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Research Article

Formulation and Investigation of Phenytoin Cream for Wound Healing in Rabbits

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Abstract

Background: Phenytoin is used commonly as an anticonvulsant agent with potential wound-healing properties. ***Objective***: To formulate and characterize topical creams of phenytoin and investigate the wound-healing effect in the animal model. ***Methods***: Three oil-in-water emulsion-based cream formulas were prepared using white soft paraffin, cetyl alcohol, lanolin, and olive oil blends as an oil phase. The stability was enhanced by the addition of cetostearyl alcohol, Tween 80, and methylparaben. After in vitro characterization, creams were loaded with phenytoin. Full-thickness wounds were created on rabbits that were divided into three groups (six animals each). The test group received 10% phenytoin creams, the positive control received a placebo, and the negative control received no treatment. The wound-healing activity of phenytoin was evaluated by the wound closure rate. ***Results***: All formulations exhibited desirable physicochemical properties, including appearance, texture, and spreadability. The in vitro release results demonstrated that formula 3 sustained the phenytoin release profile, followed by 2 and 1, respectively. Based on physicochemical properties, pH values, and release profiles, formula 2 was selected for animal studies. The wound closure rate in animals treated with phenytoin was 10%, which was significantly higher than that of other groups. These results reveal that the phenytoin promotes faster wound closure and increased reepithelialization. ***Conclusions***: Phenytoin 10% cream could be used as a safe and effective topical wound-healing agent.

Keywords: In-vivo experiment, Phenytoin, Rabbits, Topical cream, Wound-healing.

صياغة وتقييم كريم الفينيتوين لالتئام الجروح في الأرانب

الخلاصة

الخلفية: يستخدم الفينيتوين بشكل شائع كعامل مضاد للاختلاج له خصائص محتملة لالتئام الجروح. **الهدف**: صياغة وتوصيف الكريمات الموضعية للفينيتوين والتحقيق في تأثير التئام الجروح في النموذج الحيواني. **الطرائق**: تم تحضير ثلاث تركيبات كريمية تعتمد على مستحلب الزيت في الماء باستخدام مزيج من البارافين الأبيض الناعم وكحول السيتيل واللانولين وزيت الزيتون كمرحلة زيتية. تم تعزيز الاستقرار بإضافة كحول سيتوستريل، توين 80، وميثيل بارابين. بعد التوصيف في المختبر، تم تحميل الكريمات بالفينيتوين. تم إنشاء جروح كاملة السماكة على الأرانب تم تقسيمها إلى ثلاث مجموعات (ستة لكل منها). تلقت مجموعة الاختبار كريمات الفينيتوين بنسبة 10٪، وتلقى الضابط الإيجابي دواء وهميا، ولم يتلق الضابط السلبي أي علاج. تم تقييم نشاط التئام الجروح للفينيتوين من خلال معدل إغلاق الجرح. **النتائج**: أظهرت جميع التركيبات خصائص فيزيائية وكيميائية مرغوبة بما في ذلك المظهر والملمس وقابلية الانتشار. أظهرت نتائج الإطلاق في المختبر أن الصيغة 3 حافظت على مستوى إطلاق الفينيتوين، تليها 2 و 1 على التوالي. بناء على الخصائص الفيزيائية والكيميائية وقيم الأس الهيدروجيني وملامح الإطلاق، تم اختيار الصيغة 2 للدراسات على الأرانب. كان معدل إغلاق الجرح في التي عولجت بالفينيتوين 10٪، وهو أعلى بكثير من المجموعات الأخرى. **الاستنتاجات**: تكشف هذه النتائج أن الفينيتوين يعزز إغلاق الجرح بشكل أسرع ويمكن استخدام كريم فينيتوين 10٪ كعامل موضعي آمن وفعال لالتئام الجروح.

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INTRODUCTION

Wounds are defined as disruptions in the functional continuity and anatomical integrity of skin cells and tissues caused by physical, chemical, microbiological, or immunological reasons [1]. Wounds impact an estimated 14 million people per year, regardless of income level [2]. The wound healing process is divided into four stages: hemostasis, inflammation, proliferation, and tissue remodeling [3]. A variety of biological activities take place during these phases, including the interaction of blood cells, inflammatory cells, proteins, proteases, growth factors, and extracellular matrix components [4]. Many factors, including infection, foreign substances, a lack of blood supply, and poor nutritional and physiological status, might impede wound healing [5]. Despite advances in pharmacotherapy and wound care practice, many physicians still struggle with wound healing [6]. Wound management involves many processes, including hemostasis, wound cleaning, drug treatment, skin closure, dressing, and tetanus prophylaxis [7]. Phenytoin, an anticonvulsant initially developed in

1908, has been used to treat a wide range of conditions, including neuropathic pain syndromes like diabetic neuropathy [8]. Many studies revealed that 50% of people using long-term oral phenytoin developed gingival hyperplasia [9]. This apparent stimulatory activity on connective tissues has been evaluated on wound healing with less inflammation and edema [10-12,6]. Wounds were treated with topical phenytoin sodium solutions (2% and 4% w/w), respectively. However, the efficiency of these formulations was questioned due to the limited contact time with the wounds and the difficulty of even administration [13-15]. As a result, a novel medication carrier is necessary for more effective topical phenytoin control and delivery. Lipids have long been known as effective pharmacological carriers for drug administration and enhancing the bioavailability of medications with low water solubility [14,16,17]. Lipid-based formulations can be successful if the lipid phase, formulation strategies, and delivery system design are carefully selected [18]. Finally, research into the efficacy of Phenytoin cream in treating skin problems such as wounds in Yemen is justified because of its low cost, effectiveness, availability, potential to reduce morbidity, integration with local knowledge, and the discovery of novel alternative wound care products [19-21]. The aim of this study was to formulate phenytoin cream and evaluate its wound healing efficacy in an animal model of an experimentally induced wound.

METHODS

Materials

Tween 80 and olive oil were purchased from Indore, India, as well as liquid paraffin and soft white paraffin from Lodha Petro. Phenytoin was a gift from a Yemeni pharmacist; acetyl alcohol (Godavari, India), sodium lauryl sulphate (OEM, India), and cetostearyl alcohol (Prakash, India) were purchased. Yefco of Yemen provided support in the form of lanolin (Lodha Petro, India), chlorocresol, sodium benzoate (Rishi, India), and methylparaben (OEM, India). Medias agar (HiMedia LBS Marge, Mumbai, India) was bought. Purified water and glassware were obtained from the Taiz University laboratory.

Preparation of cream base

The weights of the various constituents in formulas 1, 2, and 3 are specified in Table 1. Cetyl alcohol was heated in a water bath until it liquefied. Subsequently, Tween 80 was introduced with continuous mixing until emulsifying wax was achieved. To prevent the loss of a portion of the formula, the emulsifying wax is melted without mixing. White soft paraffin and liquid paraffin are then added, and the mixture is continuously mixed until the emulsifying ointment is formed. This is referred to as the viscous phase. Lastly, combine the aqueous phase (sodium benzoate solution) and the viscous phase in a water bath simultaneously. We use a thermometer to measure the temperature in the bath until it reaches 65°C.

Table 1: Composition of different cream formulations

Formula 1	Material	%
1.	Emulsifying ointment	30
a.	Emulsifying wax	30
i.	Cetyl alcohol	75
ii.	Tween 80 (Polysorbate)	25
b.	White soft paraffin	50
c.	Liquid paraffin	20
2.	Sodium benzoate	1
3.	Purified water	69
Formula 2	**Material**	**%**
1.	Emulsifying ointment	30
a.	Emulsifying wax	30
i.	Cetostearyl alcohol	7.83
ii.	Sodium lauryl sulphate	0.87
iii.	Purified water	0.30
b.	White soft paraffin	50
c.	Liquid paraffin	20
2.	Purified water	70
Formula 3	**Material**	**%**
1	Lanolin	20
2	Olive oil	8
3	Tween 80	10
4	Methylparaben	10
5	Purified water	52

Formula 2 was prepared in the same manner as formula 1, by heating the oily components in a water bath until they dissolve, followed by continuous mixing until an emulsifying ointment is formed. The emulsifying ointment is subsequently mixed with the aqueous phase (purified water) in a water bath at the same temperature. The hydrocarbon and aqueous phases are also mixed in formula 3, following the same procedure.

Preparation of phenytoin cream formulas

In all types of cream bases and when you have added all the ingredients into the oily phase, add phenytoin into the oily phase with mixing in the same direction until form of emulsifying ointment then add aqueous phase that was prepared and mix both oily phase and aqueous phase on water bath at the same time and measure the temperature by using thermometer until reach to 65°C of bath until get a homogeneous cream.

In vitro evaluation of formulated creams

All formulations (i.e., formulations without any active ingredients or preservatives) were tested for physical appearance as color, texture, phase separation, and homogeneity that were evaluated by visual observation. Homogeneity and texture were tested by pressing a small quantity of the formulated cream between the thumb and index finger. The consistency of the formulations and presence of coarse particles were used to evaluate the texture and homogeneity of the formulations. Immediate skin feel (including stiffness, grittiness, and greasiness) was also evaluated. Spreadability of the formulations was determined by measuring the spreading diameter of one gram of sample between two horizontal glass plates (10

cm x 20 cm) after five minutes. The standard weight applied to the upper plate was 100g and each formulation was tested three times. Spreadability can be expressed as:

$S = m * L / t$

where, m= weight applied to upper slide, L= length moved on the glass slide and t= time taken.

One gram of each formulation (blank and drug-loaded) was dispersed in 25mL of deionized water, and the pH was determined using a pH meter. Measurements were made twice, one after one day and another after 12 weeks and applied in triplicate. The pH meter was calibrated with different standard buffer solutions (pH 4, 7 and 10) before each use. A Brookfield viscometer was used with a concentric cylinder spindle #29 to determine the viscosity of the different topical cream formulations. The tests were carried out at 25 °C and the spindle rotated at 5, 10, 20, 50, and 100 rpm values. All measurements were made in triplicate. Agar well diffusion method was used to determine the antimicrobial activity of the creams against test organisms using diameter of zones of inhibition as a measure of activity. The sterility testing of formulated cream was done successfully by spreading the cream on nutrient agar medium plate and incubate it for 24 hrs at 37°C. Agar media was prepared then the formulated cream was inoculated on the plate's agar media by steak plate method and a controlled is prepared by omitting the cream. After the incubation period, the plates were taken out and the microbial growth were checked and compared with the control.

In vitro drug release

The drug release of phenytoin from different cream formulations was investigated using Modified diffusion cell (Local made, Yemen). About one gram of formulated cream was placed on a 0.45 µm pore size, cellulose acetate membrane in the donor compartment. The receptor compartment was filled with 14 mL of ethanol 96% which was maintained at 32 ± 0.5°C. Aliquots of the receptor medium were withdrawn and replaced with the same amount of fresh receptor medium at time intervals of 1, 5, 10, 15, 20, 30, 40, and 60 minutes. The withdrawn aliquots were analyzed by ultraviolet visible spectrophotometer at 240 nm wavelength. The cumulative percentage of drug release was calculated and plotted against time. Franz diffusion cell study for each formulation was conducted in triplicates and the averages were reported. The release characteristics of cream formulations were further determined by fitting the release data to the following equations of zero-order, first-order and Higuchi models which are given by the following equations respectively.

$Q = k_0 t$

$\ln (Q_0 - Q) = \ln Q_0 - k_1 t$

$Q = k^2$

Where Q_0 is the initial amount of drug, Q is the amount of drug released at time *t*, k_0, k_1 and k^2 are the rate constants for zero-order, first-order and Higuchi model respectively.

Irritancy study

Mark an area of one cm^2 on the left-hand dorsal surface of a volunteer and then the selected formulated cream was applied to the specified area and time was noted. Irritancy, erythema, edema was checked, if any, for regular intervals up to 24 hours and reported.

Experimental animal study

According to the previous physicochemical studies, the in-vitro release data and other tests, the optimum formula for experimental study in rabbits was formula 2 that was prepared by the levigation method. Eighteen healthy white and colored local rabbits of both sexes weighing 2.5 – 3.5 kg were used in this study that were purchased from the central market in Taiz city (Taiz, Yemen). They were kept in the standard condition in an animal house at 27±2°C, humidity of 45-55%, and 24 hours light/dark cycles. Food and water were provided *add libitum* and no animal was sacrificed in this study. The work is reported following the ARRIVE guidelines (Animals in Research: Reporting In Vivo Experiments). The animal protocol was approved by the Ethics Committee of Taiz University – Faculty of Medicine and Health Sciences –Department of Pharmacy. Eighteen rabbits were randomly divided into three equal groups (each group were 6 rabbits). One full-thickness excisional wounds (20 x 20 mm) were created on the back of each rabbit. Group 1 received no treatment (negative control), group 2 was treated with cream base only without Phenytoin (placebo group) and group 3 was treated with Phenytoin cream 10%. Treatments were applied topically once daily, from the day after wound creation until the complete healing of the wounds that exceed 20 days. The wounds were photographed every day and the wound area was calculated in the captured images using mobile Redme 10 camera. The wound-healing percentage on a specific day was calculated based on the reduction of the wound area surface as described below:

% Wound healing = (wound area at day 1 – wound area at specific day/ wound area at day 1) x 100

Statistical analysis

The data were analyzed by using one-way ANOVA tests. The *p*-values of less than 0.05 were considered statistically significant. All tests were carried out using SPSS version 22 software (SPSS Inc., Chicago, USA).

RESULTS

Table 2 shows the cream formulations' organoleptic properties, such as their color, texture, phase separation, homogeneity, and how they feel on the skin right away.

Table 2: Physical characterization of different cream formulations

Formulation	Physical appearance	Color	Texture	Phase separation	Homogeneity	Immediate skin feel
Formula 1	Opaque	White	Smooth	No	Semi-homogeneous	Moisturizing, no grittiness, light cool, semi-greasy
Formula 2	Opaque	White	Smooth	No	Homogeneous	Refreshing, moisturizing, cool, no grittiness or greasiness
Formula 3	Transparent	Yellow	Gritty	Yes	Non-homogeneous	Dry, rough, warm, grittiness, no greasiness

Figure 1 shows pictures of different formulations. Results showed that the cream of formulas 1 and 2 had a cosmetically appealing white appearance, a smooth texture, and they were all homogenous with no signs of phase separation, whereas formula 3 was yellow, had a gritty texture, was heterogeneous, and had separated into two phases.

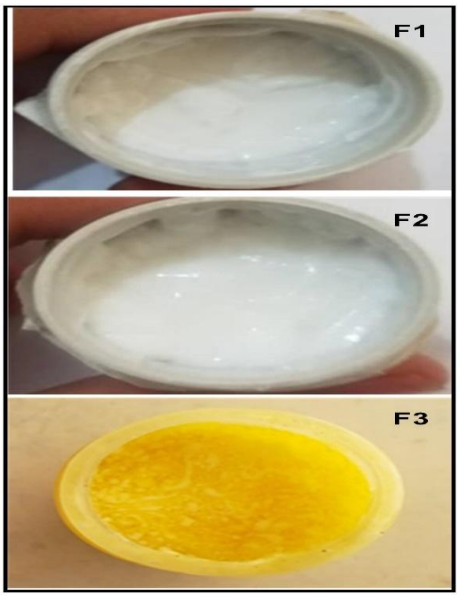

Figure 1: Physical appearance of different cream formulations (F1, F2, and F3).

There is a lot that goes into how well a medicated formulation is spread on the skin and how well a topical therapy works. One important thing to consider is how well a cream can spread evenly on the skin. Table 3 shows the spreading values, that is, diameters observed for the formulations, after five minutes. The values refer to the extent to which the formulations readily spread on the application surface by applying a small amount of shear. The results indicate that cream formulas 1 and 2 had values within the standard normal range (9–31.5) that were 17±4.73 and 30±2.93, respectively, and formula 3 had a very low value (07±2.06) compared to this, and this may be due to the gritty texture that makes it very slow to spread.

Table 3: Spreadability values for the different cream formulations (n= 3)

Formula code	Formula 1	Formula 2	Formula 3
Spreading diameter after 5 min (mm)	17 ± 4.73^{a}	30 ± 2.93^{b}	07 ± 2.06^{c}

Results are shown as mean±SD. Values with different superscripts (a,b,c) are significantly different (p<0.05)

Table 4 displays the pH values for the blank and drug-loaded creams. It is observed that the pH of the formulations decreased when the active ingredients were added to the cream bases. The pH of the skin normally ranges from 4 to 6, and the pH of the blank creams was slightly more basic than that of the skin pH values, but when added, the drugs were like the skin's normal pH value. The pH values of the formulations did not change significantly over the period of 12 weeks.

Table 4: pH values of blank and drug-loaded formulations at day 1 and at week 12 (n= 3)

Formulation	pH		
	Blank formulation	Drug-loaded (day 1)	Drug-loaded (wk 12)
Formula 1	8.2 ± 1.04^{a}	6.6 ± 2.01^{b}	6.3 ± 0.73^{b}
Formula 2	7.5 ± 0.72^{a}	6.0 ± 0.56^{b}	5.8 ± 1.43^{b}
Formula 3	7.0 ± 0.99^{a}	6.8 ± 0.87^{a}	6.4 ± 1.23^{b}

Results are shown as mean±SD. Values with different superscripts (a,b) are significantly different (p<0.05).

The best formula for dermatologic application was formula 2, which was 5.8 and was within the normal range of skin. Table 5 displays the viscosity values for the drug-loaded cream across various rotations per minute. As shown, it was observed that formula 3 had higher viscosity values than other formulas, whereas formulas 1 and 2 had nearly equal low values compared to formula 3.

Table 5: The release kinetics of different topical phenytoin cream formulations

Formula	Zero-order kinetics		First-order kinetics		Higuchi model	
	R^2_0	K_0	R^2_1	K_1	R^2_H	K_H
Formula 1	0.761	1.69	0.720	0.05	0.905	17.02
Formula 2	0.872	1.80	0.817	0.05	0.952	17.22
Formula 3	0.931	1.83	0.868	0.05	0.967	16.89

All formulas had pseudoplastic behavior, as expected, due to the decreasing viscosity with increasing rotation. It was shown that there were no signs of microbial growth after 24 hrs of incubation at 37°C, and it was comparable with the control. As shown in Figure 2, the cumulative percentage of phenytoin released after 30 minutes, in decreasing order, was 100%, 93%, and 81% from formula 1, formula 2, and formula 3, respectively. It was clear that smaller droplets have more surface area for drugs to pass through the donor compartment membrane. This created a higher concentration gradient, which is what drives drugs to pass through. All formulations were further identified by fitting the release data into the equations of zero-order, first-order, and Higuchi models. From Table 6, the best-fit release of these three formulations followed the Higuchi model with R2 > 0.905. Therefore, the drugs released from

the three formulations were concluded as drug concentration independence. The formulations showed no redness, edema, inflammation, or irritation during irritancy studies, and hence the different formulations are safe for the skin.

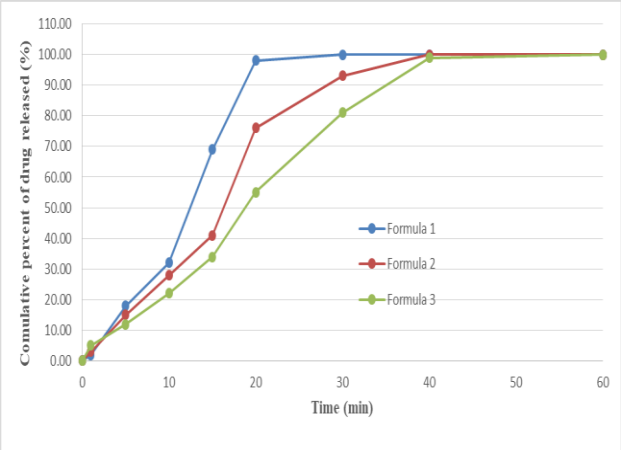

Figure 2: Cumulative percentage of phenytoin released from cream formulations (n=3, mean± SD).

Figure 3 illustrates that animals treated with 10% phenytoin experienced complete wound closure in the shortest time (20 days), demonstrating a better healing pattern. The time to complete wound closure in animals treated with cream vehicle (placebo) was about more than 28 days. The complete wound closure occurred in more than 30 days for the no-treatment group. The times to complete wound closure in phenytoin 10% cream-treated groups were significantly shorter ($p< 0.05$) than those of negative control and placebo groups.

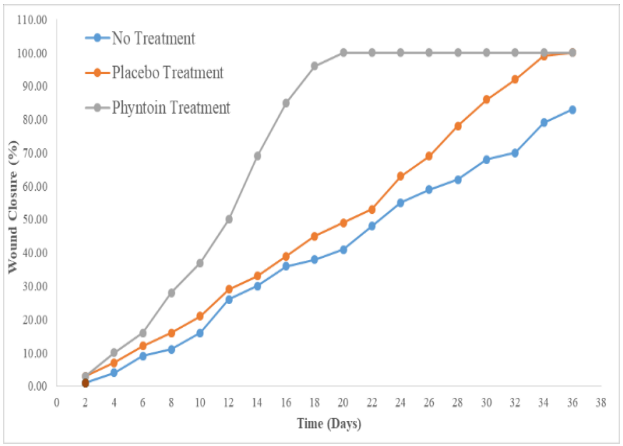

Figure 3: Percentage of wound closure of different experimental groups in different periods (days).

As shown in Figure 4, there were small but significant differences in the rates of wound closure and the time it took to heal the negative control treatment group and the placebo-treated group. Figure 4 shows pictures of the wounds. The wound closure rate was much higher in the group that was given 10% phenytoin after 10 days than in the other groups, which had to wait more than 20 days.

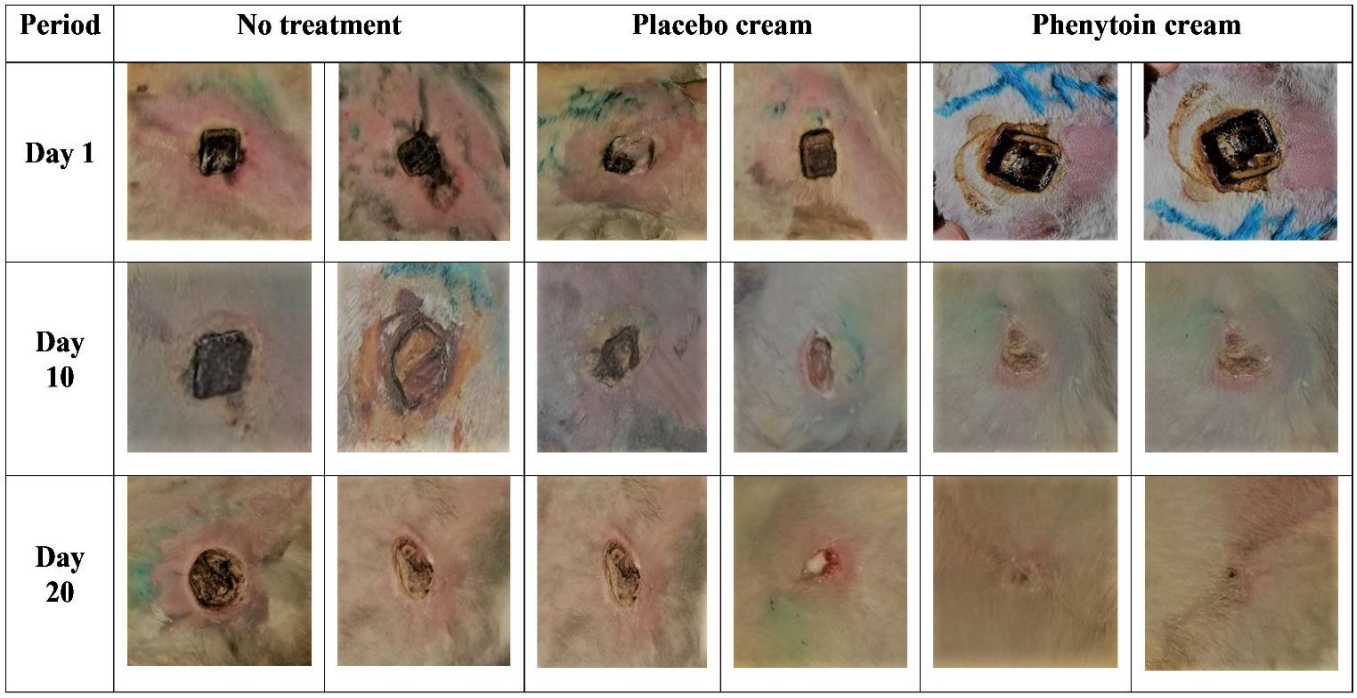

Figure 4: Wound-healing progression photographs in experimental groups.

DISCUSSION

The cumulative percentage of phenytoin released was nearly identical to the results reported in a study by Lee *et al*., which indicated that 93% of the phenytoin was released from the nano-emulgel phase. This is a clear explanation of the fact that smaller droplets have a greater surface area, which allows pharmaceuticals to pass

through the donor compartment membrane [22]. The results of this study demonstrated that phenytoin could enhance the histology of cutaneous wounds and accelerate wound closure in comparison to the control group. These findings corroborate the discovery by Qadirifard *et al*. that phenytoin that has been approved has the capacity to eradicate microorganisms. Nevertheless, the protracted inflammatory phase has the potential to impede wound healing [23]. The development of wound infections may be prevented by the antimicrobial activity of phenytoin, which could lead to a quicker healing process. The results of the current study indicate that phenytoin is essential for the normal recovery of wounds, as demonstrated by a study conducted by Kumar *et al*. [24]. It also enhances neovascularization.

Conclusion

Formula 2 has preferable physicochemical characteristics and showed that phenytoin 10% has the potential to accelerate wound healing.

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Conflict of interests

No conflict of interest was declared by the authors.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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