**Novel nanostructured lipid carrier for oral delivery of a poorly soluble antimalarial agent lumefantrine: characterization and pharmacokinetics evaluation**

**Abstract**

The objective of this study was to design nanostructured lipid carriers (NLC) for the oral delivery of a poorly soluble antimalarial agent lumefantrine (LFN), which could increase the solubility and oral bioavailability of LFN, with the aim to further improve therapeutic efficacy. The lumefantrine–nanostructured lipid carriers (LFN–NLC) were prepared by the method of ultrasonication. Based on the optimized results of single-factor screening experiment, LFN–NLC was found to be relatively uniform in size (213.30±8.54) nm with a narrow polydispersity index (PDI) (0.192±0.02). The average entrapment efficiency (EE) and drug loading (DL) were (94.90±0.51)% and (9.05±0.19)%, respectively. The differential scanning calorimetry (DSC) analysis showed that LNF was not in crystalline state in LFN–NLC. In vivo studies indicated that LFN–NLC showed higher AUC and Cmax values compared with LFN–suspension after oral administration to rats. The decrease of t1/2 and two absorption peaks indicated that LFN can be absorbed into blood faster and have higher therapeutic efficacy after encapsulated into the NLC. These encouraging results revealed that LFN–NLC would be an promising carrier for LNF to increase therapeutic efficacy on malaria.

**Keywords:** lumefantrine, malaria, nanostructured lipid carriers, oral delivery, pharmacokinetics, bio-availability

**Abbreviations:** NLC, nanostructured lipid carriers; PDI, polydispersity index; EE, entrapment efficiency; DL, drug loading; DSC, differential scanning calorimetry; LFN, lumefantrine; SP, soybean lecithin; MS, monostearin; SA, stearic acid; OA, oleic acid

**Introduction**

Malaria is today a disease of poverty and underdeveloped countries caused by the parasitic invasion of hepatocytes and red blood cells. According to the WHO reports, there were 3.2 billion people threatened by malaria in 109 countries and regions around the world in 2015. Moreover, malaria is predominantly prevalent in Africa, Asia and Latin America. The characteristics of malaria transmission speed, easy to relapse, difficult to cure and the emergence of malaria parasite resistance bring a lot of difficulties to the treatment. The key to malaria treatment is antimalarial drugs, but there are some disadvantages in the course of treatment such as resistance, short half life, recrudescence, poor patient compliance due to high dosage and long-term treatment. However, few drugs were registered for malaria in recent years. So it is very imperative to take advantage of currently existing drugs and enhance the therapeutic efficiency of these drugs. Drug delivery formulations involved low-cost research compared to that for the development of new molecules. Most of all, colloidal drug carriers can modulate physicochemical properties and pharmacokinetic properties of the anti-parasitic agent in order to improve therapeutic efficacy with lower adverse effects. So developing novel delivery systems to tackle the aforementioned difficulties is of prime importance.

Lumefantrine (LFN) is a synthetic racemic fluorene derivative with the chemical name 2--dibutylamino--1--(2,7--dichloro--9--(4-chlorobenzylidene)--9H--fluoren--4--yl)--ethanol, which was discovered at the Academy of Military Science in Beijing. LFN can kill malaria parasite completely with excellent recovery profiting from a large apparent volume of distribution and a terminal elimination half-life for malaria estimated initially at approximately 4 to 5 days. However, oral bioavailability of LFN was low without fats and the population absorption half-life of it was 4.5h, so the speed of killing malaria parasite and controlling clinical symptoms were very slow, which lead to a poor therapeutic effect in acute malaria. In order to tackle the aforementioned difficulties, many strategies have been employed, for instance, nanostructured lipid carriers (co-loaded with artemether) for peritoneal injection and nonoliposomes (co-loaded with artemether) for intravenous injection. But the patient’s compliance is not high with injection. Oral administration of drugs is considered to be a accepted route with several advantages like cost-effectiveness and patient compliance. The oral bioavailability of LFN is very dependent on food because of the beneficial role that lipids can have on drug absorption. So the aim of this research is to fabricate LFN–nanostructured lipid carrier (NLC) for oral delivery to improve the solubility and bioavailability of LFN. This design was based on the following points:

a. NLC, a novel lipid nanoparticle drug delivery system developed on the basis of liposomes and solid lipid nanoparticles (SLN) with good stability, low toxicity, high drug loading capacity, good biocompatibility, biodegradation, slow release and ease of manufacture.

b. NLC with combinational advantages has emerged as propitious carriers in the armory of oral drug delivery systems. Improved bioavailability can be attributed to the improved solubilization; suppressed degradation of drugs in environment and GIT; direct uptake of NLC in GIT; permeation enhancement effect of sur-
Experimental section

Materials and methods

Materials

LFN was obtained from Shanghai Dibo Chemical Technology Co., Ltd. (China). SP (phosphatidylcholine) available for 95%, pH5.0~7.0) was obtained from Shanghai Taiwei Pharmaceutical Co., Ltd. (China). SA was purchased from Tianjin Guangcheng Chemical Agent Co., Ltd. (China). MS was obtained from Chemical Agent factory of Tianjin Sitong. OA was provided by Chemical Agent factory of Tianjin Damao. Pluronic F68 (F68) was obtained from Sigma USA. Methanol, ethanol and other chemicals and reagents used were of analytical grade.

Methods

Preparation of LFN–NLC

Ultrasound method: LFN–NLC was prepared by ultrasonication method.18 5mg LFN and 40mg lipid (including SP, 5.6mg MS, 9.4mg SA and 10mg OA) were dissolved in 5ml ethanol in water bath at 75°C as lipid phase. In the second step, the lipid phase was slowly dropped into 20ml F68 aqueous solution (0.5%, w/v), under constant mechanical agitation in a water bath at 75°C at 1000rpm, then stirred at least half of hour. The obtained pre-emulsion was ultrasonification for 15min. The obtained nanoeulsion (O/W) was cooled down in a bath ice for 1.5h.

Optimization of formulations and production process with single-factor screening experiment: The optimal formulations and production process were determined by single-factor screening experiments. Formulations factors were considered, including: the ratio of LFN/lipid (A, W/W), the ratio of liquid/solid lipid (B, W/W), concentration of F68 (C, %), volume ratio of aqueous lipid phase (D, V/V) (labelled in Table 1). Production process factors, the speed of dropping (ml/h), the time of emulsifying (min), the speed of stirring (rpm) and the time of ultrasonication (min) were investigated (labeled as E, F, G and H in Table 2) on the basis of particle size plus entrapment efficiency as the evaluation index.

Freeze-dried of LFN–NLC: Freeze-drying is a commonly used technique to improve the dispersibility of nanoparticles. In addition, sugars proved to be very effective in preventing particle aggregation and inhibiting leakage of an active ingredient during freeze-drying process.19 To improve the resistance of LFN–NLC towards the freeze–drying stresses, 4% mannitol was added to the LFN–NLC solutions as a cryoprotectant. The sample was frozen at –80°C for 12h in an ultra-cold freezer and then the frozen sample was freeze-dried in a lyophilizer. The in vivo pharmacokinetics of LFN–NLC was also evaluated in rats to elucidate its feasibility as an oral delivery systems anti-malarial agent.

Table 1 Formulation factor-level in single-factor screening experiment

| Level | Factors |
|-------|---------|
| A (W/W) | B (%) | C (V/V) | D (W/W) |
| 1 | 1:05 | 0.05 | 1:02 | 1:02 |
| 2 | 1:08 | 0.15 | 1:03 | 1:03 |
| 3 | 1:10 | 0.5 | 1:04 | 1:04 |
| 4 | 1:12 | 0.8 | 1:05 | 1:05 |

Table 2 Production process factor-level in single-factor screening experiment

| Level | Factors |
|-------|---------|
| E(ml/h) | F(rpm) | G(min) | H(min) |
| 1 | 12 | 600 | 10 | 5 |
| 2 | 15 | 800 | 20 | 10 |
| 3 | 20 | 1000 | 30 | 15 |
| 4 | 30 | -- | 40 | 20 |

Characterization of LFN–NLC

Appearance of LFN–NLC: The prepared LFN–NLC and lyophilized form were placed in penicillin bottles and then observed its appearance.

Measurement of particle size and pH value: The average particle size and PDI of LFN–NLC were determined by Malvern Zetasizer Nano ZS instrument (Malvern Nano ZS–90, Malvern, UK). The pH value of LFN–NLC was determined with a digital pH meter (FE20, Mettler Toledo, Switzerland).

Determination of entrapment efficiency (EE) and drug loading (DL): The EE of LFN–NLC was determined by the method of ultrafiltration–centrifugation.20 0.4ml LFN–NLC mixed with 0.3ml 50% ethanol aqueous solution was added into the ultrafiltration centrifuge tube (MILLIPORE, UFC901242 15 M 10 K) and was centrifuged at 4000rpm for 40min (3K30, Sigma, Germany). Then 0.3ml ethanol aqueous solution was added into the ultrafiltration centrifuge tube and centrifuged at 4000rpm for 2min. The solution in the outer tube was collected, adding ethanol volume to 10ml and detected by Ultraviolet spectrophotometry (UV) at the wavelength of 302nm to determine the weight of free drug. The total drug content was determined as follows: 0.4mL of LFN–NLC was mixed with methanol and sonication, detected by the same UV. The EE and DL were calculated as follows.21

\[
EE(\%) = \frac{W_{total} - W_{free}}{W_{total}} \times 100\% \quad (1)
\]

\[
DL(\%) = \frac{W_{total} - W_{free}}{W_{lipid}} \times 100\% \quad (2)
\]

Where \( W_{total} \), \( W_{free} \) and \( W_{lipid} \) are the weights of drug added in the system, analyzed weight of LFN in supernatant, and the weight of lipid added in system, respectively.

Transmission electron microscope (TEM) examination: Transmission electron microscopy (H–7000, Hitachi, Japan) was used to observe the morphology of LFN–NLC. The diluted LFN–NLC using distilled water in an appropriate proportion was dropped on a 200–mesh copper grid followed by negative staining with 2% phosphotungstic acid for 30s.
Differential scanning calorimetry (DSC) analysis: Differential scanning calorimetry (DSC) measurements of LFN, excipients, physical mixture of excipients and LFN and LFN–NLC were carried out on a differential scanning calorimeter (DSC 204, Netzsch, Germany) to study the interaction of LFN and NLC. DSC measurements were performed from 10 to 400°C at a heating rate of 10°C/min under flowing nitrogen gas (50ml/min). The weighed (5–10) mg samples were placed in aluminium pan using an empty aluminium pan used as reference.

In vivo pharmacokinetic study

Animals: Six rats of female wistar rats (weighed about 200g, provided by the Medical Animal Test Center of Shandong University) were randomly divided into two groups for the in vivo pharmacokinetics studies and fasted for 12 hours before administration. Approval from the Institutional Animal Care and Use Committee of Shandong University was sought and the study protocols were approved before the commencement of the studies.

HPLC conditions: Concentration of LFN in plasma was determined by high–performance liquid chromatography (HPLC) coupled with LC–10AT HPLC pump and a SPD–10A UV–VIS detector. Drug analysis was performed by Venusil MP C18 column (4.6mm×150mm, 5μm). The mobile phase was consisted of methanol, deionized water and acetic acid (80:20:1) at the flow rate of 1.0ml/min, and the injection volume was 20μl. The detection wavelength was set to 265nm.

Sample preparation: A simple precipitation protein method was followed for extraction of LFN from rat plasma. To 100μL of plasma in centrifuge tubes, 400μL LFN solution (methanol:acetic acid=80:1) was added and vortexed for 3min, followed by centrifuged for 10min at 12,000rpm. The supernatant layer was filtered through a 0.22μm filter and 20μl of the filtered solution was injected into the HPLC instrument.

Method validation: The samples were analyzed by standard addition method. LFN standard curve samples (1, 2, 4, 8, 16, 32, 40μg/mL) were prepared by mixing a set of LFN solution with blank plasma according to the sample preparation method. The standard curve samples were analyzed by the HPLC method mentioned above. The linear relationship of peak area and concentration of LFN was calculated. Then the precision, accuracy and the rate of extraction recovery was evaluated.

Pharmacokinetic study: Pharmacokinetic study of LFN–NLC was compared with LFN–suspension. Six rats were divided into two groups. LFN–suspension and LFN–NLC were administered orally at a dose of 10mg/kg, respectively. After administration, blood sample was withdrawn from jugular venous sinus at specified time intervals (0.5, 2, 5, 8, 24, 30, 48, 54, 72, 120 h). The blood samples were processed according to 5.2.3.

Data analysis and statistics: All experimental data are presented as the mean±SD. Statistical differences were evaluated with unpaired Student’s t–test with P<0.05 indicating significant difference. Pharmacokinetic parameters were calculated by DAS 2.0 (drug and statistics for windows) software.

Results and discussion

Results of single–factor screening experiments

The results of single–factor screening experiments were shown in Figure 1–4, respectively. The particle size was mainly affected by the preparation process and the formulation factors could greatly influence the entrapment efficiency. Considering the effect of particle size and entrapment efficiency, the optimal formulation was as follows: the ratio of LFN/lipid was 1:8, the ratio of liquid/solid lipid was 1:3, concentration of F68 was 0.5%, volume ratio of aqueous / lipid phase was 1:4. The production process was as follows: the speed of dropping was 15ml/h, the time of emulsifying was 30min, the speed of stirring was 1000rpm and the time of ultrasonication was 15min.

Characterization of LFN–NLC

Appearance of LFN–NLC: The photographs of fresh–prepared...
LFN (A) and the freeze-dried powder (B) are shown in Figure 5. Fresh-prepared LFN–NLC was translucent and indicated light blue opalescence. The freeze-dried powder appeared as white fluffy powder.

**Figure 4** Entrapment Efficiency affected by production process factors

**Figure 5** Photographs of LFN-NLC
A: Fresh-prepared; B: Freeze-dried powder

**Measurement of particle size and pH value:** The particle size of LFN–NLC and PDI were (213.30±8.54) nm and 0.192±0.02 (n=3). The pH value was 6.43±0.19 (n=3). The size distribution of LFN–NLC was shown in Figure 6 which indicated the narrow distribution.

**Figure 6** Intensity distribution of LFN-NLC.

**Determination of entrapment efficiency and drug loading:** LFN has the maximum absorption peak at 302nm. The mean EE and DL were (94.90±0.51) % and (9.05±0.19)%, respectively. The high EE and DL indicated that most LFN was entrapped into NLC.

**Transmission electron microscope (TEM) examination:** Figure 7 showed that LFN–NLC had relatively spherical shapes and dispersed uniformly.

**Figure 7** Transmission electron microscopy micrograph of LFN-NLC.

**Differential scanning calorimetry (DSC):** The DSC thermograms of LFN raw material, excipients, physical mixture of excipients and LFN, and LFN–NLC were detected and shown in Figure 8. LFN has a typically sharp endothermic peak at 133°C and excipients had endothermic peak of melting at about 50°C. The DSC curve of physical mixture was slightly different from the superposition of the excipients and LFN as a result of interactions of LFN and excipients. Completely varied from that of physical mixture, in the DSC curve of LFN–NLC, the two characteristic endothermic peaks of LFN and excipients disappeared and a new exothermic peak at about 160°C and a new endothermic peak at around 170°C, which may reveal that LFN was not in crystalline state in LFN–NLC and LFN may be incorporated into the lipids. Comparing the last curve and the previous three, we can conclude that the LFN–NLC has been formed successfully.

**Figure 8** The DSC results of the samples:
A: LFN; B: Excipients; C: Physical mixture of excipients and LFN; D: LFN-NLC.
**In vivo studies**

**Method validation**

The typical chromatograms of blank plasma and plasma contained LFN were shown in Figure 9 which showed that LFN is not interfered by endogenous components of plasma. The retention time for LFN was about 5 min. At the range of 1–40 μg/mL, the standard curve was \( A = 72.244C - 12.202 \) (where \( A \), \( C \) represent absorbance and concentration, respectively) and the concentration of LFN was linearly proportional to their chromatographic peak area (\( r = 0.9992 \)). The RSD values of inter-day precision at three concentrations were less than 5%. The rate of extraction recovery was 80%~100% and the RSD values were less than 6%. These results showed that the method had high precision and good accuracy and the rates of extraction recovery were in line with the determination of requirements.

![Typical chromatograms of blank plasma](image1)

![Plasma contained LFN](image2)

**Figure 9** A: Typical chromatograms of blank plasma; B: Plasma contained LFN.

**Pharmacokinetic study**

The main corresponding pharmacokinetic parameters of LFN–NLC and LFN–suspension were calculated using DAS2.0 and the results were summarized in Table 3. According to the results, LFN–suspension and LFN–NLC were fitted to a two compartment model. As displayed in Table 2, the \( t_{1/2} \) for LFN–NLC (42.89 h) was markedly longer than that observed for LFN–suspension (23.09 h) and the extended \( t_{1/2} \) may due to the sustained release of LFN from LFN–NLC. To be specific, the \( C_{\text{max}} \) of LFN–NLC (2.57 mg/mL) was about 1.87 times compared with the LFN–suspension (4.81 mg/mL). Furthermore, the prolonged blood circulation and higher \( AUC_{0\text{-}\infty} \) of LFN–NLC (182.93 mg/mL* h) was significantly higher than that from LFN–suspension (111.07 mg/mL* h). Therefore, the prolonged blood circulation and higher \( AUC_{0\text{-}\infty} \) and \( C_{\text{max}} \) value of LFN–NLC may contribute to higher therapeutic efficacy on malaria and the improvement of bioavailability. What’s more, compared with LFN–suspension, the \( T_{\text{max}} \) of LFN–NLC decreased 3 times which could help to play a therapeutic effect quickly. The decrease of \( T_{\text{max}} \) may be caused by the increase of solubility and lipid of NLC which could contribute to LFN absorbed into blood faster.

The plasma concentration–time profile of LFN after administration of LFN–NLC and LFN–suspension was shown in Figure 10. The measured LFN plasma concentration achieved from LFN–NLC was higher than that of LFN–suspension in most of the time. In addition, there are two absorption peaks after the formation of NLC. This could be because some LFN after released undergo transport quickly through enterocytes into systemic circulation, so the concentration of the drug reached its maximum at 2 h. The second absorption peak appears because LFN can also be delivered into lymphatic system through lacteals or Peyer’s patches. In the former pathway, the digested lipid in NLC, cholesterol and phospholipids form chylomicrons encapsulating LFN, which enter lymphatic system by lacteals. In the later pathway, the particle size of LFN–NLC was less than 300 nm, so LFN–NLC can be captured by M cells of Payer’s patches delivering LFN to the lymphatic system. Lymphatic transit can avoid the effect of the first pass of the liver and promote drug absorption. In addition, two absorption peaks could help LFN continue to play a better role to improve efficacy.

**Table 3** Comparison of main pharmacokinetic parameters of LFN-suspension and LFN–NLC

| Parameter      | LFN–Suspension | LFN–NLCs |
|---------------|---------------|----------|
| \( t_{1/2} \) (h) | 23.09         | 42.89    |
| \( MRT_{0\text{-}\infty} \) (h) | 43.81         | 42       |
| \( T_{\text{max}} \) (h) | 8             | 2        |
| \( C_{\text{max}} \) (μg/mL) | 2.57          | 4.81     |
| \( AUC_{0\text{-}\infty} \) (μg/mL* h) | 111.07       | 182.93   |

**Figure 10** Mean plasma concentration curves of LFN in rats after PO administration of LFN–suspension and LFN–NLC at a dose of 10 mg/kg.

**Conclusion**

In this study, LFN–NLC was successfully prepared via ultrasonication method. The newly developed LFN–NLC demonstrated excellent performance featured by small and uniform size, high entrapment efficiency and desired pharmacokinetics. In addition, _in vivo_ studies indicated that the \( C_{\text{max}} \) of LFN–NLC was about 1.87 times and the \( AUC_{0\text{-}\infty} \) 1.64 times compared with the LFN–suspension. Further, the decrease of \( T_{\text{max}} \) and two absorption peaks indicated that LFN can be absorbed into blood faster and higher therapeutic efficacy after the formation of NLC. Taking the results mentioned above into account, LFN incorporated into NLC may be expected to increase the bioavailability and improve the therapeutic efficacy of LFN. All these current encouraging results indicated that LFN–NLC may serve as a promising formulation in the treatment of malaria with great clinical application prospects. However, In line with the World Health Organization’s recommendation in that respect, NLC for oral delivery encapsulating two antimalarial drugs–artemether and LFN will be further researched.

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Conflict of interest

The author declares no conflict of interest.

References

1. Miller LH, Baruch DI, Marsh K, et al. The pathogenic basis of malaria. Nature. 2002;415(6872):673–679.
2. Gallup JL, Sachs JD. The economic burden of malaria. Am J Trop Med Hyg. 2001;64(1–2 Suppl):85–96.
3. WHO. World malaria report 2015. World Health Organization, Geneva, Switzerland; 2015. 280 p.
4. White NJ. Antimalarial drug resistance. J Clin Invest. 2004;113(8):1084–1092.
5. Date AA, Joshi MD, Patravale VB. Parasitic diseases: Liposomes and polymeric nanoparticles versus lipid nanoparticles. Adv Drug Deliv Rev. 2007;59(6):505–521.
6. Khalil NM, de Mattos AC, Carraro TC, et al. Nanotechnological strategies for the treatment of neglected diseases. Curr Pharm Des. 2013;19(41):7316–7329.
7. Suri SS, Fenniri H, Singh B. Nanotechnology–based drug delivery systems. J Occup Med Toxicol. 2007;2:16.
8. Islan GA, Durán M, Cacicedo ML, et al. Nanopharmaceuticals as a solution to neglected diseases: Is it possible? Acta Trop. 2017;170:16–42.
9. Ezzet F, Mull R, Karbwang J. Population pharmacokinetics and therapeutic response of CGP 56697 (artemether+ benflumetol) in malaria patients. Br J Clin Pharmacol. 1998;46(6):553–561.
10. Ezzet F, van Vugt M, Nosten F, et al. Pharmacokinetics and pharmacodynamics of lumefantrine (benflumetol) in acute falciparum malaria. Antimicrob Agents Chemother. 2000;44(3):697–704.
11. Parashar D, Aditya NP, Murthy RS. Development of artemether and lumefantrine co–loaded nanostructured lipid carriers: physicochemical characterization and in vivo antimalarial activity. Drug Deliv. 2016;23(1):123–129.
12. Shakeel K, Raisuddin S, Ali S, et al. Development and in vitro/in vivo evaluation of artemether and lumefantrine co–loaded nanoliposomes for parenteral delivery. J Liposome Res. 2017;13:1–9.
13. Humberstone AJ, Charman WN. Lipid–based vehicles for the oral delivery of poorly water soluble drugs. Adv Drug Deliv Rev. 1997;25(1):103–128.
14. Müller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Adv Drug Deliv Rev. 2002;54:S131–S155.
15. Hu FQ, Jiang SP, Du YZ, et al. Preparation and characteristics of monostearin nanostructured lipid carriers. Int J Pharm. 2006;314(1):83–89.
16. Zhuang CY, Li N, Wang M, et al. Preparation and characterization of vinpocetine loaded nanostructured lipid carriers (NLC) for improved oral bioavailability. Int J Pharm. 2010;394(1–2):179–185.
17. Poonia N, Kharb R, Lather V, et al. Nanostructured lipid carriers: versatile oral delivery vehicle. Future Sci OA. 2016;2(3):FSO135.
18. Castelli F, Puglia C, Sarpietro MG, et al. Characterization of indomethacin–loaded lipid nanoparticles by differential scanning calorimetry. Int J Pharm. 2005;304(1–2):231–238.
19. Ohshima H, Miyagishima A, Kurita T, et al. Freeze–dried nifedipine–lipid nanoparticles with long–term nano–dispersion stability after reconstitution. Int J Pharm. 2009;377(1–2):180–184.
20. Yang Z, Liu J, Gao J, et al. Chitosan coated vancomycin hydrochloride liposomes: characterizations and evaluation. Int J Pharm. 2015;495(1):508–515.
21. Liu X, Wang Z, Feng R, et al. A novel approach for systematic delivery of a hydrophobic anti–leukemia agent tamibarotene mediated by nanostructured lipid carrier. J Biomed Nanotechnol. 2013;9(9):1586–1593.
22. Yao M, McClements DJ, Xiao H. Improving oral bioavailability of nutraceuticals by engineered nanoparticle–based delivery systems. Current Opinion in Food Science. 2015;2:14–19.
23. Li C, Fleisher D, Li L, et al. Regional–dependent intestinal absorption and meal composition effects on systemic availability of LY303366, a lipopeptide antifungal agent, in dogs. J Pharm Sci. 2001;90(1):47–57.