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In vitro and in vivo evaluation of levofloxacin sustained-release capsules

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Abstract

Objective: To reduce the frequency of administration and improve patient compliance, novel levofloxacin sustained-release capsules with suitable in vitro release profiles and good bioavailability were developed. *Materials and methods*: A fluidized bed was used to prepare levofloxacin pellets by spraying the drug solution onto blank pellets. Then the pellets were coated with either Surelease water dispersion or Eudragit® NE30D water dispersion to achieve sustained-release characteristics. The mixed pellets containing 15% of the uncoated pellets and 85% of the coated pellets were filled into the hard gelatin capsules. In vitro release test was performed with the capsules. A single-dose pharmacokinetic study of the capsules was carried out in beagle dogs. *Results*: Although Eudragit® NE30D-coated pellets and Surelease-coated pellets showed similar sustained-release profiles in vitro, their in vivo pharmacokinetic characteristics exhibited significant difference. Unsuccessful in vivo–in vitro correlation was shown in Eudragit® NE30D-coated pellets with a relative bioavailability of only 41.5%, whereas Surelease-coated pellets achieved best sustained-release feature both in vitro and in vivo with a relative bioavailability of 103.0%. *Conclusion*: Statistical analysis indicated that the capsules containing Surelease-coated pellets had a satisfactory sustained-release behavior and a desired pharmacokinetic property.

Key words: Bioavailability, fluidized bed, levofloxacin, pellets, sustained-release

Introduction

Currently, a great emphasis is placed on multi-particulate dosage forms like pellets. Pellet formulation has many promising properties over single-unit dosage forms, such as conventional tablets, including increased bioavailability, facilitated spreading within the contents of the gastrointestinal tract, higher flexibility for further modifications, reduced risk of systemic toxicity because of dose dumping, and decreased local irritation[1–4].

Many methods are applied to prepare pellets, for example, extrusion spheronization[5], fluidized-bed granulation[6], centrifugal granulation[7–9], and spray coating[10]. In comparison with other methods, spray coating can achieve higher yield. In the spray coating method, blank pellets are used as starting materials and the drug solution is continuously sprayed over the surface of the pellets until pellet weight reaches a target value. The final products possess several promising physical properties, including particle size uniformity, fine spherical, high flowability, and large surface area. Usually, drug-loaded pellets are film coated to achieve control-release characteristics.

Levofloxacin, a fluoroquinolone antibacterial agent, is highly sensitive to both Gram-positive and Gram-negative bacteria. Levofloxacin has been widely used for the treatment of pneumonia, chronic bronchitis, sinus, urinary tract, kidney, and skin infections. Many diseases such as urinary tract infection may need long-term therapy. However, the only products in market are levofloxacin tablets and capsules, both of which need to be administered two or three times per day, which are inconvenient for the patients. It has been reported[11–13] that levofloxacin can be more effective in the treatment of urinary tract infection than ofloxacin and ciprofloxacin which already have extended-release preparations on the market. Therefore, making an extended-release preparation for

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levofloxacin to treat urinary tract infection is necessary. We have also found that levofloxacin is an ideal model drug to make extended-release preparation through the investigation of its physical, chemical, and pharmacokinetic properties. Hence, in this study, levofloxacin sustained-release capsules were developed to delay the drug release, prolong efficacy, reduce dosing frequency, and improve patient compliance. In vitro drug release and in vivo pharmacokinetics were investigated to evaluate sustained-release effect and bioavailability.

Materials and methods

Materials

Levofloxacin raw material was purchased from Hengyu Pharmaceutical Co., Ltd. (Nanyang, China). Levofloxacin standard was obtained from the National Institute for the Control of Pharmaceutical and Biological Product (China, Lot No. 130454-200604). Opadry YS-1-7027 and Surelease water dispersion were supplied by Colorcon Coating Tech., Ltd. (Shanghai, China). Eudragit® RS30D, RL30D, and NE30D were procured from Rohm Gmbh Co. Ltd. (Darmstadt, Germany), Acetonitrile was of high-performance liquid chromatography (HPLC) grade and other reagents for levofloxacin determination were of analytical grade or better.

Phosphate buffer solutions (PBS), pH 6.8 consisted of 0.05 mol/L potassium dihydrogen phosphate and 0.0236 mol/L sodium hydroxide, and pH 7.4 consisted of 0.05 mol/L potassium dihydrogen phosphate and 0.0395 mol/L sodium hydroxide.

Determination of solubility

An excess amount of levofloxacin was added to the test tubes with 10 mL of different solvents, including distilled water, hydrochloric acid solution (pH 1.2), and PBS (pH 6.8 and 7.4), and then shaken in a water bath at 25°C for 24 hours. The suspensions were filtered through a 0.45 μm membrane filter, diluted with the corresponding medium and analyzed for levofloxacin content using a UV spectrophotometer at 293 nm.

Preparation of drug-loaded pellets

Levofloxacin-loaded pellets (110%, w/w drug loading) were prepared by spraying a drug-binder solution onto non-pareil beads using a fluidized bed (Mini-Glatt, Binzen, Germany). First, levofloxacin and hydroxypropyl methylcellulose E_5 (HPMC E_5) were dissolved in water to form a homogeneous solution at the drug concentration of 20%. The solution was then sprayed through a nozzle onto fluidized microcrystalline cellulose (MCC) beads with a size of 30–40 meshes. The detailed operating parameters were shown: the pressure of the atomization and fluidization were 0.8 and 0.5 bar, respectively; the flow rate of coating liquid was at 0.5 g/min; and the chamber temperature was set at 50–55°C. Finally, after being dried in the chamber at 60°C for 30 minutes, the immediate-release pellets were obtained.

Coating of drug-loaded pellets

Fluidized bed was applied to modify pellets on the laboratory scale. The water dispersion of Opadry with 10% solid content was sprayed onto the pellets as isolated coating film under the following conditions: atomization pressure, 1.0 bar; fluidization pressure, 0.6 bar; spray rate of coating liquid, 0.2 g/min; and coating temperature, 40°C. The products were thereafter fluidized in the chamber at 60°C for 30 minutes.

Table 1 shows different sustained-release coating materials (Eudragit® RS30D, RL30D, NE30D, and Surelease) used in this study and their coating weights and coating formulations. The water dispersion of the coating material was layered onto the drug-loaded pellets with isolated film (Opadry) to control the release of levofloxacin. The process parameters were adjusted as follows: 0.8 bar atomization pressure, 0.6 bar fluidization pressure, 0.3 g/min velocity of coating liquid, and 40°C coating temperature. The coated pellets were dried at 60°C for 30 minutes and discharged from the chamber.

Finally, 15% immediate-release and 85% sustained-release pellets containing a total of 0.15 g levofloxacin were mixed and filled into a hard gelatin capsule for in vitro and in vivo studies.

In vitro release study

The drug-release properties of levofloxacin sustained-release capsules were assessed by an in vitro dissolution test. USP 27 XXIII Dissolution Apparatus No. 1 (ZRS-8G Dissolution Tester; Tianda Tianfa Technology Co. Ltd., Tianjin, China) (basket method) was used. About 900 mL distilled water was continuously stirred at 100 rpm at 37°C. At predetermined time intervals (0.5, 1, 1.5, 2, 4, 6, 8, 12, 24 hours), a 10 mL aliquot of the dissolution medium was manually withdrawn from each container and replaced with the same volume of fresh medium. The samples were filtered with 0.45 μm microporous membrane and analyzed using a UV spectrophotometer at 293 nm.

The difference between the release rates of pellets with different sustained-release coating formulations

Table 1. Formulations of the coating materials of levofloxacin sustained-release pellets.

Formulations	Coating materials	Coating weight (%)
Rx 1	Eudragit RL/RS (1:10)	20
Rx 2	Eudragit RL/RS (1:10)	25
Rx 3	Eudragit RL/RS (1:8)	30
Rx 4	Eudragit NE 30D	10
Rx 5	Eudragit NE 30D	13
Rx 6	Eudragit NE 30D	15
Rx 7	Surelease	5
Rx 8	Surelease	7
Rx 9	Surelease	9

was evaluated using the similarity factor (f_2), a criterion for dissolution profile comparison recommended by the United States Food and Drug Administration. The similarity factor was calculated by the following equation:

$$f_2 = 50 \times \log\left\{\left[1+\frac{1}{n}\sum_{i=1}^{n}(\bar{R}_t - \bar{T}_t)^2\right]^{-0.5} \times 100\right\},$$

where, $\bar{R}_t$ and $\bar{T}_t$ are the accumulated release rates of the reference preparation and test preparation at the predetermined time points, respectively, and n is the number of the time points. The release curves are considered to be similar if $f_2 > 50$. The larger the f_2 value, the higher the similarity.

In vivo pharmacokinetic study

Pharmacokinetic study of levofloxacin in beagle dogs

A randomized, three-period crossover design was employed in the pharmacokinetic studies. Commercially available levofloxacin conventional tablet was used as reference preparations. Six male beagle dogs weighing 8.0 ± 1.9 kg were randomly divided into three groups. One group was administered two levofloxacin sustained-release capsules with Eudragit® NE30D coating (each containing 0.15 g levofloxacin), whereas another group was administered two levofloxacin sustained-release capsules with Surelease coating (each containing 0.15 g levofloxacin), and the last group was administered three levofloxacin conventional tablets (each containing 0.1 g levofloxacin) with 50 mL of warm water. The washout period between the consecutive treatment schedules was 1 week. The experimental protocol was approved by the University Ethics Committee and conformed to the Guide for Care and Use of Laboratory Animals.

Blood samples (3 mL) were collected from the epipodite vein at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 24, and 36 hours for conventional tablets-treated dogs and samples were collected at 1, 2, 3, 4, 6, 8, 10, 13, 16, 24, and 36 hours for sustained-release capsules-treated dogs. All the blood samples were immediately transferred to heparinized centrifuge tubes and then centrifuged at 822 × g for 10 minutes. Plasmas were transferred into polypropylene tubes and stored at −20°C for subsequent analysis.

Preparation of plasma sample

0.5 mL plasma sample was mixed with 50 μL internal standard solution (0.6 g/L tinidazole in ethanol solution) by vortex. About 0.5 mL perchloric acid solution (5%) was added to the mixture to precipitate plasma proteins. Then the mixture was vortexed for 1 minute and centrifuged at 9668 × g for 10 minutes. Twenty microliters of the supernatant was directly injected for the HPLC analysis.

Data analysis and statistics

The maximum plasma concentration (C_{max}) and time to reach maximum plasma concentration (T_{max}) were obtained directly from the plasma concentration–time profile. The area under the plasma concentration–time curve (AUC) was calculated by the trapezoidal method. AUC and C_{max} values were log-transformed to normalize the distributions and assessed using a T-test. Nonparametric Wilcoxon test was used to evaluate the differences in T_{max} values between reference preparation and test preparation. Significant differences were indicated as $P \leq 0.05$. The relative bioavailability (F) of levofloxacin sustained-release capsules was evaluated by the ratio of the test preparation AUC to the reference preparation AUC.

Results and discussion

Preparation of levofloxacin sustained-release pellets

Solubility of levofloxacin in different media

The aqueous solubility of the drug is a crucial parameter for the formulation of coated pellets as the drug release is dominated by diffusion of the dissolved drug molecules through the film or water-filled pores and channels within the coating. In addition, aqueous solubility is a major factor affecting osmotic pressure of the pellet cores when the pellets are in contact with the dissolution medium. The osmotic pressure plays an important role in the release of drug from coating membrane. Poorly water-soluble drugs may not be able to completely release from the water-insoluble film[14–16]. The solubility of levofloxacin in distilled water, hydrochloric acid solution (pH 1.2), and PBS (pH 6.8 and 7.4) at 25°C was 225, 180, 209, 212 mg/mL, respectively. It showed that levofloxacin had high solubility in all the four media. The high concentration of levofloxacin made spray coating of levofloxacin solution onto the blank pellets feasible, with a possibility of high drug loading efficiency.

Screening of blank pellets

Different blank pellets can affect the drug release. Carefully chosen blank pellets based on the physicochemical properties of the drug and the characteristics required for the preparation are necessary[17]. Starch, sucrose, and MCC cores are widely used as non-pareil beads. Starch beads are less expensive, but with unfavorable hardness and spherical degree. Sucrose beads are highly soluble in water with the ability to make pores. For highly water-soluble drug, such as levofloxacin, sucrose beads may lead to rapid release of the drug. Hence, hydrophobic MCC beads were chosen as the blank pellets in this study. In addition, the high water solubility of levofloxacin was conducive to its spraying onto the MCC pellets.

Influence of adhesive levels on the preparation of drug-loaded pellets

The adhesive HPMC E_5 makes levofloxacin much easier to stick to the surface of the pellets and is also helpful in the ensuing coating. In the process of preparing drug-loaded pellets, different adhesive concentrations of 2%, 5%, and 7% were examined. The results showed that 5% adhesive could effectively decrease the loss of drug solution, make more than 90% of the drug layered onto the surface of the pellets, and prevent adherence between the pellets.

Release of uncoated levofloxacin pellets in different media

The in vitro release test showed that levofloxacin was completely released from the uncoated pellets within 10 minutes in distilled water, hydrochloric acid solution (pH 1.2), and PBS (pH 6.8 and 7.4). Therefore, coating the pellets with a membrane is required to control the release of levofloxacin.

Influence of isolated coating formulations on release

For water-soluble drugs, an isolated coating is very important to maintain the integrity of the coating film and inhibit drug diffusion from the internal part. Hence, Opadry, a premix of HPMC, hydroxypropyl cellulose (HPC), and polyvinylacetate phthalate (PVAP), was selected as the isolated coating material. With the increasing concentration of Opadry, the time spent on coating was decreased. However, the conglutination between the pellets was increased. Hence, a medium concentration of Opadry with 10% solid content was chosen.

Levofloxacin pellets with different isolated coating weights of 3%, 5%, and 7% were investigated. The results showed that the weight of Opadry coating had no significant effect on the in vitro release of levofloxacin. Although pellets were prone to conglutinating at high isolated coating weight (7%), a relative high isolated coating weight could reduce drug migration to the sustained-release coating film and decrease the risk of burst release of the drug. Therefore, a medium isolated coating weight of 5% was selected.

Influence of sustained-release coating formulations on release

Film coating is an ideal approach to prepare controlled-release multi-particulate dosage forms. Compared with controlled-release matrix pellets and mini-tablets, coated pellets can generally achieve higher drug loadings. To prepare film-coated sustained-release delivery systems, it is essential to select a suitable polymeric membrane. Surelease, a water dispersion of ethyl cellulose, is an excellent coating material which is nontoxic, nonirritant, safe, non-sensitive to pH, and does not cause pollution[3,14,18]. In the screening of sustained-release coating materials, three types of acrylic-based water dispersions, Eudragit® RS30D, Eudragit® RL30D, and Eudragit® NE30D, were compared with Surelease. Eudragit® RS30D and Eudragit® RL30D are water-insoluble. They swell in water to form porous channels in the coating membrane. Drugs inside the membrane can be released through these channels. Eudragit® RL30D has higher water permeability and swellability than Eudragit® RS30D because it contains higher proportion of hydrophilic quaternary ammonium groups. Besides, the anions in the core and the dissolution medium can change the release rate, which is related to the ion exchange between these anions and the polymer. Eudragit® RS30D and Eudragit® RL30D can be mixed in any proportions to adjust the permeability of the film to achieve desired release profile, thus they are widely used in various controlled-release drug delivery systems[19–21]. Eudragit® NE30D, a polymer composed of methyl methacrylate and ethyl acrylate at a ratio of 1:2, has a low glass transition temperature (T_g) and minimum film forming temperature (MFT). Because of its pH-independent permeability and neutrality, Eudragit® NE30D is generally used as a sustained-release film material for both ionic and nonionic drugs[8,22,23]. In the present study, different ratios of Eudragit® RS/RL 30D failed to produce a satisfactory sustained-release effect in distilled water. In comparison, Eudragit® NE30D and Surelease produced better sustained-release profiles (Figure 1).

The release results of pellets with different Eudragit® NE30D coating weights are shown in Figure 2. Because

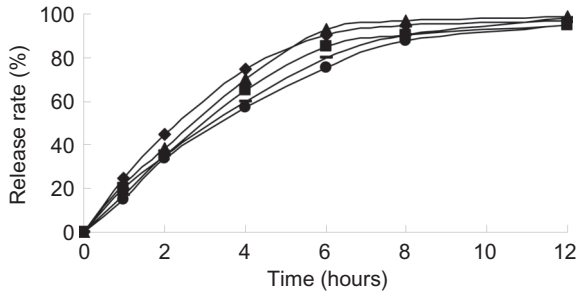

Figure 1. Release rate of levofloxacin pellets with different sustained-release coating materials and coating weights in distilled water. (◆) RS:RL (10:1) with 20% coating weight; (■) RS:RL (10:1) with 25% coating weight; (▲) RS:RL (8:1) with 30% coating weight. (—) Eudragit® NE30D with 13% coating weight; (●) Surelease with 7% coating weight.

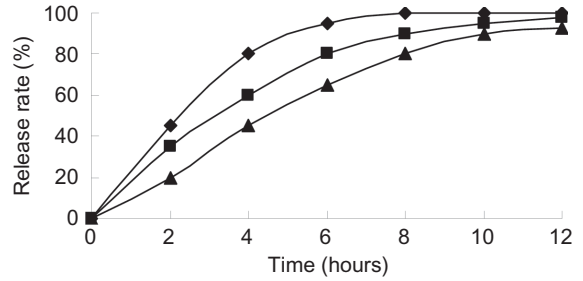

Figure 2. Release rate of levofloxacin pellets with different Eudragit® NE30D coating weights. (◆) 10% coating weight; (■) 13% coating weight; (▲) 15% coating weight.

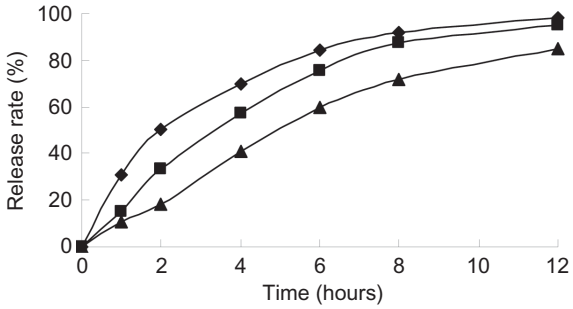

Figure 3. Release rate of levofloxacin pellets with different Surelease coating weights. (◆) 5% coating weight; (■) 7% coating weight; (▲) 9% coating weight.

all the carboxyl groups were esterified, there were no functional response groups in the polymeric membrane, thus the release of the drug was mainly controlled by the coating thickness. Release rate of levofloxacin decreased with the increasing of Eudragit® NE30D coating weight. When the coating weight reached 13%, a moderate release rate was obtained as determined at different time points (2, 4, 6, 8, 10, and 12 hours). The release results of pellets with different weights of Surelease coating are included in Figure 3. Release of levofloxacin was slower with increasing amount of Surelease. It might be because water-insoluble Surelease film decreased the permeability of levofloxacin in water[24]. When the coating weight reached 9%, drug release became too slow with only 70% of levofloxacin released after 8 hours. A satisfactory release profile was achieved by the formulation with 7% coating weight. Because levofloxacin is a water-soluble drug, further reduction in coating film may lead to burst release of the drug, and result in poor reproducibility. Considering both release behavior and reproducibility, 7% Surelease coating weight was chosen. The f_2 value calculated between the release rates of pellets for 13% Eudragit® NE30D and 7% Surelease coating was 76.52, indicating that the release rates of Eudragit® NE30D-coated pellets and Surelease-coated pellets were similar. Hence, the pellets with 13% Eudragit® NE30D coating weight and 7% Surelease coating weight were subjected to subsequent in vivo pharmacokinetic studies.

Adjustment of the parameters in coating process

In the coating process, parameters such as the atomization pressure, fluidization pressure, flow rate of coating liquid, and coating temperature were all important to the product quality. The pellets were prone to conglutination at low atomization pressure and fluidization pressure, and prone to crack at high pressures. A suitable atomization and fluidization pressures were chosen as shown in Materials and methods section. Under a certain atomization pressure, increasing flow rate of coating liquid would weaken atomizing effect and lead to adherence between pellets. However, too low flow rate decreased the coating efficiency. So, suitable flow rate was chosen as 0.2 g/min for isolated coating and 0.3 g/min for sustained-release coating. To form an ideal film, the coating temperature must be higher than the MFT of the coating materials; otherwise, the particle of the polymer cannot coalesce to form continuous film. Because of low MFT of Surelease and Eudragit® NE30D, the coating temperature was set to be at 40°C for Surelease and at 25°C for Eudragit® NE30D coating, respectively.

Setting of the ratio of immediate-release and sustained-release pellets

Upon administration, a good formulation should reach blood drug level above the minimum inhibitory concentration (MIC) at relatively short time and then maintain blood drug level above MIC for a prolonged period. Formulation composed of immediate-release and sustained-release parts, which had rapid onset and prolonged duration of anti-inflammatory effect, would be a promising approach[25]. Hence, immediate-release and sustained-release pellets were combined at the ratio of 15:85 (w/w) to achieve this purpose.

In vitro release study

The levofloxacin capsules contained both immediate-release and sustained-release pellets, so the release behavior was controlled by both components. The release rates in distilled water, hydrochloric acid solution (pH 1.2), and hydrochloric acid solution (pH 1.2) for the first 2 hours followed by PBS (pH 6.8) for the subsequent time were studied (Figure 4). There were no significant differences in release rates in different dissolution media, demonstrating that the release of levofloxacin from the pellets was pH independent. As a result, distilled water was chosen to be the release medium.

In vivo pharmacokinetic study

A validated HPLC method for the determination of levofloxacin in dog plasma was established. HPLC analysis was carried out under the following conditions: the stationary phase, Diamonsil C_{18} column (5 μm, 250 × 4.6

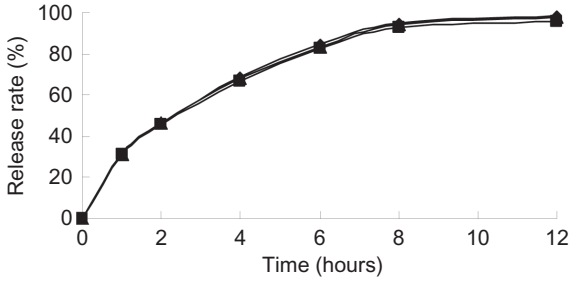

Figure 4. Release rate of levofloxacin sustained-release capsules in different media with different pH values. (◆) Water; (■) pH 1.2 hydrochloric acid solutions; (▲) pH 1.2 hydrochloric acid solutions for 0–2 hours, pH 6.8 phosphate buffer saline for 2–12 hours.

mm), was kept at 35°C; the mobile phase was a mixture of acetonitrile and 0.05 mol/L citric acid (20: 80, v/v, pH of the aqueous phase was adjusted by triethylamine to 5.5); the flow rate was 1.0 mL/min; and the effluent was examined at 293 nm. No interference was observed for either levofloxacin or the internal standard from the endogenous components of the plasma. The theoretical plate number was more than 4000. The results demonstrated good method specificity. The lower limit of quantification of levofloxacin was 50 ng/mL. The standard curve was linear (r = 0.9997) over the concentration range of 0.2168–21.68 μg/mL. The absolute recoveries for low, medium, and high concentrations of levofloxacin (0.5419, 5.419, 21.68 μg/mL) were 84.29 ± 6.04%, 83.15 ± 4.98%, and 85.77 ± 2.59%, respectively. The relative recoveries were 107.31 ± 22.56%, 104.63 ± 10.74%, and 98.29 ± 5.35%, respectively. The relative standard deviation (RSD) of precision was 13.7%, 6.49%, and 4.17% for intra-day analysis, and 14.8%, 1.21%, and 5.01% for inter-day analysis. The data indicated that both recoveries and precisions were satisfying. The RSD of the three concentrations in plasma sample stability test for 5 days were 8.14%, 3.67%, and 3.64%, respectively. The results demonstrated that levofloxacin was still stable in plasma after being stored at -20°C for 5 days. Therefore, the sample could remain stable in analysis period of 5 days.

In vivo evaluations of Eudragit® NE30D-coated pellets and Surelease-coated pellets were performed at same dose of levofloxacin conventional tablets. Crossover test was applied to avoid the influences of individual differences between the dogs[26,27]. The AUCs for the reference preparations and test preparations with Eudragit® NE30D coating and Surelease coating in six beagle dogs are illustrated in Figure 5. Two-compartment model was fitted to AUCs of both test and reference preparations. All the pharmacokinetic parameters are listed in Table 2. When Eudragit® NE30D was used as the coating film, the relative bioavailability of the sustained-release capsules was only 41.5% compared with the conventional tablets. The result suggested that there was no in vivo–in vitro correlation for the pellets with Eudragit® NE30D coating. The release of levofloxacin from Eudragit® NE30D-coated pellets might be sensitive to the in vivo environment. Even though a satisfactory sustained-release profile was produced by Eudragit® NE30D coating film in distilled water in vitro, the release of levofloxacin was probably incomplete after oral administration. Because of complicated in vivo environment and multiple physiological factors, such as gastrointestinal tract transit time, pH gradient, and hydrodynamics, in vivo absorption time-scale might be much shorter than that of in vitro release. These factors might all contribute to the low bioavailability. Therefore, classical approaches based on the use of sustained-release pellets coated with Eudragit® NE30D did not fulfill the expected pharmacokinetic properties[4,26,28,29]. Eudragit® NE30D was unsuitable to be used as the coating material in this study. When Surelease coating was applied, no significant difference in AUC was observed by statistical analysis ($P > 0.05$). The bioavailability of the sustained-release capsules was equivalent to the conventional tablets, and 90% confidence interval of the AUC of the test preparation was 100.11–105.78% of the reference preparation. However, C_{max} and T_{max} differed from each other significantly ($P < 0.05$). Compared with the conventional tablets, C_{max} of the test preparations was decreased, whereas T_{max} was prolonged. The result indicated that drug release from Surelease-coated pellets was independent of the release conditions, and best sustained-release effect was achieved both in vitro and in vivo. Hence, Surelease water dispersion was ultimately chosen to be the sustained-release coating material.

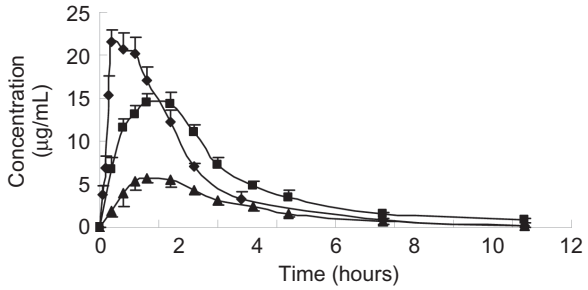

Figure 5. Mean plasma concentration–time curves of the reference preparation and teat preparations in six beagle dogs after oral administration. (◆) Reference preparation; (■) test preparation with Surelease coating; (▲) test preparation with Eudragit® NE30D coating (n = 6).

Table 2. Pharmacokinetics parameters of levofloxacin in beagle dogs after oral administration (n = 6).

	C_{max} (μg/mL)	T_{max} (hours)	$t_{1/2}$ (hours)	AUC $_{0–36\,h}$ (μg.h/mL)	AUC $_{0–\infty}$ (μg.h/mL)	F (%)
Conventional tablets (300 mg)	21.80 ± 1.65	1.2 ± 0.4	4.92 ± 1.94	170.28 ± 11.15	172.60 ± 11.24	–
Sustained-release capsules with Eudragit® NE30D coating (300 mg)	6.19 ± 0.59	4.2 ± 1.5	7.15 ± 2.13	70.55 ± 9.33	73.67 ± 12.23	41.5 ± 5.2
Sustained-release capsules with Surelease coating (300 mg)	14.68 ± 1.09	5.0 ± 1.1	8.40 ± 1.01	175.27 ± 12.23	185.33 ± 13.65	103.0 ± 4.3

All the data are presented in the form of mean ± SD.

Conclusions

In this study, novel levofloxacin sustained-release capsules were prepared by fluidized bed. Through prescription screening, the optimal formulation was obtained with MCC pellets as the blank core, 5% HPMC E_5 as the adhesive, Opadry and Surelease water dispersion as the isolated film and sustained-release film, respectively. Then, 15% immediate-release uncoated pellets and 85% sustained-release pellets were mixed and filled into the hard gelatin capsules for in vitro and in vivo studies.

The in vitro dissolution experiment demonstrated that the developed capsules could prolong the release of levofloxacin and the release rate was not affected by the pH of the release media.

Pharmacokinetics after oral administration of levofloxacin conventional tablets and sustained-release capsules were also investigated. Although similar in vitro release profiles were obtained by using Eudragit® NE30D and Surelease coating, their in vivo behavior differed significantly. Compared with the conventional tablets, relative bioavailability of the sustained-release capsules containing Eudragit® NE30D-coated pellets was only 41.5%, even though they possessed a fine sustained-release property in vitro, suggesting that there might be a time-scale difference between in vitro and in vivo test. Whereas, sustained-release pellets with Surelease coating had a favorable release profile in vitro as well as a satisfactory pharmacokinetics property in vivo. The relative bioavailability reached 103.0% with a lower C_{max} and a longer T_{max}. The result indicated that levofloxacin sustained-release capsules with Surelease coating could prolong the efficacy of the drug and diminish its concentration fluctuation in blood. Especially for the diseases requiring long-term drug administration, it is necessary to develop sustained-release delivery systems with improvement in compliance and safety.

In conclusion, we successfully prepared levofloxacin sustained-release capsules for oral administration and revealed their pharmacokinetics in beagle dogs. However, considering the gastrointestinal differences between beagle dogs and humans, further clinical experiment should be pursued to determine the pharmacokinetic and pharmacodynamic characteristics of the sustained-release capsules.

Acknowledgements

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Declaration of interest

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