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Research Progress in the Preparation of Enrofloxacin for Use in Veterinary Medicine

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ABSTRACT

Enrofloxacin is a special antibacterial agent for animals and is a synthetic third-generation fluoroquinolone broad-spectrum antibacterial agent. It has excellent antibacterial effects and is widely used in clinical practice. However, the solubility of enrofloxacin is extremely low and this has greatly limited its clinical use. We assessed progress in overcoming this deficiency by tracking pharmaceutical alterations to enrofloxacin *in vivo* delivery systems. We used the keywords 'enrofloxacin', 'pharmaceuticals' and 'preparations' to assess relevant literature sources collected in CNKI, Wanfang, Vepsa, China Patent Information Network, PubMed, Web of Science and other domestic and foreign databases from 2010 to 2022 to summarize the research progress of enrofloxacin pharmaceutics. A total of 62 valid literature were retrieved and we found that pharmaceutic technologies successfully were able to increase enrofloxacin solubility, palatability, bioavailability and half-life. The continuous development and promotion of new drug formulations and new materials will give enrofloxacin preparations broad application prospects in veterinary medicine.

Key words: Controlled release preparation, *Enrofloxacin*, Palatability, Preparation, Solubility, Sustained, Targeting.

The broad spectrum antibiotic enrofloxacin is widely used to treat and prevent a wide range of bacterial diseases in livestock and poultry and is administered via powders in feeds and by injection (Pei *et al.*, 2020; Corum *et al.*, 2019). The oral preparations are often rejected by animals due to the bitterness and gastrointestinal irritation of the enrofloxacin raw materials. Enrofloxacin consumption can also result in an antifeedant-type phenomena in animals. The drug has a short elimination half-life in animals such as swine (6 h) and repeated administrations are required for maximal effectiveness (Xiong *et al.*, 2021; Liu *et al.*, 2021; Ahmad 2021). If these shortcomings could be overcome, more suitable enrofloxacin preparations would be a valuable asset to the veterinary clinic.

In the current study, we examined the relevant literature from 2010 to 2022 using key words 'enrofloxacin', 'pharmaceuticals' and 'preparations' to locate 62 valid studies for the development of novel and more suitable enrofloxacin preparations.

Improvements to the solubility of enrofloxacin as a result of pharmaceutical research

Solubility is one of the most important factors affecting drug gastrointestinal absorption. Enrofloxacin is soluble in water at 161 to 202.56 mg L^{-1} (1.6 ~ 2 % at 25°C) and modifications to increase its solubility have been pursued (Wu *et al.*, 2005). Nanoemulsions were able to decrease the particle size to 22.45 nm and this increased solubility ~10-fold to 15%. This advance effectively addressed the solubility problem and resulted in the widespread use of these nanoemulsions in veterinary clinical practice (Yang *et al.*, 2012). Cyclodextrin carrier formulations such as 2-hydroxypropyl-β-cyclodextrin were able to form stable inclusion complexes with enrofloxacin and this also increased its water solubility 1.65 to 9.16 times greater than its original solubility (Ding *et al.*, 2020; Wang *et al.*, 2012). Solid dispersion technology is one of the most effective ways to improve the drug solubility and several inert carriers including polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP) have been used for this purpose. For example, enrofloxacin films prepared using PVP significantly increased the solubility of enrofloxacin and enhanced it release using *in vitro* studies (Kumar *et al.*, 2014). In particular, the commercial excipient PVP K30 was able to disperse the drug in solution via hydrogen bonding resulting in an enrofloxacin : stearic acid ratio of 1:5 (Wang *et al.*, 2013). Amorphous solid dispersion has also been successful and resulted in a solubility of 1190 mg.L^{-1} (Zhou *et al.,*

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2021). The use of enrofloxacin salt formulations and enrofloxacin mesylate soluble powder produced a solubility of 483 g L^{-1} that was 10-1000 times greater than enrofloxacin and 10-100 times that of enrofloxacin HCl (Fu *et al.*, 2019; Yang 2019). Enrofloxacin can be made more soluble or its dissolution rate accelerated using solubilizers (Chen *et al.*, 2019), cosolvent (Lin 2022) and latent solvents (Cui *et al.*, 2017).

Pharmaceutical advancements for improving the palatability of enrofloxacin

In addition to its bitter taste, enrofloxacin has poor oral adaptability and strongly irritates the gastrointestinal tract. Enrofloxacin fed directly to animals most often produces rejection and results in insufficient intake and pharmacological activity is not achieved. Thus, improving the palatability of enrofloxacin and increasing its animal compliance is a primary goal to achieve herd-wide administration plans. Palatability of bitter drugs commonly employ taste corrector excipients. However, physical mixing of veterinary drugs can result in a poor taste correction effect. The use of enrofloxacin : saccharin at 2:1 (w : w) effectively masked the bitter taste in rat feeding experiments and the experimental group consumed~1.5 times as much feed as rats in the control (no saccharin) group (Zhang *et al.*, 2017). Microencapsulation can also improve drug palatability as well as stability (Lu *et al.*, 2014). Calcium alginate- chitosan-enrofloxacin microcapsules were also effective in masking the taste of enrofloxacin (Deng *et al.*, 2013; KeTing 2019). A single coacervation method was used to prepare enrofloxacin taste-masking microcapsules and improved animal compliance (Dai *et al.*, 2016; Bai 2019). Stearic acid solid dispersions and chitosan-alginate particle coating technologies were used to prepare enrofloxacin double-coated taste masking particles. Pigs fed enrofloxacin-containing feed had food intake levels 28.65% less than animals fed the double-coated taste masking preparation and pigs fed a normal diet (Liu *et al.*, 2017). Enteric film coating technology can also conceal the bitter taste of enrofloxacin and enhanced its compliance. A solid enrofloxacin dispersion was prepared by mixing the skeleton materials hydroxypropyl methylcellulose (hydrophilic) with wax stearic acid and lactose, PVP K30 or other excipients to create enrofloxacin particles (Zhang 2013). Interestingly, reducing the enrofloxacin dissolution rates could also improve palatability (Li 2015).

Progress in the development of enrofloxacin sustained-and controlled-release preparations

Enrofloxacin is highly soluble in acid and alkali solutions although its in *vivo* half-life is relatively short. The drug is often administered frequently at regular intervals to maintain steady blood concentrations but this is inconvenient especially for the simultaneous treatment of animal herds. One solution is the use of sustained- and controlled- release preparations and this reduces the pharmacological “peak and valley” phenomena and animal stress and associated adverse reactions.

Solution-type sustained and controlled release preparations are a highly mature technology in the pharmaceutical industry. Enrofloxacin solution dispersions were used to prepare an enrofloxacin sustained-release injectable preparation. *In vitro* release studies revealed 20% cumulative release after 0.5 h and 80.2% of the drug had been released in 12 h. The mean retention time (MRT) in rabbits was ~ 34 ± 9 h (Ren *et al.*, 2012).

Nano-preparations used to create small particles with large specific surface areas allow longer blood circulation times and extend the drug half-life to achieve the purpose of a controlled release (Park 2014). For instance, high pressure homogenization of enrofloxacin nano-suspensions for injection was found to be efficient and achieved maximum plasma concentration (C_{max}) in pigs at ~ 0.32 mg L^{-1} that was reached 0.35 h faster than the control group. The peak time (T_{max}) was 2.88 ± 0.96 h and elimination half-life ($t_{1/2ke}$) was 5.99±1.37 h and these were 2.08 and 1.5 h greater than for the controls, respectively (Yu *et al.*, 2017). Eicosanoic acid as a carrier for enrofloxacin nanoparticle preparation increased bioavailability 1.63-and 2.38-fold compared with commercial injection and soluble powders, respectively. The MRT was also increased from 11.2 and 12.33 h to 37.76 and 35.15 h, respectively (Tao *et al.*, 2019).

Coating technologies not only improve enrofloxacin palatability but also affect the release rate of enrofloxacin *in vivo* resulting in a slow and controlled release of the drug. Enrofloxacin intestinal granules were prepared using a combined solid lipid nanoparticle preparation with enteric coating technology and compared to soluble powder. The area under the plasma concentration-time curve (AUC) and the lifetime decreased from 4.26±0.85 μg h mL^{-1} and 6.80± 2.28 h to 11.24±3.33 μg h mL^{-1} and 17.97±4.01 h, respectively (Li *et al.*, 2019). Therefore, enrofloxacin was significantly improved in both its sustained release and oral bioavailability. A 10% enrofloxacin enteric-coated granule resulted in $t_{1/2}\beta$, T_{max} and AUC values of 14.99±4.19, 3.99±0.10 and 38.93±1.52 μg h mL^{-1}, respectively. In comparison with the third generation cephalosporin c*efpiramide* (Tamicin), enrofloxacin enteric-coated granules displayed superior antibacterial and clinical efficacy *in vivo* (Lei *et al.*, 2017).

Drug release rates can be regulated *via* matrix sustained and controlled release preparations using hydroxypropyl methylcellulose skeletal materials. Enrofloxacin was tested as a model drug with hydroxypropyl methylcellulose that employed a melting method and wet granulation process to prepare enrofloxacin-sustained release granules and tablets, respectively (Li *et al.*, 2017; Gan *et al.*, 2015). These types of polymer materials can also play a significant role in ensuring a controlled and slow release of the drug (Dharadhar *et al.*, 2019). A casein-based delivery system for enrofloxacin for oral administration in rats significantly increased the average plasma concentration of enrofloxacin

and The mean retention time increased from 9.287±0.524 to 11.372±1.139 h and the AUC increased 3.8 times to 20.850±1.7 ìg h mL^{-1}. Therefore, casein significantly enhanced the absorption of enrofloxacin and increased its half-life (Yuan *et al.*, 2021). Another example is the use of a self-emulsifying solvent evaporation method to prepare enrofloxacin polymer micelles using the plastic filament material poly-lactic acid (PLA 16000) combined with the monomethyl ether form of polyethylene glycol (mPEG 2000) as carriers. These micelles increased $t_{l/2}\beta$ of enrofloxacin in mice after intravenous injection from 5.107±0.742 to 12.32±4.676 h and decreased the clearance rate (CL) from 0.869±0.164 to 0.448 ± 0.098 mg kg^{-1} h^{-1}. There was also an increase in the AUC from 5.896±0.935 to 11.691±3.161 µg h mL^{-1} indicating that enrofloxacin micelles were able to provide sustained release *in vivo* (Lian *et al.*, 2011).

Liposomes are ultrafine particles with diameters ranging from several nanometers to several microns and are arranged directionally via phospholipids and drugs can be released slowly through the bilayers (Large *et al.*, 2021). The pharmacokinetics of enrofloxacin after intramuscular injection of enrofloxacin nanoliposomes in mice revealed that tetradecanoic, palmitic and stearic acid-solid lipid nanoparticles (SLN) increased enrofloxacin bioavailability 6.67-, 3.56- and 2.39- fold, respectively. The enrofloxacin MRT (10.60 h) was reached in 180.36 h (Xie *et al.,* 2011). The release rate of enrofloxacin from liposomes prepared with the carriers DL-α-dipalmitoyl phosphatidylcholine (DPPC), cholesterol and α-tocopherol could be modulated by altering the ratios of DPPC, cholesterol and enrofloxacin (Sezer, A.D. *et al.*, 2011). Moreover, enrofloxacin emulsions examined in rabbits extended the drug half- life from 0.249±0.035 to 0.89±0.102 h and $t_{l/2}\beta$ was extended from 1.985±0.862 h to 14.256±4.315) h (Lu 2014).

Research progress of enrofloxacin targeting preparation

Targeting technologies such as the use of microspheres also have significant impacts on drug safety and effectiveness. Enrofloxacin incorporated into lung- targeting microspheres resulted in an increase in the AUC in the lung from 11.66 to 508.00 h µg g^{-1} and Cmax increased from 5.95 to 93.36 µg g^{-1}. Enrofloxacin incorporated into microspheres increased the lung relative uptake rate (Re) to 44.02 while blood and other tissues displayed uptake rates of <1. In addition, the drug was more selective toward the lung and lung targeting was superior to that of muscle (5.3 times) and blood (11.2 times) (Yang *et al.,* 2015). Lung peak concentration of microspheres were also 15.68 times greater indicating that the microsphere significantly altered drug distribution (Kang 2010). Furthermore, enrofloxacin can also be targeted to macrophages using nanoliposomes and thereby effectively treating intracellular bacterial infections (Meng *et al.*, 2020). Drug delivery systems based on the carrier skeleton structures can also be used to deliver targeted drugs (Lai *et al.*, 2013) and γ-cyclodextrin skeletons loaded with potassium ions and enrofloxacin were also successful targeted-delivery vehicles (Wei *et al.*, 2021).

Research progress on other enrofloxacin preparations

Novel enrofloxacin preparations based on the objects of use and the methods of administration can provide new perspectives on the use of enrofloxacin in clinical practice. Based on the physiological characteristics of yak, an enrofloxacin oral gel was developed along with an enrofloxacin nano-emulsion for spray application (Jiang 2016; Xu *et al.*, 2021). In an attempt to prevent and treat systemic infections caused by *Salmonella pullorum* and *Escherichia coli,* enrofloxacin was combined with *Eucalyptus* oil in a self-emulsifying formulation for poultry spray delivery (Qiu *et al.*, 2019). A new enrofloxacin uterine perfusion preparation was also developed and introduced a new approach to the use of enrofloxacin in veterinary clinics (Zeng 2017). Furthermore, enrofloxacin was also formulated as a transdermal application to treat pyoderma in dogs (Wang 2016).

CONCLUSION

In summary, enrofloxacin is a highly effective and broad-spectrum quinolone drug that is widely used in veterinary medicine. It is possible to effectively improve the solubility and palatability of enrofloxacin through pharmaceutical transformation, the addition of appropriate medicinal excipients and the adoption of new technology and means. This can greatly enhance the bioavailability of enrofloxacin in animals. Furthermore, veterinary drugs are continuously being innovated and promoted in new dosage forms and veterinary clinics will also be able to use enrofloxacin preparation products in a more extensive manner.

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Conflict of interest

The authors declare that they have no conflict of interest.

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