IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
August 2016 Vol.:7, Issue:1

Controlled Release Niosomal Gel as a Colloidal Carrier for Topical Drug Delivery of Ketorolac Tromethamine

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ISSN 2349-7203
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Submission: 7 August 2016
Accepted: 12 August 2016
Published: 25 August 2016

Keywords: Niosomal gel, Controlled release, Colloidal Carrier, Ketorolac Tromethamine

ABSTRACT
The main objective of this study is the preparation of different topical formulations of controlled release niosomal gel containing Ketorolac tromethamine (KT) niosomes to avert problems associated with KT such as gastrointestinal irritation and short half-life. Niosomes as a colloidal carrier of KT were prepared by ether injection method then incorporated into different gel bases as sodium alginate (Na alg.), Sodium carboxymethyl cellulose (Na CMC), Hydroxypropyl methyl cellulose (HPMC), Carbopols 934, 940 and Pluronic F-127. All formulations were characterized for their viscosity, the *in vitro* and *in vitro* release kinetics. The viscosity of the prepared gel bases could be ranked in the following order, Carbopol 940 (2%) > Na CMC (5%) > Carbopol 934 (2%) > Pluronic F-127 (30%) > Pluronic F-127 (20%) > HPMC (2.5%) > Na alg. Maximum release of the drug is obtained from Na alg. gel base, while the worst one from pluronic F-127 (30%). The results show that the release of KT from plain drug and niosomal gels follows Higuchi diffusion mechanism**.** The drug in its niosomal form exhibited a decrease in the release from gels as compared with plain drug. The slower release of drug from niosomes is due to the entrapment of drug within the vesicle so prolong drug release. Niosomes act as micro reservoir within the transdermal delivery systems at the surface of the skin, allowing the controlled release of the drug from the vesicles and a modulation of the drug penetration across the skin**.**

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1. INTRODUCTION

Ketorolac Tromethamine (KT) is marketed as a racemic mixture of S (-) and R (+) enantiomers. Animal studies have been shown that the pharmacological activity is due to S (-) enantiomer [1]. Its analgesic and anti-inflammatory activity derive from a common mechanism which is the inhibition of the *cyclooxygenase*. Additional mechanism has been assumed, including a participation of opioid receptors although it does not bind to these receptors [2]. It is extensively used to treat moderate to severe pain and it has been studied in a broad spectrum of pain status including postpartum and postoperative arthritic pain, pain of trauma, severe dental pain, renal colic, cancer, abdominal and gynecological pain [3]. The half-life of KT is quoted to be 5.4 hrs. KT is more than 99% bound to plasma protein[4] most likely to albumin**.** Unfortunately, side effects primarily in gastrointestinal tract are often seen after oral administration and in addition, it has a short half-life. In addition, KT has poor skin penetration ability, which limits its usefulness as a potent drug used in topical formulations. Liposomes and niosomes are spheroidal moieties composed of amphiphilic molecules assembled into bilayers. Recently, significant consideration has been paid to niosomes as an option potential medication superior to conventional liposomes. Niosomes are non-ionic surfactant vesicles having a bilayer structure formed by self-assembly of hydrated surfactant monomer [5] which can be used as carrier for both hydrophilic and lipophilic drugs [6, 7]**.** Niosomes have distinct advantage over conventional dosage forms because they can act as drug containing reservoir [8]. Gels were prepared from various agent such as Na alg. (5%), Na CMC (5%), HPMC (2.5%), Carbopol 934, 940 (2%) and Pluronic F-127 (20 and 30%) W/W. These agents are safe and the obtained gel show good texture, homogeneity and ease of spreading. The present study was focused on development of controlled release niosomal topical formulations of KT niosomes to modify *in vitro* permeation ability and avoid problems associated with orally administered KT such as gastrointestinal irritation and short half-life.

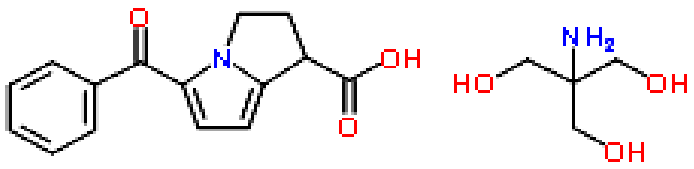

Fig. 1. Chemical structure of KT (2-Amino- (hydroxyl methyl) propane-1,3-diol (1RS) – 5-benzyoyl-2, 3-dihydro-1H-pyrolizine- 1- carboxylate).

2. MATERIALS AND METHODS

Materials

KT powder kindly supplied from Amriya Pharm. Ind. Co., Alex., Egypt. Sorbitan monolaurate (Span 20), sorbitan monostearate (Span 60), Sigma Chemical Co, Steinheim, Germany. Cholesterol, Pluronic F-127, hydroxypropyl methylcellulose (HPMC) and standard cellophane membrane (molecular cutoff range = 12000) were purchased from Sigma chemical Co., Louis, MO, (U.S.A). Sodium hydroxide, sodium chloride, potassium dihydrogen orthophosphate anhydrous and dipotassium hydrogen orthophosphate anhydrous, Na alg., sodium carboxymethyl cellulose (Na CMC), El-Nasr Pharm. Chem. Co. ,Cairo, Egypt. Diethyl ether, Labscan Ltd, Dublin, Ireland. Hydrophobic filter, membrane filter, diameter pore 0.2 µm, Versapor, German Sciences. Carbopol 934 and 940, C. P. Evans Co., England. All the above materials were in analytical grade and were used without further purification.

Equipment:

An electric balance, Sartorius GMBH, Gottingen (Germany), UV double beam spectrophotometer, Shimadzu Kyoto (Japan), pH meter, Getway, Ltd (UK),Water bath, RE 2000B, Bibby sterilin LTD (UK) , Sonicator, Ultrasonic cleaner set, WUG-D06H (Korea), Fourier transform IR- 476-Shimadzu Koyto (Japan), DSC (Shimadzu, DSC-60 with TA-60 WS analyzer, Tokyo, Japan), Centrifuge, Biofuge, primo Heraeus (Germany), JEM-100 S Electron microscope, Joel Ltd (Japan), Magnetic stirrer (Type MMS, Poland Co., Poland), Thermostatically controlled shaking water bath (Kotterman Labortechnik GmBh, Germany), Homogenizer (Mechanika Precyzyina-MPW-309, Poland). Diffusion cell apparatus (Locally manufactured)

2.1. Preparation of KT niosomes

Niosomes were prepared by ether injection method [9-11]. Accurately weighed quantities of cholesterol and non-ionic surfactant were dissolved in diethyl ether. Afterward, the solution was injected through 14 gauge needle into a preheated aqueous phase (drug dissolved in phosphate buffer saline pH 7.4) maintained at 60^0C and agitated simultaneously. Rate of injection was maintained at 0.25 ml/minute. Vaporization of ether will take place during injection process leading to niosomes formation.

2.2. Preparation of gels:

The composition and viscosity of the investigated gel bases are illustrated in Table 1.

2.2.1 Preparation of cellulosic and Na alg. gels:

Accurately weighed quantities of HPMC, Na CMC and Na alg. powder were sprinkled, gently into the required quantities of water, and magnetically stirred until a thin hazy dispersion without lumps were formed. Mixing was continued till smooth homogeneous gel is formed. prepared gels were left overnight to ensure complete gel dispersion [7]

2.2.2 Preparation of Pluronic F-127 Gels (20 and 30 % W/W):

The required amount Pluronic F-127 were mixed with cold water under agitation with glass rod. The mixture was stored at 4 ^{0}C for 24 hours till clear solution was obtained. The gel was formed when pluronic F-127 solution was left at room temperature for 30 minutes at least. [12]

2.2.3 Preparation of Carbopol Gels (Carbopol 934 and 940):

The specified weighed amount of the polymer was slowly added to half amount of the required water. The mixture was stored at room temperature for 24 hour to allow complete polymer swelling. Sodium hydroxide (400 mg for each gram of carbopol powder) was dissolved in the remaining amount of required water and added with gentle stirring. In this way we avoid incorporation of air bubbles [2]. KT and KT loaded niosomes separated from unentrapped drug, were mixed thoroughly into the prepared gels in a concentration of 1% W/W [13, 14]

Table (1): Composition of the investigated gel bases and its viscosity ± SD

Base type	Composition (W/W %)	Viscosity (cP) ± SD
Cellulose derivatives		
HPMC	2.5	80467 ± 7015
Na CMC	5	154000 ± 9539
Sodium Alginate	5	61000 ± 1070
Carbopol bases		
Carbopol 934	2	153667 ± 11590
Carbopol 940	2	195667 ± 3055
Pluronic bases		
Pluronic F-127	20	84900 ± 1670
Pluronic F-127	30	92433 ± 2495

2.3. Measurement of the viscosity of the investigated gels

Viscosity measurements of the prepared gels were performed on a Brookfield DV-III ultra-viscometer (RV model) using T bar spindle T-D 94, spindle speed 50 rpm and at temperature 25 ^{0}C. Each experiment was performed in triplicates and mean viscosity of each formula was calculated as shown in Table 1.

2.4. *In vitro* release of KT from gels

The *in vitro* release studies of KT from the prepared gels were carried out using locally manufactured diffusion cell. Accurately weighed amount from each formulation containing 5 mg of the drug was placed on a semipermeable cellophane membrane (cut off range = 12000). The membrane was previously soaked in distilled water for 24 hrs. The loaded membrane with the sample of the topical formulation (containing KT or KT loaded niosomes) was stretched over the open end of the glass tube with an effective diffusion area 6.63 cm^2. The membrane was clipped tightly over the tube end (between donor and receptor compartments) by means of a cotton thread. The tube is placed vertically inside the receptor compartment composed of 250 ml phosphate buffer (pH 5.5) maintained at 37 ^{0}C and stirred at 50 rpm in a thermostatically controlled shaking water bath. At pre-determined time intervals up to 12 hrs ,5ml of aliquots were sampled and were replaced with an equal volume of the release medium at the same temperature to ensure sink conditions [7]. Released amount of KT was determined spectrophotometrically at 323.5 nm using phosphate buffer pH

5.5 as blank. Each experiment was carried out three times and the average was calculated. The obtained data are illustrated in Figs. 2 and 3.

2.5. Kinetic study of the *in-vitro* release of KT from gels

Different kinetic parameters of the *in vitro* release data were determined using curve fitting method. The process was carried out to different kinetic models namely, zero, first and second orders, as well as controlled diffusion model [15-17]

Zero-order release	$M_t = M_o + K_o t$
First-order	$\text{Log } C = \text{Log } C_o \; K_1 \, t / 2.303$
Second order	$1/C = 1/C_o + K_2 \, t$
Higuchi-Model	$M_t = Kt^{0.5}$

In which M_o and M_t are the amount of ketorolac tromethamine released initially and at time t respectively.

C_o and C are the amount of KT released initially and released at time t respectively.

K_o, $K_1$and K_2 are constants.

3. RESULTS AND DISCUSSION

3.1. Viscosity measurement data:

Table 1: show the viscosity of the prepared gels. The viscosity of the prepared gel bases could be ranked in the following order: Carbopol 940 (2%) > Na CMC (5%) > Carbopol 934 (2%) > Pluronic F-127 (30%) > Pluronic F-127 (20%) > HPMC (2.5%) > Na alg.

3.2. *In vitro* release of KT from the investigated gel bases

This study shows the significance of using different gel forming agents on the release behavior of KT from these bases. The obtained data shows that the release rate from niosomal gel is lower than that from plain drug gel. An important implication of these findings is that encapsulation of the drug into the vesicles (aqueous core) providing prolonged drug release rate. These criteria provide controlled release niosomal gel which averts problems associated with KT as short half-life and avoid frequent dosing as in case of conventional topical formulations. These results are consistent with other studies which have shown that niosomes

have a depot action within transdermal delivery system at the surface of skin and consequently, provide controlled release of the drug from the vesicles and modulate drug penetration across the skin [18-21]

3.2.1. *In-vitro* release of KT from Carbopol gel base:

The cumulative percent released from KT plain and KT loaded niosomes from Carbopol 934 and Carbopol 940 is shown in Figs. 2a and 2b. An important implication of these findings is that the cumulative percent release of KT from Carbopol 934 was higher than Carbopol 940 These results can be contributed to the lower gel base viscosity of Carbopol 934 (15677 cP) than Carbopol 940 (195667 cP) and therefore the release of drug is higher from Carbopol 934 [12], or due to variation in cross linking density. Polymers with high cross linking density possess high tortuosity of the matrix through which the drug diffusion increases and consequently decreasing the drug release [22].

3.2.2. *In-vitro* release of KT from Na alg. gel base:

As can be seen from Fig, 2c which shows that the cumulative percent release of KT (KT and KT loaded niosomes) from Na alg. gel base is greater than that obtained from other gel bases. The permeation of drug from the gel bases were retarded in accordance with their viscosities as reported in many studies so, these results may be imputed to the lower viscosity of Na alg. gel base than other gel bases [23].

3.2.3. *In-vitro* release of KT from cellulosic derivatives.

Consider Figs 2d and 3e shows that the cumulative release of KT from HPMC gel base was higher than that of Na CMC. The lower viscosity of HPMC gel (80467 cP) plays an important role in enhancement of drug release, whereas the higher viscosity of Na CMC gel (154000 cP) retards drug release. [24]

3.2.4. *In-vitro* release of KT from Pluronic F-127 gel bases.

Regarding the release of KT either from Pluronic F-127 gel or niosomal Pluronic F-127 gel, it is noticed that increasing Pluronic F-127 concentration from 20 % to 30 % W/W led to significant decrease in the release rate. This may be due to the lower viscosity of Pluronic F-127's 20% compared to Pluronic F-127's 30 % as practically measured and summarized for different gel bases viscosities in Table 1. These results concur with laffer's diffusion theory in

gels which states that the diffusion coefficient of a solute is inversely proportional to the volume fraction occupied by the gel forming material [25]. In addition, Pluronic F-127 gel consists of large population of micelles resulted in concentration reduction of diffusible solute also the drug is included within the micelles [12, 22, 26].

The release of KT loaded niosomes from different gel bases was arranged in descending order as follows: Na alg. > HPMC > Carbopol 934, Na CMC > Carbopol 940 > Pluronic F-127 (20%) > and finally Pluronic F-127 (30%). These results prove that the nature of the vehicle has a great influence on drug release. In this study different gel bases with different polymer structure were used to compare the release profile of the drug. The release rate of the drug through any base depend on the nature and composition of the individual base [27]

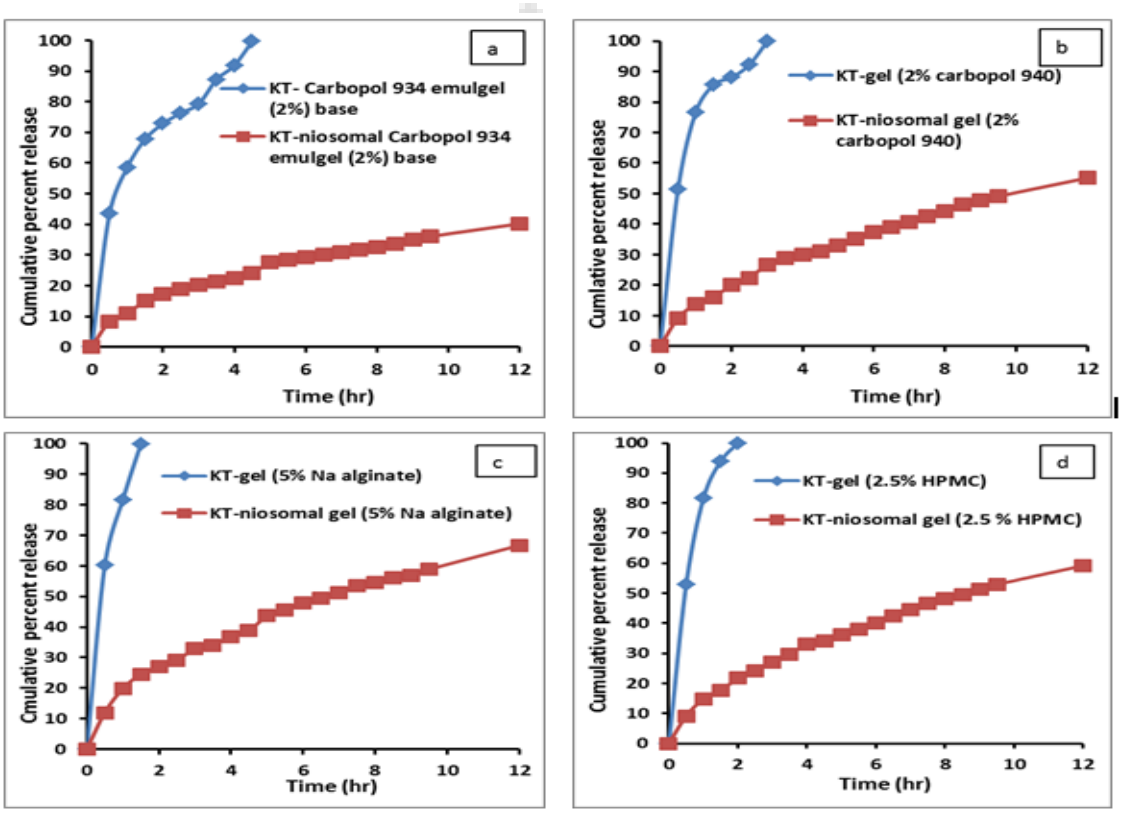

Fig. (2): Cumulative percent release of KT and KT loaded niosomes from (a) 2% Carbopol 934, (b) 2% Carbopol 940 gel base, (c) 5% Na alg., (d) 2.5% HPMC.

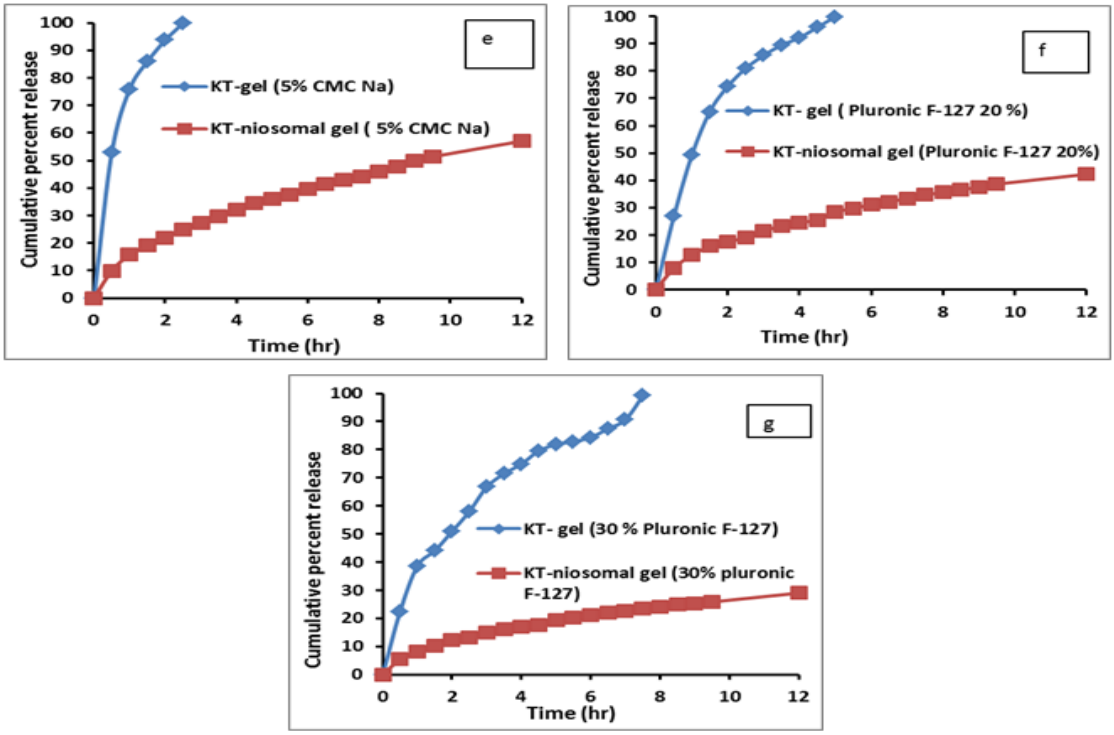

Fig. (3): Cumulative percent release of KT and KT loaded niosomes from (e) 5% Na CMC, (F) 20% Pluronic F-127 and (g) 30% Pluronic F-127 gel bases.

3.3. Kinetic study of the *in-vitro* release of KT from the investigated gels

The Kinetic treatment was carried out by plotting the time in hours versus the cumulative percent released of KT, the time versus log cumulative percent retained and by plotting the time versus the reciprocal of the cumulative percent retained for zero-order, first-order second-order respectively. The kinetic treatment for Higuchi diffusion model was calculated by plotting the square root of time versus the cumulative percent released of KT. The best kinetic order can be calculated from the highest correlation coefficient values obtained. The kinetics of the *in vitro* release of KT from the prepared gels in phosphate buffer pH 5.5 can be best described by Higuchi diffusion model as summarized in Tables 2 and 3.

Table (2): The calculated correlation coefficient for the *in-vitro* release of KT from niosomal gels employing different kinetic order or systems.

Niosomal Formulae	Correlation coefficient (r)				
	Zero	First	Second	Diffusion	Order
Carbopol 934 gel	0.982905	0.995416	0.996038	0.998057	Diffusion
Carbopol 940 gel	0.986035	0.996875	0.99736	0.998357	Diffusion
Na alg. gel	0.981351	0.996742	0.992906	0.997793	Diffusion
HPMC gel	0.985469	0.997868	0.997523	0.999293	Diffusion
Na CMC gel	0.98432	0.996844	0.997995	0.999552	Diffusion
Pluronic F-127gel (20%)	0.977544	0.988646	0.995828	0.998456	Diffusion
Pluronic F-127gel (30%)	0.975477	0.983321	0.98963	0.998748	Diffusion

Table (3): The calculated correlation coefficient for the *in-vitro* release of KT from gels employing different kinetic order or systems.

Formulae	**Correlation coefficient (r)**				
	Zero	First	Second	Diffusion	Order
KT Carbopol 934gel	0.92525	0.883444	0.718874	0.958565	Diffusion
KT Carbopol 940 gel	0.917778	0.857619	0.667512	0.954816	Diffusion
KT Na alg. gel	0.998815	0.918355	0.867125	0.999631	Diffusion
KT HPMC gel	0.946985	0.941517	0.786187	0.974114	Diffusion
KT Na CMC gel	0.959633	0.900484	0.719708	0.984776	Diffusion
KT Pluronic F-127 gel (20%)	0.931114	0.863757	0.541367	0.973935	Diffusion
KT Pluronic F-127 gel (30%)	0.968451	0.814072	0.430437	0.988617	Diffusion

CONCLUSION

Based on the results, it can be concluded that the *in vitro* release of KT loaded niosomal gel formulations were slower than the corresponding release of KT from other plain gel bases. The slower release of drug from niosomes is due to the entrapment of drug within the vesicle so prolong its release. Niosomes act as micro reservoir within the transdermal delivery systems at the surface of the skin, allowing the controlled release of the drug from the vesicles and a modification of the drug penetration through the skin. The order of release of KT from both KT and KT loaded niosomes from different gel bases were found to follow diffusion model. These niosomal gels may provide a useful tool for controlling the release of drug from different topical formulation which overcomes some problems such as frequent dosing. In our future research we intend to concentrate on composition of different niosomes formulation to optimize drug release pattern and enhance drug permeation ability across the skin.

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