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Comparative Pharmacokinetics of Enrofloxacin After Subcutaneous Administration of a Novel in situ Gel Forming Preparation and a Conventional Product to Rabbits

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Abstract

BACKGROUND: Frequent drug dosing and animal handling are usually required in conventional antimicrobial therapy but sustained release formulations can improve compliance.

OBJECTIVES: This study aimed to evaluate the pharmacokinetic (PK) parameters of a novel sustained release enrofloxacin (ENR) hydrogel in comparison to a conventional ENR formulation in rabbit animal model.

METHODS: A total of 20 rabbits were randomly divided into three groups and received a single dose of ENR or blank by subcutaneous (SC) injection as following: Group 1 (n=8) received ENR (10 mg/kg) using a conventional product (Enrovet®); Group 2 (n=8) received ENR (33.3 mg/kg) using a hydrogel formulation; and Group 3 or control group (n=4) received equal volumes of a blank hydrogel formulation. Blood samples were collected at different time points post-dosing. ENR concentrations in plasma were estimated by high-performance liquid chromatographic (HPLC) method and PK parameters were calculated using a non-compartmental analysis.

RESULTS: The ENR hydrogel released the drug in a sustained manner with mean residence time (MRT) of 78.4 ± 15.3 h, which was significantly more than that of the conventional formulation (7.39 ± 2.37 h, $P<0.05$). However, maximal plasma concentration (Cmax) for ENR hydrogel (1.41 ± 0.76 µg/mL) was significantly less than that of the conventional product (2.86 ± 0.79 µg/mL). The relative bioavailability (F_{rel}) was not significantly different between the two formulations.

CONCLUSIONS: The hydrogel formulation significantly increased the MRT of ENR. Hence, it could be a promising delivery system to prolong the pharmacological activity of ENR in animals and enhance compliance.

KEYWORDS: Enrofloxacin, In situ gel forming, Pharmacokinetics, Rabbit, Sustained release

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Introduction

Enrofloxacin (ENR) is a broad-spectrum fluoroquinolone antimicrobial drug with high efficacy against a wide variety of important bacterial infections in animals. It is well tolerated in most animal species, especially when used according to the product label. In general, ENR has high bioavailability with rapid absorption after intramuscular (IM), subcutaneous (SC), or oral administration (Trouchon and Lefebvre, 2016). Moreover, it has a large volume of distribution, good tissue penetration, and an elimination half-life in the range of 3 to 6 hours (López-Cadenas *et al.*, 2013).

Based on a recent report, more than 34 veterinary products of ENR are available on the market under different dosage forms including oral and injectable formulations (Trouchon and Lefebvre, 2016). Since conventional ENR formulations are immediate-release products used mostly twice a day for several days or weeks, they can end up with poor compliance. Therefore, some efforts have been made to develop alternative long-acting formulations of ENR to reduce the frequency of administration and make the antimicrobial therapy more convenient and practical (Kumar *et al.*, 2015; Yu *et al.*, 2016).

Frequent drug dosing is usually required to maintain the therapeutic efficacy of conventional antimicrobial drug products; however, this method can decrease the compliance of clients in veterinary medicine. To overcome this problem and encourage compliance, the use of sustained release drug delivery systems is promising. By using these systems, the entrapped drugs are released slowly and their pharmacological actions are prolonged. In this way, long acting veterinary dosage forms may offer some advantages, including the reduced stress burden in animals and workers through less frequent dosing, reduced animal handling, reduced cost of drug therapy, and improved herd management (Rathbone, 2012).

The term hydrogel describes three-dimensional network structures made of a class of synthetic and/or natural polymers which can absorb and maintain significant amount of water (Gulrez *et al.*, 2011). The important features of hydrogels for in vivo applications include swelling ability, mechanical strength, biocompatibility, and biodegradability in host tissues (Ahmadi *et al.*, 2015).

The development of thermosensitive chitosan hydrogels has led to promising drug delivery systems in animals through forming semi-solid gels in situ following the injection of the chitosan solutions (Balamurugan, 2012). Thus, they could act as reservoirs of entrapped drugs in the body and slowly release their drug content over time (Rathbone, 2012).

Pharmacological evaluation of a novel formulation including ENR hydrogel warrants its pharmacokinetic (PK) study in an animal model since PK data with successful drug delivery in animal models facilitates the pathway for testing and possibly application of the formulation in target animals. Accordingly the present study aimed to compare the PK, parameters of a newly designed in situ forming gel of ENR with a conventional formulation in rabbits.

Materials and Methods

Drugs and Reagents

Medium molecular weight chitosan with degree of deacetylation (DDA) of 75-85% and β-glycerophosphate disodium salt pentahydrate were purchased from Sigma-Aldrich (St. Louis, MO). Acetic acid was purchased from Merck (Darmstadt, Germany). Enrovet® (ENR aqueous solution, 100 mg/mL) was provided by Aburaihan Pharmaceutical Company (Tehran, Iran) and ENR standard (ENR content 99.57%) was purchased from TEMAD Pharmaceutical Company (Tehran, Iran). Other chemicals were reagent grades.

Preparation of the ENR Hydrogel

The preparation and properties of the hydrogel formulation have been published in our recent paper (Khanamani Falahatipour *et al.*, 2017). Briefly, ENR hydrogel was prepared by dissolving chitosan powder in 0.1 mol/L diluted acetic acid to achieve concentrations of 2.0% (w/v) along with 5.0% (w/v) β-GP, and using 10 g/L ENR to form hydrogels.

Animals

In this study, 20 healthy white albino rabbits weighting 2.8-3 kg were used. The animals were housed in cages with 12 h dark/light cycle with free access to water and a balanced feed. Temperature was kept at 22-28°C and humidity was between 45-65%. The adaptation period was one week and rabbits were monitored for any abnormal clinical signs. The study was approved by the Ethics Committee of the Faculty of Veterinary Medicine, University of Tehran, Iran (code: 7506006-6-10).

Experimental Design

Using random allocation method, three groups of rabbits including two experimental groups (conventional and hydrogel groups, each 8 animals) and one control group (n=4) were used. The first group received a single SC injection of conventional product of ENR (Enrovet®) (10 mg/kg) (Broome *et al.*, 1991). The second group received a single SC dose of 10 ml of hydrogel formulation, equivalent to 33.3 mg/kg of ENR. Meanwhile, animals in the control group received equal volumes of blank hydrogel formulation, which had the same composition and formulating process as the hydrogel but without ENR. SC administration was done directly beneath the loose skin at the back of the neck of the rabbit after zero time-point blood collection.

Blood Collection

Blood samples (about 1.5 mL) were collected from the jugular vein of rabbits into heparin containing sterile tubes at different time points. In each experimental group, the samples were collected prior to administration (0 h) and at 1, 2, 4, 7, 24, 48, 72, 96, and 120 h after drug administration. In addition, one more blood sample was collected at 0.5 h from each animal in the group of conventional products. The blood samples collected on the first day were taken by placing a catheter into the jugular vein and then by venipuncture once a day on next days. Within 1 h following blood collection, they were centrifuged at ~ 4825 ×g (Eppendorf, Model 5810 R, Germany) for 10 min. The plasma samples were harvested and stored at -20°C until drug analysis.

Analytical Method

To prepare plasma samples for estimation of ENR levels, 50 µL of NaOH 1 N was added to 500 µL of each rabbit plasma and shaken for 30 seconds. Then, 100 µL perchloric acid and 100 µL deionized water were added to each sample, vortexed for 1 min and centrifuged at ~ 4825 ×g for 5 min. The supernatant was transferred into special glass tube and 20 µL of each sample was injected into the high-performance liquid chromatographic (HPLC) system for analysis.

ENR concentrations in plasma were analyzed by using an HPLC system (Waters, USA), including a multi-solvent pump, ultraviolet (UV) detector, autosampler, Chromate software, as well as a Chromolith-RP18e column (50 × 4.6 mm) from Merck (Darmstadt, Germany). The method of McKellar *et al.* (1999) was used for analysis of ENR levels in plasma. HPLC separation was carried out by using a mobile phase containing 14% acetonitrile, 85% water, 0.4% triethylamine, and 0.6% phosphoric acid. The mobile phase was filtered by using a 0.45 µm membrane filter. A flow rate of 1 ml/min and UV detection at 294 nm were used for chromatographic separation.

ENR stock solution (1.0 mg/mL) was provided through addition of 10 mg of ENR standard in 10 mL of acetonitrile: water (1:1, v/v). It was further diluted in rabbit plasma to

get 0.1, 0.25, 0.5, 0.75, 1, 1.5, 2, and 2.5 µg/mL solutions.

To validate the HPLC method for the measurement of ENR levels in rabbit plasma samples, the linearity, accuracy, precision, recovery, selectivity, and sensitivity of the analytical method were calculated. Standard calibration curve was obtained by using eight concentrations of ENR (0.1–2.5 µg/mL) and it was used for estimation of ENR levels in the plasma samples.

PK Data Analysis

Data of each rabbit ENR plasma levels were used for depicting their concentration-time profiles. The maximal ENR plasma concentration (Cmax) and the time to reach Cmax (Tmax) were obtained from the observed concentration versus time profiles (Rassouli *et al.*, 2016). Non-compartmental analysis was applied for calculating the PK parameters including area under the concentration-time curve (AUC), area under the first moment concentration-time curve (AUMC), and MRT. The linear trapezoidal rule was used to estimate AUC from 0-120 h ($AUC_{0\text{-}120}$). The F_{rel} was estimated by using the following equation and PK parameters calculated using Excel 2013.

$$F\ rel = \frac{AUC\ (0-120)\ of\ hydrogel\ \times\ Dose\ of\ conventional\ drug}{AUC\ (0-120)\ of\ conventional\ drug\ \times\ Dose\ of\ hydrogel}$$

Statistical Analysis

Data were expressed as mean ± SD and analyzed using SPSS 19 (SPSS Inc., Chicago, IL., USA). One-way ANOVA was used for analysis of the PK parameters. P-value<0.05 was considered as a significant difference.

Results

A linear calibration curve for HPLC analysis of ENR was obtained over the range of 0.1–2.5 µg/mL (Figure 1). The limit of detection (LOD) of ENR in rabbit plasma and limit of quantification (LOQ) were 0.05 and 0.1 µg/mL, respectively. Accuracy, precision, and recovery data of the method of analysis are shown in Table 1. It should be noted that there was no interfering peak corresponding ENR retention time in chromatograms obtained using the plasma samples of control group.

Table 1. Method validation data including between and within-day variability as relative standard deviation, RSD, accuracy, and recovery for determination of enrofloxacin in plasma (n=5).

	Concentration (µg / mL)	Between-day variability		Within-day variability		Recovery	
		RSD (%)	Accuracy (%)	RSD (%)	Accuracy (%)	(%)	RSD (%)
Enrofloxacin	0.05	8.9	102.4	11.3	103.1	96.4	9.8
	0.1	6.9	97.8	7.6	98.2	100.2	8.6
	0.5	5.8	101.5	4.2	101.2	98.6	7.2
	1.0	6.1	99.7	7.1	99.0	96.7	6.3
	2.0	3.8	101.8	5.2	100.6	98.6	6.9

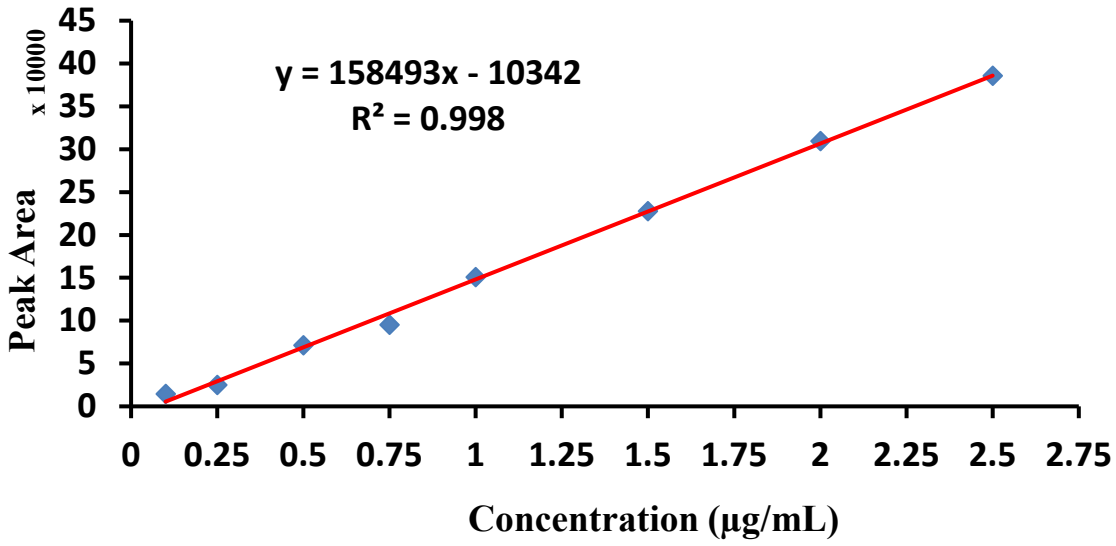

Figure 1. The calibration curve for HPLC analysis of enrofloxacin levels in plasma.

Rabbits receiving ENR or blank formulations did not show any adverse effect during the experiment. The mean concentration-time profiles for the conventional product and ENR hydrogel are shown in Figure 2. The PK parameters of the ENR formulations are presented in Table 2.

Table 2. PK parameters of enrofloxacin in rabbits following a single SC injection of hydrogel (33.3 mg/kg) and conventional formulations (10 mg/kg).

PK parameters	Conventional	Hydrogel
AUC_{0-120} (µg.h/mL)	14.1 ± 4.30	45.7 ± 27.9
$AUMC_{0-120}$ (µg.h^2/mL)	123.7 ± 63.8	3334 ± 1546
MRT (h)	7.39 ± 2.37	78.4 ± 15.3*
C_{max} (µg/mL)	2.86 ± 0.79	1.41 ± 0.76*
T_{max} (h)	0.81 ± 0.26	6.0 ± 1.93
F_{rel} (%)	100	97.2

Data are expressed as mean ± SD (n=8).

AUC: area under the plasma concentration-time curve; AUMC: area under the first moment curve; MRT: mean residence time; Cmax: maximal concentration; Tmax: time to reach Cmax; F_{rel}: relative bioavailability.

*Data with significant difference (P<0.05).

As the dose sizes of the formulations were different, the significance analysis of the PK parameters including Tmax, AUC and AUMC which are positively correlated with dose is meaningless.

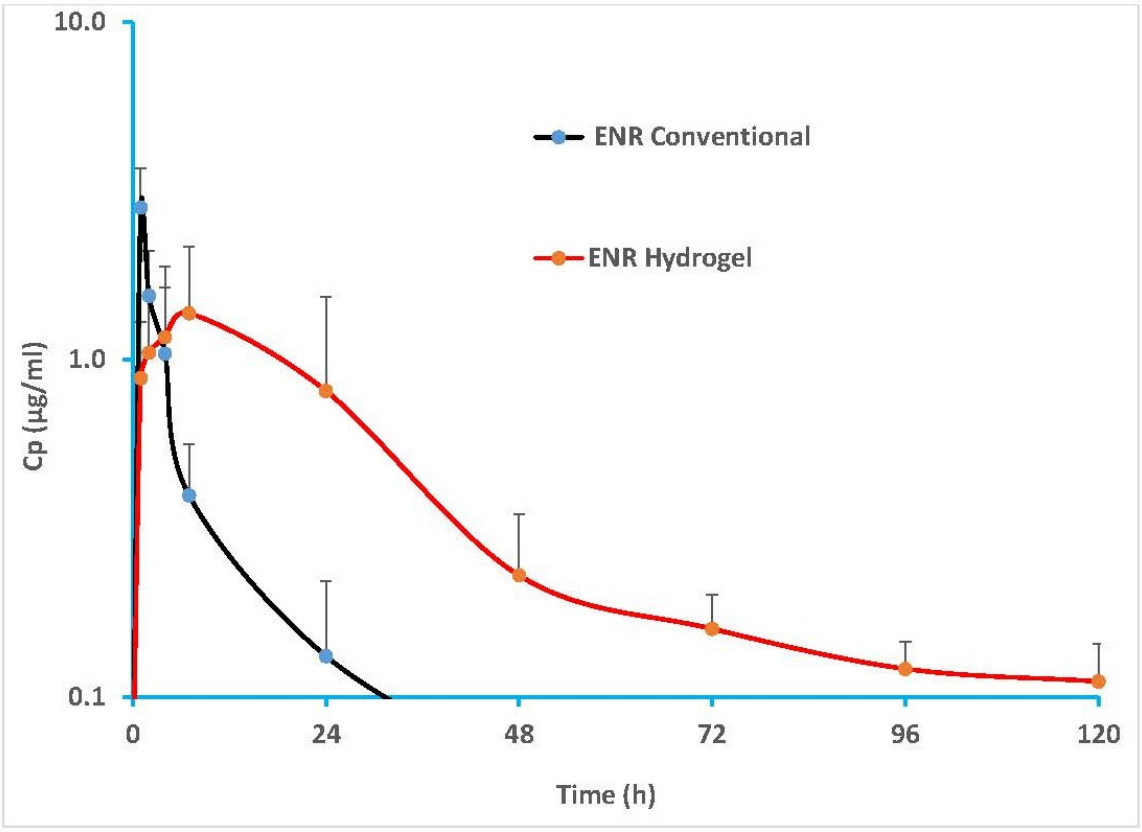

Figure 2. Semi-logarithmic plot of plasma concentration (Cp) vs. time profiles of enrofloxacin after SC use of a single dose of ENR hydrogel (33.3 mg/kg) and ENR conventional formulation (10 mg/kg) in rabbits. Data are expressed as mean ± SD (n=8).

The Cmax mean values of the conventional formulation was significantly higher than ENR hydrogel formulation (P<0.05). As a whole, the mean value of MRT for the hydrogel was much larger than that of the conventional formulation (P<0.05). The F_{rel} (%) values of the two formulations were not significantly different.

As the doses between hydrogel and conventional formulation were different, the PK parameters including Tmax, AUC, and AUMC, which are positively correlated with the dose, were significant.

Discussion

According to our results, the novel hydrogel formulation could prolong the release of ENR and keep its plasma levels above LOQ levels (0.1 µg/mL) up to 120 h. A single SC injection of ENR hydrogel at 33.3 mg/kg body weight (BW) in this animal model was able to provide drug plasma concentration above MIC_{90} (0.03-0.25 µg/mL) reported for common susceptible organisms in animals about 3 to 4 times longer than the conventional product (Sheldon *et al.,* 2014; Ahn *et al.*, 2012; Sulyok *et al.*, 2014; Thomas *et al.*, 2015). Indeed, the benefit of hydrogel for drug delivery may be largely due to creation of a depot formulation from which drug is slowly released. This slow release formulation could present certain advantages, including the improvement of the PK and pharmacodynamic properties of a drug such as increasing its therapeutic index, hence increasing the efficiency of drug therapy and enhancing compliance (Rathbone, 2012; Saikia *et al.*, 2015). However, from the therapeutic point of view, other parameters should also be considered including the animal species to be treated, MIC_{90} of causative microorganisms, the risk of antimicrobial resistance, and the duration of treatment.

In the present study, we compared PK parameters of a novel ENR hydrogel with its

conventional formulation. It was found that the hydrogel had significantly higher MRT values than the conventional formulation. The MRT mean value of ENR from conventional formulation in plasma was 7.39 ± 2.37 h. By using conventional product, the concentrations of ENR in the blood decreased sharply and fell to unquantifiable levels after 24 h. However, the plasma ENR levels following the use of the hydrogel showed slower elimination phase, lasting for more than 5 days. Based on the results of the present study, the hydrogel with a MRT of 78.4 ± 15.3 h showed much longer ENR persistence in plasma in comparison to the conventional product (7.39 ± 2.37 h). Thus, the hydrogel formulation could effectively demonstrate sustained release of ENR in this animal model. Shi *et al.* (2013) prepared and evaluated the PK of an injectable thermosensitive hydrogel of diminazene aceturate following SC dosing in rabbits (Shi *et al.*, 2013). They showed that hydrogel could significantly increase MRT in comparison to its aqueous solution. Li *et al.* (2014) developed a thermosensitive chitosan/β-GP hydrogel loaded with docetaxel (DTX) for intra-tumoral delivery. They showed that MRT of DTX in plasma was approximately 9 h for DTX solution but 9 days for chitosan/β-GP hydrogel. These results demonstrated that the chitosan-based in situ forming gel system could increase drug MRT, and as a result, could reduce dosing frequency, enhance compliance, and particularly would be much useful during long-term treatment.

In spite of its lower dose (10 mg/kg), the conventional formulation in the present study produced significantly higher Cmax values in comparison to the hydrogel formulation (33.3 mg/kg) (P<0.05), which is consistent with the sustained release nature of the ENR hydrogels. In the hydrogel formulation, the entrapped drug in hydrogel networks provided much prolonged drug release. The plasma levels of ENR using hydrogel formulation were above the detection limit until 120 h. In this manner, the plasma ENR concentrations were kept more stable but at lower levels, which could significantly decrease the potential drug toxicity. However, it is necessary for further studies to determine if these ENR levels can reach to the effective drug concentrations in target animal species, particularly in sick animals. With regard to Cmax values, Geng *et al.*, (2015) studied PKs of an in situ forming gel system for delivery of florfenicol in pigs. They also reported significantly lower Cmax values for in situ forming gel compared to the conventional florfenicol injection.

It is also worthy to note some inconsistencies between the findings of in vitro drug release tests and in vivo results of the present study. The hydrogel formulation showed gradual drug release up to 75% of total drug within 120 h in the in vitro release studies performed at 37°C under sink conditions without any noticeable initial burst release during the first 2 h. It released about 20% of total drug release during 5 h and 40% by 24 h (Khanamani Falahatipour *et al.*, 2017). But the ENR plasma profiles of hydrogel formulation in rabbits showed relatively fast drug release and absorption with Tmax value of 6.0 ± 1.93 h.

The fast release of hydrogel formulations in rabbits compared with in vitro release tests might be due to a number of factors, including the characteristics of the animal species used, route of administration, composition of the formulation, and environmental factors (Moghimi, 2010). The hydrogel may have been diffused substantially in vast SC space in rabbit before the sol-to-gel transformation process. So, it may have increased the surface area available for drug release. On the other hand, chitosan, which is used in the preparation of these sustained release systems, has the properties of rapidly adsorbing water and higher swelling degree in aqueous environment, leading to the fast drug release (Sonia and Sharma,

2001). It has been reported that rabbits can easily tolerate 120 mL/kg per day by SC provided that the administration of such volume of fluids be divided into two or three parts; therefore, rabbits seem to have a large capacity for water turn over in SC space (Graham, 2006). Thus, following the exposure of these formulations to an aqueous solution, water attacks the hydrogel surface and penetrates into the polymeric network. Then, the meshes of the network in the rubbery phase start expanding and allow other solvent molecules to penetrate within the hydrogel network well (Abruzzo, 2013).

Comparison of the ENR PK data obtained in the present study by using a single SC dose of a conventional product at 10 mg/kg BW with the data of other studies in rabbit as a target animal indicated some similarities as well as differences, which are mainly related to dose size, product composition, and route of administration. Broome et al. (1991) studied the PK properties of ENR solution (as 2.27% w/v in a potassium hydroxide [KOH] base) in rabbits after three routes of administration (IV, SC, and oral) using four New Zealand White rabbits at 5 mg/kg BW. For SC route, they reported Cmax and Tmax of ENR, which are somewhat similar to the findings of the present study. However, regarding MRT and AUC values, they were much different from the data of the present study, possibly due to dose size and formulation differences.

In the last two decades, antimicrobial resistance has become a worldwide health problem in human and veterinary medicine. It is generally accepted that the main risk factor for the expansion of antibiotic resistance is a wide use of antimicrobial drugs (Sattar et al., 2014). In addition, there is controversy regarding the use of long-lasting antimicrobial formulations in veterinary medicine, particularly in food animals because of their potential benefits and risks. In one hand, they make drug therapy more convenient and practical by reducing the dosing frequency in animals. On the other hand, they can increase MRT of antimicrobials and persist the drug residuals that may increase the spread of microbial resistance in animals. They could also increase the withdrawal times and worsen the problem of drug residues in food producing species.

Therefore, these conflicts should be considered appropriately in the development and usage of long-acting formulation. According to the novel formulation used in the present study, due to biodegradability of chitosan-based hydrogel, it seems that the hydrogel is decomposed after a few days; thus, there would be no more depot to prolong the absorption phase and then the elimination process of the hydrogel product would be the same as that of the conventional drug. The time to the disintegration of the formulation depends on some factors including the composition of the formulation and environmental conditions of the site of injection in target animal. Consequently, before achieving the state-of-the-art long-acting formulations for food producing animals, these types of sustained release formulations seem to be much more interesting in companion animal practice. Thus, more studies are needed to reach the antimicrobial formulations with desired properties in target animal species.

Conclusion

In conclusion, the novel in situ forming gel was able to decrease the release rate of ENR and prolong its residence time in blood circulation. This ENR hydrogel would be promising as a sustained-release preparation for further research, and eventually for the treatment of susceptible microbial infections in veterinary practice.

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Conflict of Interest

The authors declared no conflict of interest.

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مجله طب دامی ایران، ۱۳۹۹، دوره ۱۵، شماره ۱، ۶۸-۷۸

مطالعه فارماکوکینتیک یک فرآورده جدید انروفلوکساسین تشکیل‌دهنده ژل در محل در مقایسه با یک فرآورده رایج در خرگوش

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زمینه مطالعه: در درمان با داروهای ضدمیکروبی رایج معمولاً تجویز مکرر دارو و دستکاری حیوانات مورد نیاز است اما فرآورده‌های آهسته‌رهش می‌توانند کامپلیانس یا رعایت دستورالعمل درمانی را بهبود بخشند.

هدف: این مطالعه به‌منظور بررسی پارامترهای فارماکوکینتیک یک هیدروژل آهسته‌رهش انروفلوکساسین در مقایسه با یک فرآوردۀ رایج پس از تزریق زیر جلدی در خرگوش به‌عنوان یک مدل حیوانی انجام شد.

روش کار: بیست رأس خرگوش به‌طور تصادفی در سه گروه تقسیم شدند و به آنها یک دوز انروفلوکساسین یا بلانک به‌صورت زیرجلدی به این شرح تزریق گردید: گروه ۱ (۸ رأس) انروفلوکساسین را به میزان ۱۰ میلی‌گرم بر کیلوگرم با استفاده از یک فرآوردۀ رایج (انرو وت) دریافت کردند؛ گروه ۲ (۸ رأس) انروفلوکساسین را به میزان ۳۳/۳ میلی‌گرم بر کیلوگرم با استفاده از فرمولاسیون هیدروژل دریافت کردند و گروه ۳ یا گروه شاهد (۴ رأس) حجم‌هایی مشابه از یک فورمولاسیون هیدروژل بلانک را دریافت کردند. نمونه‌های خون در زمان‌های مختلف بعد از تزریق دارو اخذ گردید. غلظت انروفلوکساسین در پلاسما با استفاده از روش کروماتوگرافی مایع با کارآیی بالا اندازه‌گیری شد و پارامترهای فارماکوکینتیکی با آنالیز غیر کومپارتمانی محاسبه گردید.

نتایج: هیدروژل انروفلوکساسین، دارو را به‌صورت آهسته‌رهش آزاد کرد با میانگین زمان حضور ۱۵/۳ ± ۷۸/۴ (MRT) ساعت که به‌طور معنی‌داری بیشتر از فرآوردۀ رایج (۲/۳۷ ± ۷/۳۹ ساعت) بود ($P<0/05$). با این حال، حداکثر غلظت پلاسما (Cmax) برای هیدروژل انروفلوکساسین (۰/۷۶ ± ۱/۴۱ میکروگرم در میلی‌لیتر) به‌طور معنی‌دار کمتر از فرآورده رایج (۰/۷۹ ± ۲/۸۶ میکروگرم بر میلی‌لیتر) بود. زیست‌فراهمی نسبی دو فرآورده تفاوت معنی‌داری نداشت.

نتیجه‌گیری نهایی: فرآوردۀ هیدروژل میانگین زمان حضور داروی انروفلوکساسین را به‌طور معنی‌داری افزایش داد و این فرآورده می‌تواند یک سیستم دارورسانی نویدبخش برای طولانی کردن فعالیت فارماکولوژیک انروفلوکساسین در حیوانات و افزایش کامپلیانس باشد.

واژه‌های کلیدی: انروفلوکساسین، تشکیل‌دهنده ژل در محل، فارماکوکینتیک، خرگوش، آهسته‌رهش

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