Preparation and evaluation of Diacerein Novasomes transdermal HPMCK15M Gel

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Abstract

Diacerein is an anthraquinone derivative used as a disease-modifying agent in the treatment of osteoarthritis. Because of the laxative effect that is associated with the oral administration of diacerein, treatment is often discontinued. The present study aims to prepare diacerein novasomes transdermal HPMCK15M Gel to enhance drug permeation. The transdermal gel was prepared by hot-cold method in which the polymer is dispersed in hot water while the prepared novasomal vesicles of diacerein were isolated by cold centrifugation and dispersed in cold water. The prepared gel was evaluated for its drug content, pH, spreadability, and in vitro drug release from the gel. The selected gel formula was further evaluated for its release kinetic, rheological properties, and ex vivo permeation parameters. Results showed that the prepared gels were clear and homogeneous, with a drug content from 92.86±3.1 to 99.89±0.18, pH value was 6.75-6.88, and spreadability of 5.4±0.3to 9.1±0.8. The in vitro drug release kinetic was best fitted to the Higuchi model of drug release with a Fiackian mechanism. Rheological evaluation of the selected gel formula displayed non-Newtonian pseudoplastic share thinning flow behavior. The ex vivo permeation study found that transdermal flux was 60.349 ± 0.375 µg/cm2/h, the lag time was 2.8±0.1 and the permeability coefficient was 60.349*10-3 cm/hr. In conclusion, the prepared HPMCK15M transdermal gel at a concentration of 3% w/w was found to be an appropriate vehicle for better transdermal delivery of diacerein from its novasomes.

Keywords: Diacerein, Novasome, HPMCK15M, Osteoarthritis, Transdermal Delivery.

تحضير وتقييم حويصلات الدياريسين النوفاسومية كجل عبرالجلد

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الخلاصة

الدياسيرين هو أحد مشتقات الأنثراكوينون، ويستخدم كعامل معدّل للمرض في علاج التهاب المفاصل العظمي. يرتبط تناول الدياسيرين عن طريق الفم بتأثير ملين يؤدي إلى وقف العلاج. الهدف من هذه الدراسة هو تطوير هلام عبر الجلد يعتمد على حويصلات الدياسيرين. النوفاسومية لتعزيز تغلغله عبر الجلد وتجنب الآثار الجانبية المعدية المعوية. تم تحضير الجل عبر الجلد بواسطة طريقة دمج الجزء البارد مع الساخن التي يتم فيها تشتيت البوليمر في الماء الساخن بينما يتم عزل الحويصلات النوفازومية المحضرة من الدياسيرين بواسطة الطرد المركزي البارد وتشتيتها في الماء البارد. تم تقييم الجل المحضر من حيث محتوى الدواء، ودرجة الحموضة، وقابلية الانتشار، وإطلاق الدواء في المختبر من الجل. تم تقييم تركيبة الجل المختارة أيضًا من حيث إطلاقها للخصائص الحركية والانسيابية ومعلمات تخلل الجسم الحي. أظهرت النتائج أن المواد الهلامية المحضرة كانت صافية ومتجانسة، مع محتوى دوائي من 92.86±3.1 إلى 99.89±0.18، وكانت قيمة الرقم الهيدروجيني 6.75-6.88، وقابلية الانتشار من 5.4±0.3 إلى 9.1±0.8. تم ملاءمة حركية إطلاق الدواء في المختبر بشكل أفضل لنموذج هيجوتشي لإطلاق الدواء باستخدام آلية فيكيان. أظهر التقييم الريولوجي لصيغة الجل المختارة سلوك تدفق رقيق غير نيوتوني. وجدت دراسة التغلغل خارج الجسم الحي أن التدفق عبر الجلد كان 60.349 ± 0.375 ميكروغرام/سم2/ساعة، وكان زمن التأخر 2.8±0.1 وكان معامل النفاذية 60.349*10-3 سم/ساعة. في الختام، كان الجل المعد عبر الجلد وسيلة فعالة لتسهيل إعطاء الحويصلات المحضرة لضمان نتائج علاجية فعالة.

الكلمات المفتاحية: دياسيرين، نوفوسوم، HPMCK15M، هشاشة العظام، التوصيل عبر الجلد.

Introduction

Diacerein (DCN) is a derivative of anthraquinone that is indicated for the treatment of osteoarthritis **(1)**. It is regarded as a slow-acting disease-modifying agent. Upon oral administration, DCN is completely converted to rhein **(2).** Both DCN and/or rhein are capable of inhibiting IL-1; as a consequence, the ensuing events that are caused by IL-1 induction will also be prevented **(3).** These kinds of processes will be blocked, including the synthesis and activity of various pro-inflammatory and pro-catabolic cytokines, reactive oxygen species, and other free radicals including nitric oxide (NO), which has been linked to inflammation (**4).**

The administration of the BCS class II diacerein through oral administration is linked to a high permeability and a limited dissolution in the fluid of the gastrointestinal tract**(5).** Oral bioavailability is low (35-56%), and bacteria in the colon oxidize the undissolved rhein to generate rhein-9-anthrone, which has a laxative effect. Rhein has a restricted oral bioavailability. It is possible that this impact is connected to diarrhea or soft stools, both of which might result in poor compliance and the termination of therapy because of the condition **(6).**

In addition, the European Medicines Agency (EMA) imposed limitations on the use of drugs that include diacerein in patients who were over the age of 65 and suffering from osteoarthritis in the year 2015. It was determined that this suggestion was necessary because of serious concerns regarding the frequency and severity of diarrhea**(7).** Several attempts have been made to limit the side effects of DCN. Some researchers tried to enhance its dissolution in the GIT fluid by several approaches such as solid dispersion, co-crystallization, and complexation **(8-10)**. Others suggested alternative routes of administration such as intra-articular and transdermal delivery **(11,12).** The physicochemical and pharmacokinetic properties of diacerein are encouraging for transdermal delivery such as short half-life (4.2 hours), moderate hydrophobicity Log p = 1.79, and a molecular weight less than 500 Dalton **(13,14).** Furthermore, transdermal delivery is a patient-friendly approach and is self-administered leading to increased patient compliance**(15).**

The major obstacle in transdermal delivery is related to the limited permeability of the stratum corneum layer of the skin**(16).** Several approaches tried to overcome this barrier layer by chemical, physical, and formulation techniques**(17).**

Novasomal vesicles(ns) are made up of a number of concentric lipid bilayers between two and seven in number. These bilayers are composed of non-ionic surfactants and free fatty acids, with or without cholesterol**(18).** It is believed that the components of vesicles alter the structure of the stratum corneum by fluidizing its lipids, which results in an increase in the drug's capacity to pass through into the stratum corneum**(19).**

The aim of the current study is to formulate a gel preparation to act as a vehicle for the transdermal delivery of DCN NS.

Material and Methods

Materials

Diacerein and HPMCK15M were purchased from Hangzhou Hyper Chemicals Limited, China. Cholesterol was from Lee Pharmaceutical, China. Stearic acid was obtained from BDH Chemicals Ltd. Poole, England.Span 60 Xi 'an Sonwu biotech Co., Ltd, China. Methyl and propylparaben were obtained from Suprim Chemicals.

Methods

Preparation of gel-based transdermal delivery system for DCN-NSs

Transdermal gels based on DCN-NSs were prepared from different concentrations of HPMCK15M as a forming polymer as illustrated by **Table 1**. Firstly, DCN-NSs (F6) prepared by thin film hydration in another study from Span 60, cholesterol, and stearic acid were subjected to cold centrifugation (16,000 rpm at 4 ºC) to isolate the vesicles containing 1 g of DCN based on F6 entrapment efficiency which eas equal to 69.415± 0.234 .(20). The gel was prepared by the hot-cold method in which the required weight of HPMCK15M was slowly added to 30 mL of water heated to 70 ºC. Propylparaben and methylparaben were dissolved in 0.5 g of glycerine and added to the previous polymeric solution. Then the collected vesicles (amount equivalent to 1 g) were redispersed in 60 mL of cold water and then added to the polymeric dispersion while the mixture was stirred at a speed of 1000 rpm for 10 minutes. Following that step, the weight of the gel was brought up to 100 g by adding distilled water. Taking everything into consideration, the concentration of DCN in the gel will be 1% of the weight per weight of the gel.

F-code	Amount of DCN-NS (g)	Amount of HPMCK15M(g)	Glycerine (g)	Methyl paraben (g)	Propyl paraben (g)	Distilled Water (g)
DCN-NS Gel 1	1	1	0.5	0.01	0.01	q.s.100
DCN-NS Gel 2	1	2	0.5	0.01	0.01	q.s.100
DCN-NS Gel 3	1	3	0.5	0.01	0.01	q.s.100

Table 1: Composition of DCN-NSs-based transdermal gels

Evaluation of DCN-NSs-based transdermal gels

The prepared gels were evaluated for the following parameters:

1. Physical appearance and homogeneity

Visual inspection was used to determine whether or not the gels that had been created were homogeneous after the gels had been allowed to set in the container. In addition, the gels were examined to determine their appearance as well as whether or not they included any aggregates, particles, or fibers**(21).**

2. Determination of the pH

The pH readings were obtained with the use of a digital pH meter that was checked for accuracy with a buffer before each reading. To determine the pH of the formulations, a glass electrode was dipped into the topical gel **(22).**

3.Determination of the drug content

Transferred to a volumetric flask containing PBS with a pH of 7.4 was an amount[MOU1] of DCN-NSs loaded gels that had been accurately weighted to be five grams and was equivalent to 50 mg of the DCN. After sonicating the combination for 30 minutes, it was left alone for the night. Using a UV-visible spectrophotometer, the absorbance of the sample was measured at 258 nm in order to calculate the amount of drug present**(23).**

[MOU1]I have isolated vesicles containing 1 gm of diacerein in several steps to obtain this amount as th ee% was 69.415± 0.234

4. Determination of the spreadability

On a glass plate measuring 15 by 15 centimeters, a circle with a diameter of 3 centimeters was marked out and a weighed quantity of DCN-NS-laden gel was placed inside of it. On top of the gel was another glass plate that measured 15 by 15 centimeters. On the upper glass plate, a weight that was comparable to 500 grams was left for five minutes. It was discovered that the diameter had grown as a consequence of the gel spreading **(24)**.

5.**In vitro release study of DCN-NSs-based transdermal gels**

In vitro release research was performed by inserting 300 mg of gel formulations (containing 3 mg of DCN) onto a dialysis membrane (MWCO 8,000-14,000Da). The membrane had been soaked overnight in dissolving media before the investigation began. After tying both ends of the dialysis bag, it was placed in 200 mL of PBS (pH 7.4), which served as the dissolution medium. The rotation speed was set at 50 rpm, and the temperature of the medium was kept at 37 ±1 °C **(25).** At each of the predetermined time intervals of 0.5, 1, 2, 4, 6, and 8 hours, an aliquot of 5 mL of the dissolution media was removed and replaced with an equivalent volume of the new dissolution fluid. This was done to keep the sink condition constant **(26).** A spectrophotometric analysis was performed on the samples at 258.8nm. Every single step was performed three times to ensure accuracy.

6. Kinetic modeling of DCN release from the selected DCN-NSs-based transdermal gel

With the assistance of the DDsolver add-in application for Microsoft Excel**(27),** the data that were obtained as a result of the in vitro release tests that were performed on the prepared gels were then fitted to various mathematical expressions to understand the kinetics and mechanisms of the DCN release as illustrated in **Table 2** below. Because the model had the highest correlation coefficient, it was deemed to be the model that was the best fit for the data **(28).**

Zero order kinetic	$M_t = M_0 + K_0 t$----------**eq1**
First-order kinetic	**Log** M_t = **log** $M_0 + K_1$ t/2.303-----**eq2**
Higuchi model	$M_t/M_\infty = K_H\ t^{1/2}$ -----**eq3**
Korsmeyer-Peppas	$M_t / M_\infty = K_{KP}\ t^n$-----**eq4**

M_t is the amount of the released active ingredient in time t, M_0 is initial amount of active ingredient in the solution.,$M^\infty$is the cumulative amount of active ingredients released at an infinite time,K is the release kinetic constant obtained from the linear curves of the above models and n is the release exponent, which characterizes the mechanism of drug release.

Table 2: Mathematical kinetic modeling to understand DCN release

7.Determination of the rheological properties of the selected DCN-NSs-based transdermal gel

The determination of the rheological properties of topical products is of the utmost importance because it has a direct influence on the formulation of the active drug ingredient and the development of the dosage form. Additionally, this has an impact on the quality of the raw and finished product, the efficacy of the drug, the degree to which a patient adheres to the prescribed drug, and the overall cost of healthcare.**(29,30).** When it comes to determining the amount of medicine that will be released from the prepared gel formulation the viscosity plays a significant role**(31).** The rheological characteristics of the gel formula were analyzed with a (Myr VR3000) Viscometer using spindle R7. This particular viscometer is of the cup and bob type[MOU1] .

The gel formulation is filled into a cup having a diameter of (2.5cm), the high of the gel in the cup should cover the mark in the spindle of 6 cm. The measurement was performed by an increase in rotation speed from 10 to 60 rpm. The measurement was recorded at a temperature of 35°C. Specifying the temperature is considered to be important Since the rheological parameters of semisolid pharmaceutical-to-be systems can vary in a wide range with temperature **(32).** The readings reported by the viscometers are the rotational speed per minute and the torque. These data are used to calculate the shear rate and stress from Margules **(33)**equations below:

$$\sigma = T/2\pi L R_b^2 \ldots\ldots\ldots\ldots \textbf{eq5}$$

$$\gamma\ . = 4\pi R_b^2 rpm\ /(60(R_c^2 - R_b^2)) \ldots\ldots\ldots\ldots \textbf{eq6}$$

Where:σ is the shear stress equal to Force / Area (N/m^2 = Pa).γ .is the shear rate equal to Velocity / Distance (s^{-1}). R_b and R_c are the radii of the bob and cup respectively (cm).L is the height of the bob in contact with liquid in the cup (cm).T is the measured torque of the bob (N.m).rpm is the angular velocity (rad/s) and η (Pa.s) is the dynamic viscosity

Rheological data was fitted to the Power law model in order to determine the flow behaviour according to Equation 7 below **(33):**

$$\textbf{Log}\ \sigma = \textbf{Log}\ K + (n)\textbf{Log}\ (\gamma.) \ldots\ldots\ldots\ldots \textbf{eq7}$$

Where: K is the consistency index ($Pa.s^{-1}$) and n is Farrow's constant (the flow behavior index) and it is dimensionless.

In these equations; n stands for the index of the deviation from Newtonian flow behavior. If n=1 Newtonian flow , 0<n<1: Pseudoplastic share thining system and n>1 dilatant flow

8. The ex vivo permeation study of DCN-NSs-based transdermal gel

A Franz diffusion cell with an effective diffusion area of 0.502 cm2 was utilized in order to carry out the ex vivo permeation investigations of the DCN-NS gel. An ethical committee gave its approval (RECAUBCP262022A) to the technique for the investigation, which involved obtaining skin from male Swiss albino rats. The skin was obtained from the animal house of the institution. There was a skin layer that served as a barrier between the receptor and donor areas. Thirteen milliliters of pH 7.4 PBS were added to the receptor compartment **(34).** The permeation study was conducted under sink conditions as calculated by equation 8 as shown below**(35).**

$S_{ratio} = Cs / Cd$ ------ **eq 8**

where Cs is the saturation solubility of the drug and Cd is the dose of the drug divided by the volume of dissolution media used.

Into the donor compartment, 0.1g of the gel (containing 1 mg of DCN as NSs) was applied. The amount of DCN permeated was evaluated at 1,2,4,6,8,10,12,18 and 24 hours by taking 1 mL of the receptor compartment and replacing it with fresh media to maintain sink condition(**36).** The amount of DCN permeated was determined spectrophotometrically at 258.8 nm. The amount of DCN permeated per unit surface area was plotted against time and the steady-state flux was derived from the slope of the linear line according to Equation 9 below**(37).**

$J_{ss} = P * C_{donor}$ ..... **Eq 9**

Where P is the permeability coefficient (µg/hr), J_{ss} is the flux, and C is the drug concentration on the donor side.

The flux can be calculated from the slope of the linear component of the curve and the "lag time" (θ) can be obtained from the time-axis intercept of the linear component of the curve.

Statistical Analysis

Version 9 of Graph Pad Prism was used to perform the statistical analysis. Mean ± SD was used to express experiment outcomes. Analytical statistics using ANOVA. A significant P-value is < 0.05.

Results and discussion

Transdermal gels of DCN-NSs

Three types of gels based on different concentrations of HPMC K15M were successfully prepared and loaded with DCN-NSs.

Evaluation of DCN-NSs-based transdermal gels

1. Physical appearance and homogeneity

All of the prepared DCN-NS transdermal gels were examined visually for their color. All preparations were clear, transparent, and homogenous with the absence of clusters as indicated by Table 3 below. The pH value for all prepared gels was in the range of 6.75-6.88 which indicates their suitability for topical application and the absence of skin irritation potential

The drug content is a significant difference between the gel formulas regarding their drug content and the highest content is in DCN-NSs Gel -3. This is explained by the appropriate consistency of DCN-NSs Gel -3 that provides uniform dispersion of the NSs vesicles loaded with DCN within the gel base. When the diameter of the circle was measured, it had a range value of 8.1-6.5 centimeters, which indicated that all of the gels that were formed had spread due to the low amount of tension. This was determined by reading the range value. These values explain that increasing the concentration of HPMC K15M will always be associated with a decrease in the spreadability as expressed by the low diameter of the spread circle. Similar findings were also obtained in another study **(39).**

F-code	DCN-NSs Gel -1	DCN-NSs Gel -2	DCN-NSs Gel -3	p-value
Color	Clear-Yellow	Clear-Yellow	Clear-Yellow	-
Homogeneity	Homogeneous	Homogeneous	Homogeneous	-
Texture	No grittiness	No grittiness	No grittiness	-
pH	6.76±0.15	6.87±0.01	6.69±0.11	0.199
Drug content(%)	92.86±3.1	95.76±1.85	99.89±0.18	0.017*
Spreadability(cm)	9.1±0.8	7.9±0.5	5.4±0.3	0.000683*
*significant p-value < 0.05 , ANOVA test was used to compare between groups				

Table 3: Visual inspection of the prepared DCN-NSs-based transdermal gels

2. In vitro release study of DCN-NSs-based transdermal gels

The in vitro release of DCN from DCN-NSs-based transdermal gel is shown in Figure 1 below. A significant (p-value < 0.05) decrease in Q8hr is seen in[MOU1] gels prepared from 3% HPMCK15M as compared to those prepared from lower polymeric concentration indicating the retardant effect of the polymer on drug release at its highest concentration in DCN-NSs Gel -3. Similar studies reported the inverse relationship between the high viscosity of the gel and the release rate **(40,41).**

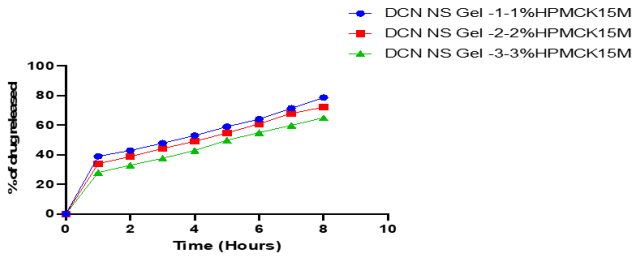

Figure 1: The in vitro release of DCN from DCN-NSs-based transdermal gels in phosphate buffer saline (pH 7.4) at 37 ± 1 °C (mean ± SD; n = 3).

3. The kinetic modeling of DCN release from DCN-NSs-based transdermal gels

According to the determination coefficients (R2) reported by Table 25., the in vitro release data were in favor of the Higuchi model since it resulted in the highest correlation. The release mechanism was found to be obeying the Fickian diffusion as values of n were 0.438. These findings could be explained by drug diffusion in the gel matrix after releasing from vesicles as noticed by another. study**(42).**

Formulation	Zero Order(R^2)	First Order (R^2)	Higuchi plot (R^2)	Peppas plot(n)
DCN-NSs Gel-3	0.7402	0.8977	0.9873	0.438

Table 25: The kinetic release data for the DCN-NSs-based transdermal gel

4.The rheological properties of the selected DCN-NSs-based transdermal gels

The viscosity of the DCN-NSs loaded gel was measured at different share rates using a cup and bob-type viscometer. The viscosity was between (106200-55400cP) and as shear rate increased the viscosity decreased as can be seen in **Figure 2.**

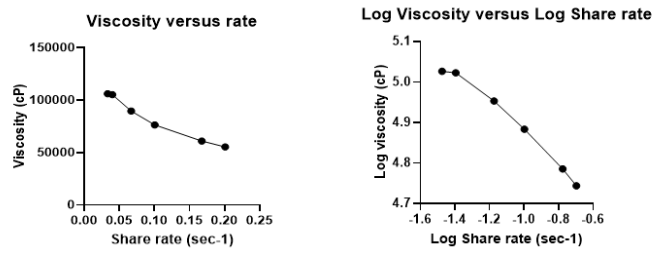

Figure 2: The viscosity versus shear rate of the selected DCN-NSs-based transdermal gel. Double logarithmic representation of the power law of DCN-NSs-based transdermal gel

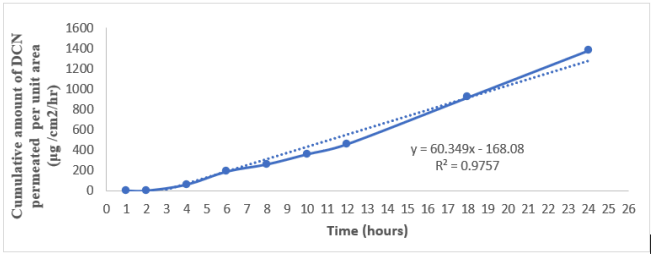

Figure 3: The ex vivo drug permeation profiles for the DCN-NSs based HPMC K15M transdermal gel in phosphate buffer saline (pH 7.4) at 32 ± 1 °C (mean ± SD; n = 3)

A further analysis of the data is performed to determine the flow behavior of the prepared gel by the double logarithmic representation of the Ostwald–de Waele model or (Power Law) as illustrated in Figure 2B. The value of n is calculated from the slope of the straight-line equation. The value of n was found to be n=0.628, therefore deviation from Newtonian behavior is confirmed and the system exhibited shear thinning behavior as the n value was less than 1 declaring a pseudoplastic flow. This outcome was also reported by many other studies that found that semi-solid systems containing nanocarriers present pseudoplastic behavior **(43,44).**

5. Ex vivo permeation study of DCN-NSs-based transdermal gel

The permeation profile of DCN from the prepared DCN-NSs GEL-3 is illustrated in Figure 3 below. The calculated ex vivo permeability parameters for the gel were 60.349 ± 0.375 µg/cm2/h for the flux, 2.8±0.1 for the lag time, and 60.349*10-3 cm/hr for the permeability coefficient. The cumulative permeated amounts after 24 h per unit area (C24h) were found to be 1376.406±0.639µg.

Conclusions

Gels based on HPMCK15M at a 3% concentration provided the intended properties in terms of drug content, pH, in vitro release, and rheological characteristics to serve as vehicles for the transdermal delivery of DCN-NSs.

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