controlled and prolonged drug release was obtained by niosomal preparations.

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