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Preparation, Characterization and Evaluation of Dissolution and Taste Masked Enrofloxacin Formulations using Inclusion/Solid Dispersion/Ion-Exchange Resin Approach

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In the present study, solid dispersion and ion-exchange resin techniques were widely used for improving drugs dissolution properties. Several techniques were used to analyze the properties of these enrofloxacin (ENR) formulations, using differential scanning calorimetry, X-ray diffraction, Fourier transform infrared, dissolution study and masking taste. The results obtained showed that the rate of dissolution of enrofloxacin was greatly improved when formulated in ENR/PVP K30 solid dispersion as compared with other formulations and pure enrofloxacin. Ion-exchange resin had the best effect on masking taste.

Keywords: Enrofloxacin, Inclusion complex, Solid dispersion, Ion-exchange resin complex.

INTRODUCTION

Enrofloxacin (ENR), a fluoroquinolone antibiotics, the first developed only for veterinary application. This synthetic drug as bactericidal antimicrobials had shown an excellent antibacterial activity, at relatively low concentrations and produce a post-antibiotics effect[1]. Enrofloxacin has a broad spectrum of antibacterial activity against Gram-negative bacteria, Gram-positive bacteria and mycoplasma species in animals. The mode of action of fluoroquinolones involves interactions with both DNA gyrase, the originally recognise drug target and topoisomerse IV, a related type II topoisomerase[2,3]. In several countries, enrofloxacin has been authorized for application in treatment of bacterial infections in urinary tract, respiratory tract and skin[4].

Enrofloxacin possesses excellent pharmacokinetic properties such as high bioavailability and high volume of distribution. The characteristics of enrofloxacin in most species include good absorption after parenteral and oral application, large volume of distribution, suggesting wide tissue penetration and a terminal half-life in the range of 2 to 6 h. However, the popularization of the traditional enrofloxacin preparation in animal treatment, rapidly developed adverse effects, such as resistant bacteria, drug residue and allergic hypersensitivity reactions[5]. At the same time, the oral absorption of enrofloxacin in adult ruminants is poor, approximately 10 %[6]. This is because of poor aqueous solubility of drug gives rise to difficulties in the design of pharmaceutical formulations and leads to variable bioavailability[7]. In order to improve the solubility and bioavailability of poor water soluble drugs many methods are reported[8,9]. Solid dispersion and cyclodextrin inclusion complexes are actually among the most frequently used[10].

As is reported, oral dosage forms are easily available due to their simple method of administration way, but there are some limitations to the drugs with bitter taste, such drugs are not necessarily easy to swallow for animals. Therefore, various techniques have been developed for improving the problems of the bitter tastes. Use of capsules, coating with polymers, microencapsulation and chemical modification have been reported[11,12]. These methods are very useful for masking the drug taste, but preparation of these dosage forms is not necessarily easy[13].

Compared with other formulations, cyclodextrin inclusion, solid dispersion and ion-exchange resin techniques are easier to prepare, so these techniques were used in improving solubility and masking taste of enrofloxacin. In order to analyze these formulations, several different detections were applied, such as X-ray diffractometry, FTIR spectroscopy, differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). The aims of these detection methods were to investigate the influence of inclusion, solid dispersions and ion-exchange resin on the physico-chemical characteristic of enrofloxacin. For this purpose, comparative studies on the dissolution rates and bitter tastes of enrofloxacin were carried out on these formulations.

EXPERIMENTAL

Enrofloxacin was bought from Zhejiang Xinhua pharmacy Co, Ltd. (Zhejiang, China). Sulfobutyl ether-β-cyclodextrin (SBE_7-β-CD) was synthesized as per according to the literature[14]. Hydroxy propyl methyl cellulose (HPMC) and ethyl cellulose (EC) were purchased from Sigma-Aldrich Co.LLC (Beijing, China), Amberlite IRP64 were provided by Rohm & Hass Company (Pennsylvania, USA). Polyvinyl pylrrolidone K30 (PVP K30) and polyethylene glycol 6000 (PEG 6000)was purchased from Anhui Shanhe Pharmaceutic Adjuvant Co. Ltd. (Huainan, Anhui). Other chemicals and reagents not specified in the text were of analytical grade or equivalent.

Phase-solubility studies

Binary systems' phase solubility: Accurately weighed samples of enrofloxacin 0.15 g, in quantities exceeding its aqueous solubility, with 10 mL aqueous solutions of SBE_7-β-CD in different concentrations (0, 4, 8, 12, 16, 20, 24 mmol/L) in 25 mL conical flasks, then added distilled water to 25 mL. These conical flasks were shaken at 75 °C, for a period of 48 h, until equilibrium was established.

Ternary systems' phase solubility: The other operations were same to binary, just added HPMC (w/v 0.1 %) into each vial.

The content of each vial was filtered though a 0.45 μm membrane filter (millipore, Shanghai), then the concentration of enrofloxacin in the filtered solutions analyzed by spectrophotometer (Shimadzu UV-2450 160A UV/visible spectrophotometer, Shimadzu Corp, Kyoto, Japan) at 278 nm. The standard plot of enrofloxacin in distilled water over a concentration range of 2 to 9 μg/mL at 278 nm was linear with a correlation coefficient of 0.99 ($r^2 = 0.9999$). The presence of SBE_7-β-CD and HPMC did not interfere with the spectrophotometric assay of the drug. Three replicates have been made for each experiment and the results reported were the mean values. The apparent stability constant (K_c) of the 1:1 (guest: host) complex was calculated from the slope of the phase solubility diagrams and the solubility of enrofloxacin in water (S_0):

$$K_c = \frac{\text{Slope}}{S_0(1-\text{slope})}$$

Preparation of drug-CD complex

Binary complex's preparation: Accurately weighed SBE_7-β-CD 4.6766 g, dissolved in 50 mL distilled water, then transformed into round-bottom flask. 0.75 g enrofloxacin was added to the solution of SBE_7-β-CD in a molar quantity corresponding to stoichiometric ratio of 1:1. The resulting solution was mixed and sonicated for 10 min and then heated in water bath at 30 °C for 48 h. After an equilibrium period of 48 h at room temperature, the clear solution was pour into material plate, frozen for 24 h at -20 °C and subsequently lyophilized in a freeze-dryer for 72 h.

Ternary complex's preparation: the other preparations were same to above, just added HPMC (w/v 0.1 %) into the solution.

The binary and ternary physical mixtures were prepared by simply mixing enrofloxacin with SBE_7-β-CD and/or HPMC in responding ratio, respectively. All resultant dried systems were sieved and fractions smaller than 500 μm were collected for further studies.

Solid dispersions and physical mixture preparation: Solid dispersions and physical mixtures were prepared with drug: PVP K30 in 5:5, 4:6, 3:7, 2:8, 1:9 weigh ratios, solid dispersions were by means of evaporation method[15]. Physical mixtures were prepared by mixing manually. The mixtures were passed through a 500 μm mesh sieve.

Solid dispersion particles of enrofloxacin were prepared by evaporation method. PVP K30 and enrofloxacin in 5:5, 4:6, 3:7, 2:8, 1:9, totally weighed. The minimum amount of dichloromethane was added to dissolve the above-mentioned physical mixtures. This suspensions were evaporated in an evaporator with a rotation speed of 40 rpm at 40 °C for 25 min. The resultant solid dispersion in a flask was softly ground by a mortar and pestle. All solid dispersion particles were dried in a desiccator with blue silica gel under reduced pressure for 1 day before testing their physico-chemical properties.

Preparation of ion-exchange resin complex: Purified Amberlite IRP64 resin (2 g) was placed in 0.1 mol/L HCl 26 mL of enrofloxacin (1 g) aqueous solution, added water to 250 mL scale. The mixture was stirred for 4 h on a magnetic stirrer at 30 °C constant temperature water bath and intermittently the supernatant was removed to find out the amount of drug loaded in the resin. The enrofloxacin /ion exchange resin complex was retrieved by filtration and washed repeatedly with 250 mL distilled water until the free drug was removed. The complex were dried at 60 °C for 3 h and stored in a desiccator. The drug content in the final filtrate and the supernatant were measured absorbance at 278 nm.

DSC and TGA measurement: Each sample was weighed (5 mg) in an aluminum crucible and subjected to a temperature gradient ranging from room temperature to 300 or 500°C (heating rate of 10°C/min) using a TGA/ DSC1/1100LF (Meltter/ Tory Company, Switzerland) in inert atmosphere (argon) at a flow rate of 30 mL/min.

XRD measurement: X-Ray diffraction analysis were performed in a D/MAX-1200 X-Ray diffractometer instrument (Neo-Confucianism Motor Co. Ltd., Japan) with CuK_α monochromatic. Diffractograms were collected under conditions of 40 KV, 30 mA, with the scanning angle 2θ set from 3° to 45° at a scanning rate of 0.02 °/s.

Fourier transform infrared spectroscopy (FTIR): FTIR spectra were collected using a Nicolet iN10 (Thermo Fisher Scientific Inc.) by the KBr method at ambient room temperature. Transmission spectra were obtained for KBr disks containing 1-1.5 % sample at a resolution of 0.5 cm^{-1} within the range of 4000-400 cm^{-1}.

Dissolution studies: Dissolution studies were performed using eight station dissolution test apparatus (ZRS-8G, Tianjin TATF science and technology Co, Ltd China). Dissolution study was carried out in a 900 mL pH 6.8 phosphate buffer, maintained at 37 ± 0.5 °C. The dissolution medium was stirred with a rotating paddle (50 rpm). 5 mL samples were withdrawn at time intervals of 5, 10, 15, 20, 25, 30, 40, 45 and 60 min. The withdraw volume of dissolution medium was not compensated to 900 mL. The concentrations of drug in samples were filtered and determined by measuring the absorbance at 278 nm. Cumulative percent drug release was determined at each time interval. All experiments were carried out in triplicate.

Taste perception test: Taste perception tests were carried out according to the method described by Lee *et al*[16]. Six human volunteers, in the age group of 24-30 years, were chosen. Volunteers were ordered to taste samples kept in the mouth for 5s. All unknown samples were randomly supplied to each volunteer in a blind manner, then spat out and the volunteers recorded bitterness level. A numerical scale was used with the following values: 0 = tasteless, 0.5 = very slightly bitter, 1 = slightly bitter, 1 = slightly bitter, 1.5 = slightly to moderately bitter, 2 = moderately bitter, 2.5 = moderate to strong bitter, 3 = strong bitter, 3+ = very strong. After each trial, the oral cavity was rinsed with tap water to remove excess sample in the buccal membrane. To find a suitable amount of drug for the evaluation of the bitter taste intensity, perception tests were conducted to identify the bitterness recognition threshold of pure enrofloxacin. In order to evaluate the effect of tastes masking by inclusion complex, solid dispersion and ion-exchange resin complex, a taste perception test was performed.

RESULTS AND DISCUSSION

Phase solubility studies: Traditional phase solubility analysis the effect of complex agents on the drug compound provides not only the stability constant of the complex but also insight into the stoichiometry of the complex at equilibrium. The phase solubility diagrams were obtained by plotting the apparent equilibrium concentrations and are shown in Table-1 and Fig. 1.

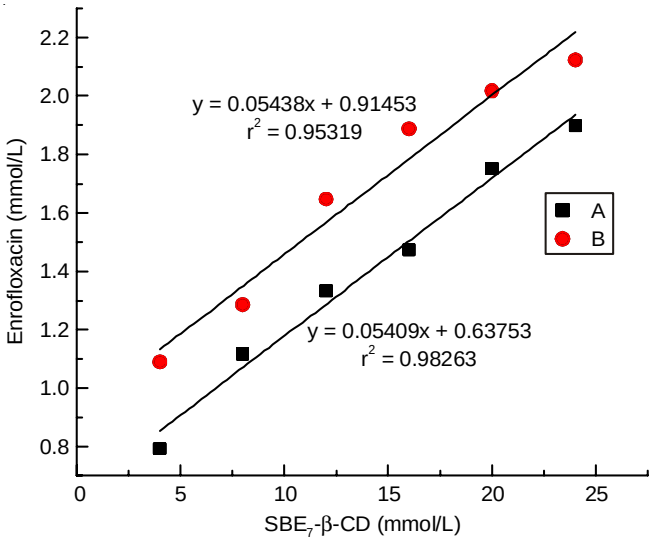

Fig. 1. Phase solubility diagrams for enrofloxacin in the presence of SBE_7-β-CD without HPMC (A) and with 0.1 % (w/v) HPMC (B)

For the binary and ternary system, SBE_7-β-CD enhances the aqueous solubility of enrofloxacin. This diagram showed a linear relationship between the amount of enrofloxacin solubility and the concentration of SBE_7-β-CD in solution over the entire concentration range studied. This linearity was characteristic of an A_L-type system, as described by Higuchi and Connors[17] and suggested the formation of inclusion complexes in a 1:1 ENR/SBE_7-β-CD molar ratio and the formation of a soluble complex. The stability constant (K_c) for binary and ternary of the complex calculated from the slope of the initial straight portion of the solubility diagrams was 111.2 M^{-1} and 90.4 M^{-1}. Both stability constants were relative small, suggest that the enrofloxacin and SBE_7-β-CD had formed complex, but with poor stability.

DSC and TGA: Fig. 2.1 shows characteristic thermograms for pure enrofloxacin, physical mixtures and inclusion complexes. The first run on enrofloxacin showed a pronounced melting endothermic peak in 226 °C, accompanying weightlessness suggested that begins to break down. At about 340 °C had a weak endothermic peak, may be a flash point of enrofloxacin. At about 425 °C had an obvious exothermic peak, accompanied with great weightlessness, suggested that the decomposition and exothermic of enrofloxacin. SBE_7-β-CD(A1)at about 75 °C had an endothermic peak, at the same time with less weight loss. This was caused by the evaporation of water. At 200 °C had an endothermic peak, may be caused by the melting, at the same time, started to break down. At 250 °C had an exothermic peak, with about 14 % of weightlessness, could be decomposed releasing the gas. HPMC (A2) had a unique endothermic peak in 70 °C, with 5 % of weightlessness, which is caused by the moisture to evaporate. Binary physical mixture (A3) and inclusion complex (A4) at 226 °C showed enrofloxacin of endothermic melting peak. But because of its high proportion of SBE_7-β-CD, the intensity is low. Also at 75 °C showed an endothermic peak of evaporation process, the latter peak shape was relatively wide. At 250 °C, there was no SBE_7-β-CD endothermic peak. This may be due to enrofloxacin and SBE_7-β-CD in physical mixture after melting have occurred inclusion. Physical mixture at about 200 °C had a weak endothermic peak, but hardly seen this peak in inclusion complex. This may due to interaction between SBE_7-β-CD and enrofloxacin. The ternary physical mixtures and inclusion complex were similar to the binary.

Fig. 2.2 shows that PVP K30 (B1) at about 83 °C had an endothermic peak, with 10 % lose weight, which was contributed to evaporation. Ethyl cellulose (B4) had a slight weightless before 100 °C, owning to moisture evaporation. At about 190 °C, had a slight endothermic peak. The ENR/PVP K30 physical mixture present the peak at 80 °C, without melting peak of enrofloxacin, which suggested that before reach the fusion point, the crystal of enrofloxacin has slowly melt in PVP K30. The ENR/PVP K30 solid dispersion (B3) had sole endothermic peak at 83 °C, which suggests that enrofloxacin is highly dispersed in PVP, exists as amorphous and crystal inhibited. The ENR/PVP K30/EC physical mixture (B5) and solid dispersion (B6) are similar to binary systems.

TABLE-1
CONCENTRATION OF ENROFLOXACIN IN DIFFERENT SBE_7-β-CD SOLUTIONS

SBE_7-β-CD (mmol/L)	0	4	8	12	16	20	24
Enrofloxacin (mmol/L)	0.522	0.793	1.117	1.335	1.473	1.752	1.899
Enrofloxacin (mmol/L, 0.1 % HPMC)	0.636	1.089	1.287	1.648	1.888	2.018	2.125

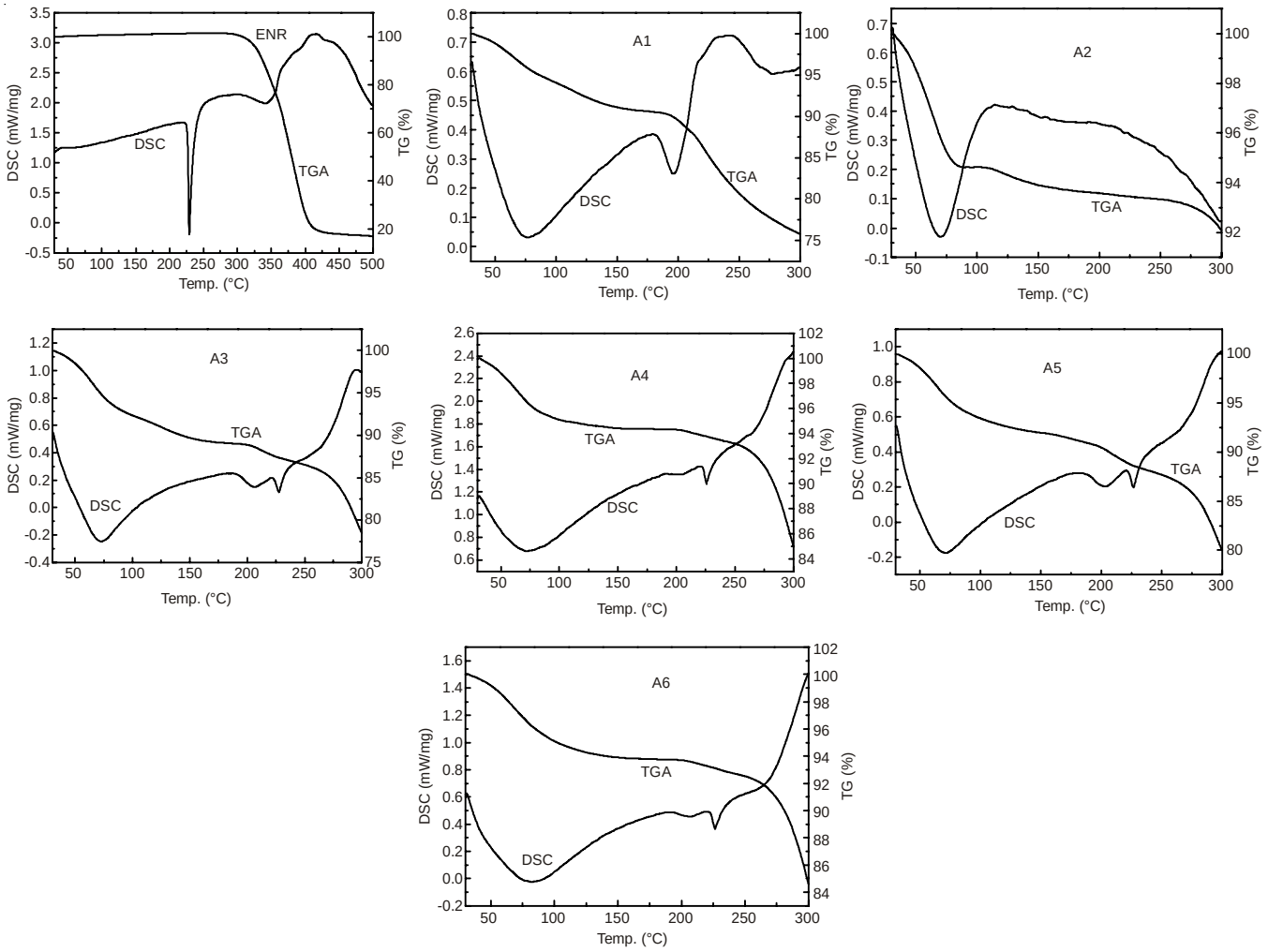

Fig. 2.1 DSC-TGA curves of enrofloxacin (ENR), SBE_7-β-CD(A1), HPMC(A3), ENR/SBE_7-β-CD physical mixture (A3) and inclusion complex (A4) at 30°C, enrofloxacin ENR/SBE_7-β-CD/HPMC physical mixture (A5) and inclusion complex (A6) at 30 °C

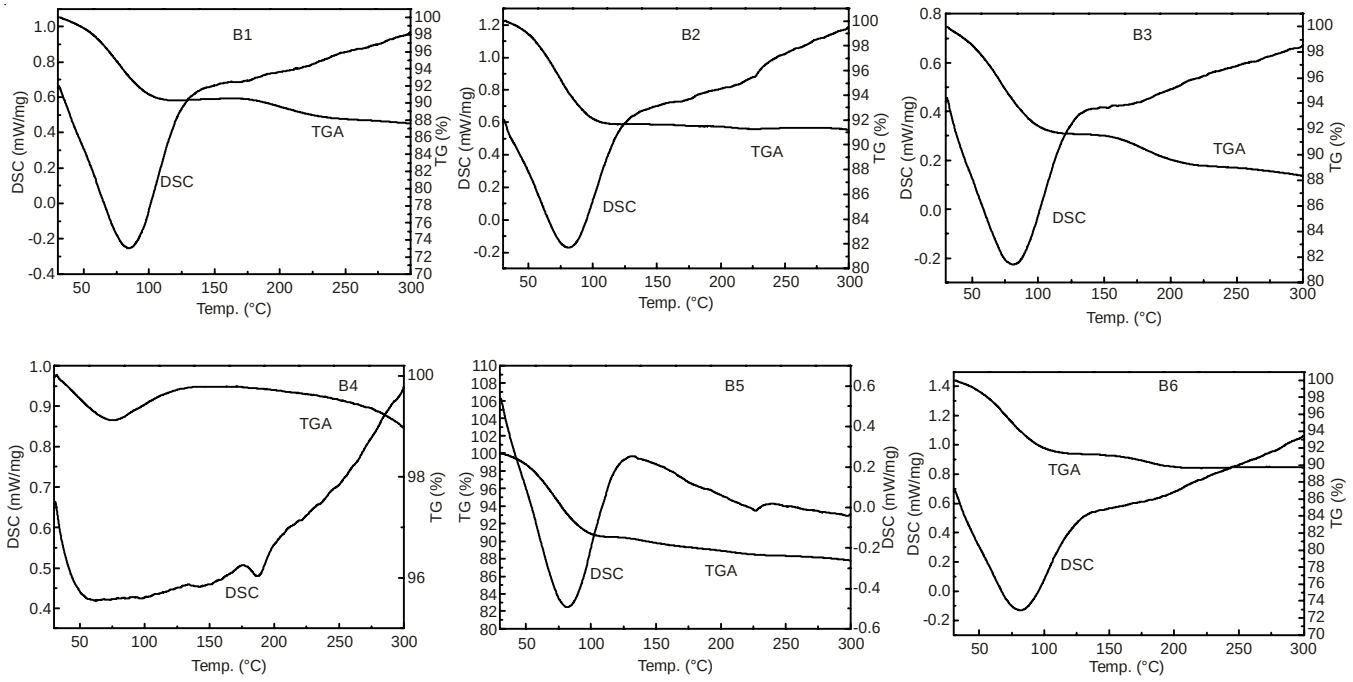

Fig. 2.2 DSC-TGA curves of PVP K30 (B1), ENR/PVP K30 physical mixture (B2), ENR/PVP K30 solid dispersion (B3), EC(B4), ENR/ PVP K30/EC physical mixture (B5), ENR/PVP K30/EC solid dispersion (B6)

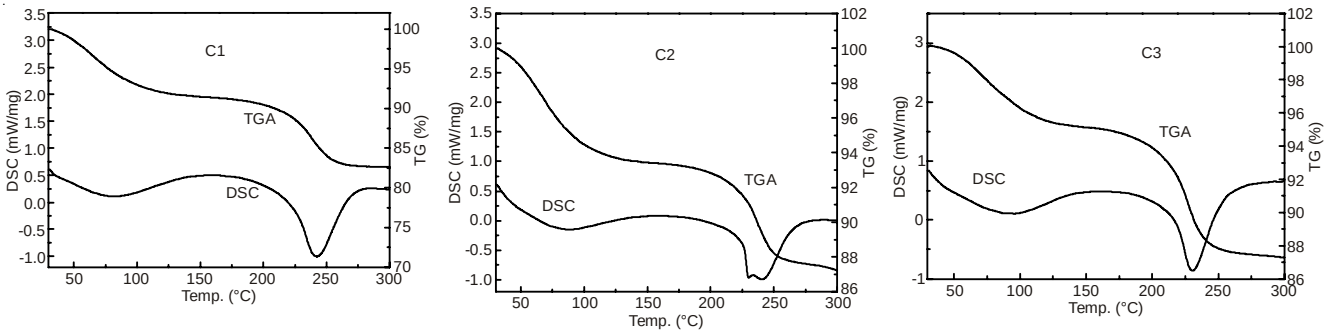

Fig. 2.3 DSC-TGA curves of amberlite IRP64 resin (C1), ENR/Resin 1:2 physical mixture (C2) and ENR/Resin 1:2 Complex (C3)

Fig 2.3 shows that Amberlite IRP64 resin (C1) had an endothermic peak, accompanying with lightly weightless, which contributes to moisture evaporation. There was an endothermic peak at 240 °C, with 8 % weightless, maybe released some small molecule material. enrofloxacin/resin physical mixture had several endothermic peaks except 80 °C, but also at 227 and 240 °C, respectively reserved peaks, the melting peak of enrofloxacin and endothermic peak of resin. It is obvious that thermogram of physical mixture is simply thermal behaviour overlay enrofloxacin and resin. While the enrofloxacin/resin compound had endothermic effect at 100 °C, companying with evaporation. In addition, at 230 °C present a endothermic peak, the shape of the peak is not intense as the peak of enrofloxacin at 226 °C. This suggests that there are some interaction between the enrofloxacin and resin.

XRD: X-ray patterns (Fig 3.1) of enrofloxacin shows sharp peaks between 7.36° and 27.59°, while SBE_7-β-CD (A1) and HPMC (A2) show no sharp peaks, suggesting that they are existing as amorphous. All spectrograms of binary and ternary system (A3, A4, A5 and A6) show more or less characteristic peaks of enrofloxacin. The peak intensity are weaker than enrofloxacin, which attributes to auxiliary material is

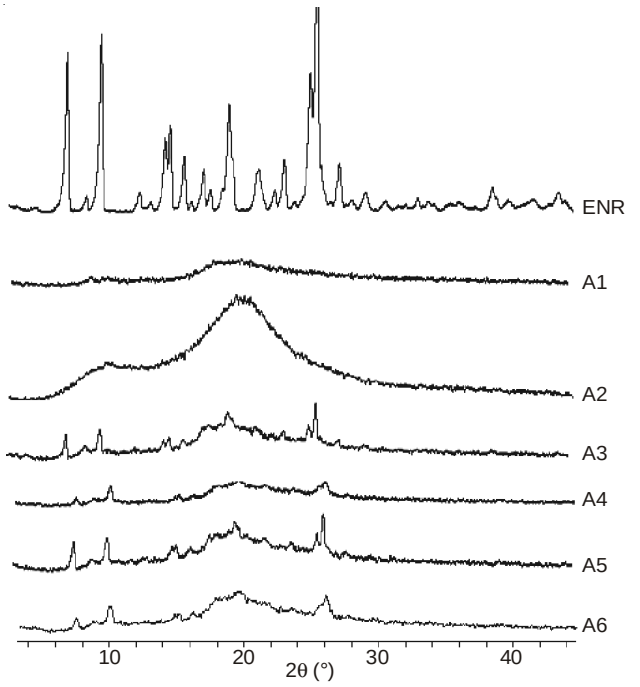

Fig. 3.1 X-ray diffraction patterns of enrofloxacin (ENR), SBE7-β-CD (A1), HPMC (A2), ENR/SBE_7-β-CD physical mixture (A3) and inclusion complex (A4), ENR/SBE_7-β-CD/ HPMC physical mixture (A5) and inclusion complex (A6)

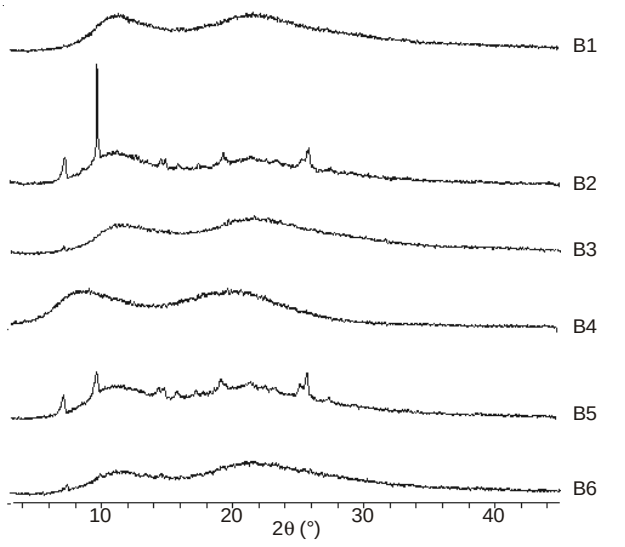

Fig. 3.2 X-ray diffraction patterns of PVP K30 (B1), ENR/PVP K30 physical mixture (B2), ENR/PVP K30 solid dispersion (B3), EC(B4), ENR/PVP K30/EC (1:8:1) physical mixture (B5) and ENR/PVP K30/EC (1:8:1) solid dispersion (B6)

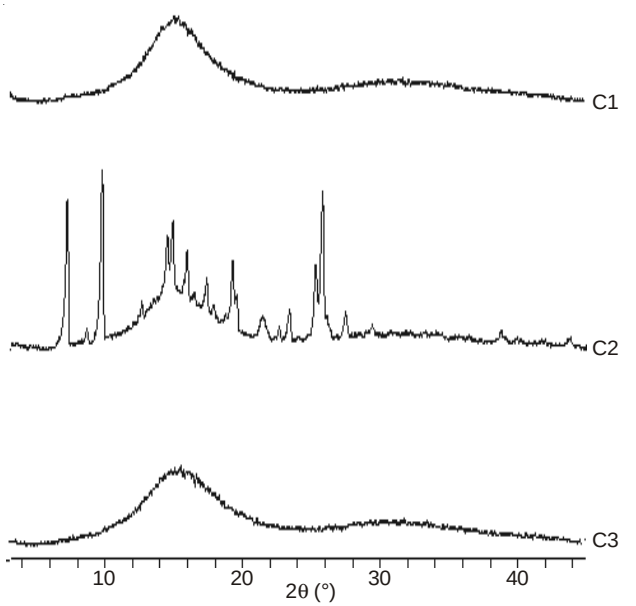

Fig. 3.3 X-ray diffraction patterns of Amberlite IRP64 resin (C1), enrofloxacin/resin 1:2 physical mixture (C2) and enrofloxacin/resin 1:2 complex (C3)

quantity, while enrofloxacin is relatively few. The enrofloxacin spectrograms of inclusion complexes (A4, A6) are obviously weaker than the physical mixtures (A3, A5). These characteristic peaks proved that the enrofloxacin and SBE_7-β-CD has produced inclusion effect, but the interaction between enrofloxacin and SBE_7-β-CD is not very obvious. In addition, the spectrograms of binary and ternary compound have no significant difference. In some ways, the promotion of HPMC is lightly. Thus indicates that add a small amount macromolecular polymer in the complex couldn't promote the inclusion effect.

PVP K30 is an amorphous polymer compound, X-ray pattern (Fig 3.2) shows no characteristic peaks. X-ray pattern of enrofloxacin/PVP K30 physical mixture shows the several characteristic peaks of enrofloxacin, such as diffraction in 7-10° and nearby 26°. But in corresponding spectrograms of solid dispersion, characteristic peaks of enrofloxacin were not showed, indicating that enrofloxacin crystals were transformed to an amorphous or a microcrystalline form and scattered in PVP K30 in molecular form. By this way, dissolution of enrofloxacin in the solid dispersion improved obviously. X-ray diffraction spectrum of ethyl cellulose showed no sharp peaks attributes to it is an amorphous material. In ENR /PVP K30/ EC physical mixture spectrum shows several enrofloxacin characteristic peaks, but the intensity was weak, which donates to drug content is low. The corresponding solid dispersion spectrum shows hardly characteristic peaks of enrofloxacin. The spectrum of ENR/PVP K30/EC indicate that add a portion of ethyl cellulose have some effect on suppression of crystal.

Amberlite IRP64 resin X-ray pattern (Fig 3.3) shows no sharp peaks, indicating resin is an amorphous polymer. enrofloxacin/resin physical mixture spectrum shows several enrofloxacin characteristic peaks, but no one in the complex, which is similar to Amberlite IRP64 resin spectrum. This may attribute to enrofloxacin highly distract in resin, present in molecular shape after ion exchange.

Fourier transformation infrared spectroscopy: In order to further study the possibility of an interaction of enrofloxacin with PVP K30, EC and resin. Fig 4.1, 4.2 and 4.3 illustrate FTIR spectra of enrofloxacin, PVP K30, solid dispersion, resin, physical mixtures and ion-exchange resin. IR spectrum of enrofloxacin was characterized by principal absorption peak at 3433 cm^{-1}(O-H stretch carboxyl groups), 1737 cm^{-1} (C=O stretching carboxyl groups), 1629 cm^{-1} (-C=O in 4-pytidine ketone), 1256 cm^{-1} (C=O stretch carboxyl groups), 1509 cm^{-1} (benzene ring frame vibration), 1471 cm^{-1} (benzene ring frame vibration).

The IR spectrum of PVP K30 shows a wide absorption peak at 3414 cm^{-1} due to -OH and the carbonyl stretching band of the carboxyl groups at 1664 cm^{-1}. ENR/PVP K30 physical mixture spectrum shows peaks of enrofloxacin with decrease in the peak intensity. However some peaks of enrofloxacin at 1737 and 1629 cm^{-1}, along with benzene rings frame vibration characteristic peaks. While in solid dispersion counterpart, the spectrum shows no absorption peak, but at 3443 cm^{-1} had a wide absorption peak. These changes occurred in IR spectra of binary system indicate formation of complex in solid state, from the structure groups. It was probably formed hydrogen bonds. This is similar to the reports that the cooperative

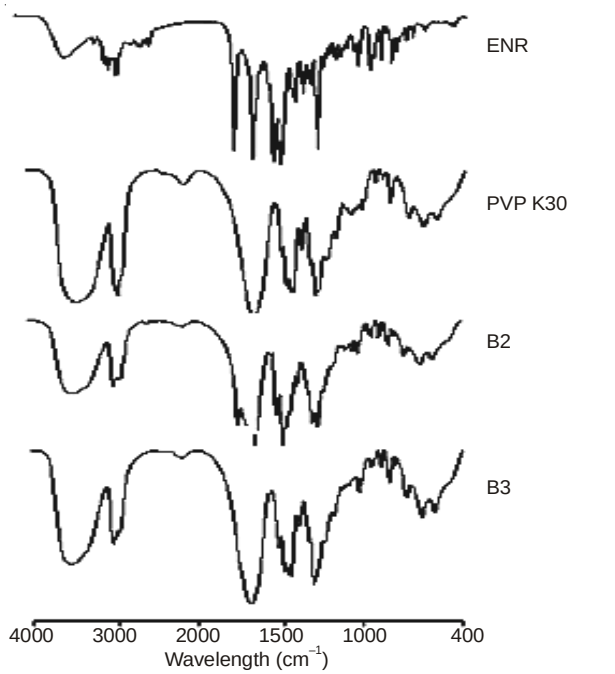

Fig. 4.1. IR spectra of enrofloxacin (ENR), PVP K30, ENR/PVP K30 PM (B2) and ENR/PVP K30 (B3)

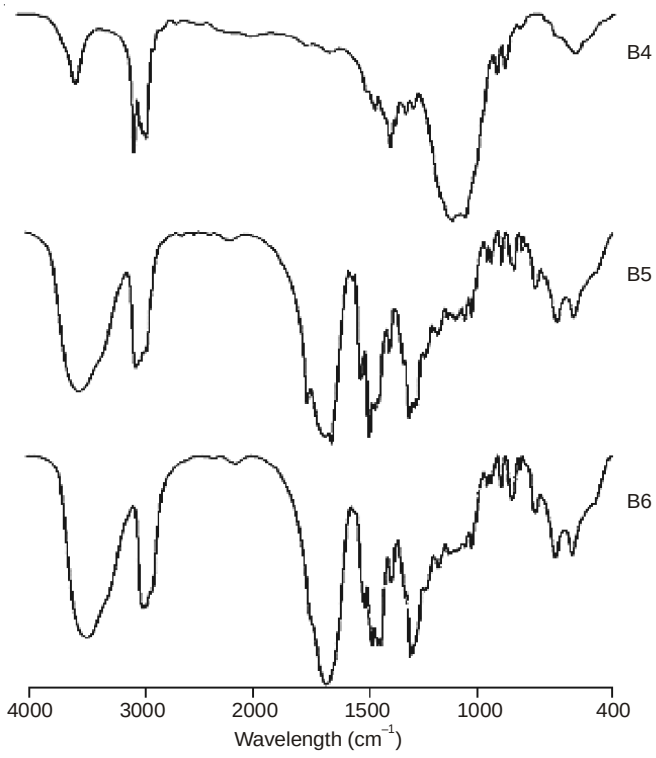

Fig. 4.2. IR spectrum of EC (B4), ENR/PVP K30/EC PM (B5) and ENR/ PVP K30/EC SD (B6)

interaction among polymer chains plays an important role in complex formation[18,19].

The FTIR spectrum of ethyl cellulose shows at 3487 cm^{-1} had a sharp absorption peak, speculating this was O-H of hydroxyl stretching vibration absorption peak, a sharp absorption peak at 2978 cm^{-1}, a sharp strong absorption peak, respectively belonged to C-H and C-O stretching vibration of -OCH_2-. The physical mixture and solid dispersion of enrofloxacin/

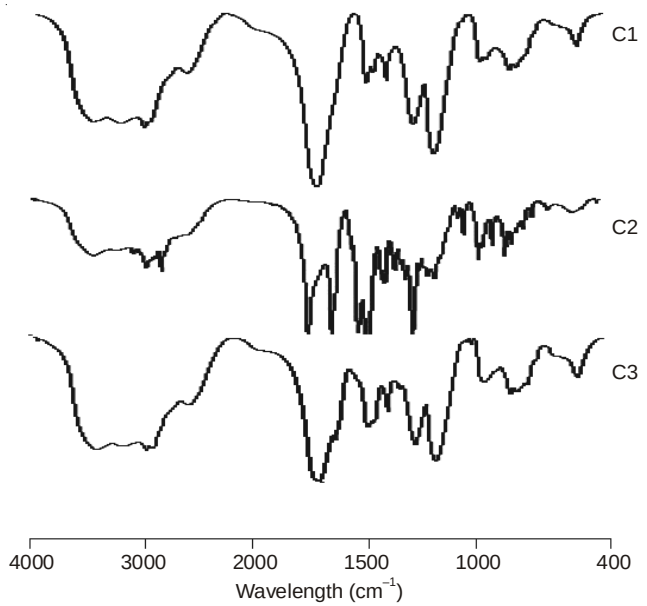

Fig. 4.3 IR spectra of IRP64 resin (C1), ENR/IRP64 resin PM (C2) and ENR/IRP64 resin complex (C3)

PVP K30/EC spectrums show that all of them had broad absorption peak at 3460 cm^{-1}, no absorption peak of ethyl cellulose at 1111 cm^{-1}. The characteristic peak of enrofloxacin presents in the physical mixtures, but disappeared in solid dispersion, which shows the characteristic peak of PVP K30 at 1663 cm^{-1}. These results suggest that there were some chemical interaction between enrofloxacin, PVP K30 and ethyl cellulose, which deduce to hydrogen-bond interaction.

Amberlite IRP64 resin IR spectrum shows absorption peak at 3457 cm^{-1}, donating to O-H of carboxyl stretching vibration, absorption peak at 1706 cm^{-1}, donating to C=O of carboxyl stretching vibration, characteristic peaks at 1173 and 1268 cm^{-1}, donating to vibration coupling of carboxyl C-O stretching vibration and O-H bending vibration. The spectrum of enrofloxacin/resin physical mixture reserved characteristic absorption peaks of enrofloxacin, while the complex spectrum just reserved absorption peak at 1630 cm^{-1}. The physical mixture spectrum had strong absorption peaks at 1171, 1263 and 1711 cm^{-1}, corresponding to absorption peaks of resin spectrum at 1173, 1268 and 1706 cm^{-1} and a strong peak at 3448 cm^{-1}. With enrofloxacin disposed by the resin, the absorption peaks of enrofloxacin disappeared and displaced. Thus it can be seen that there are some interactions between enrofloxacin and Amberlite IRP64 resin, indicating formed complex.

Dissolution rate studies: Fig. 5 shows *in vitro* dissolution profiles of enrofloxacin from its inclusion complexes, solid dispersions and ion-exchange resin compound. Untreated enrofloxacin exhibited a relatively slower dissolution rate, in which about 11 % were dissolved within the first 5 min. In addition, only 64 % of enrofloxacin was dissolved after 120 min. The extent and rate of enrofloxacin from binary and ternary inclusion complexes increased obviously compared with that of free enrofloxacin. Different dissolution rates of free enrofloxacin and inclusion complex might be due to their different solubility and hydrophilic characteristics. Cumulative dissolution rate for binary and ternary system are about 60 %, at 5 min. In the end, the rates of binary and ternary are 88 and 93 % respectively.

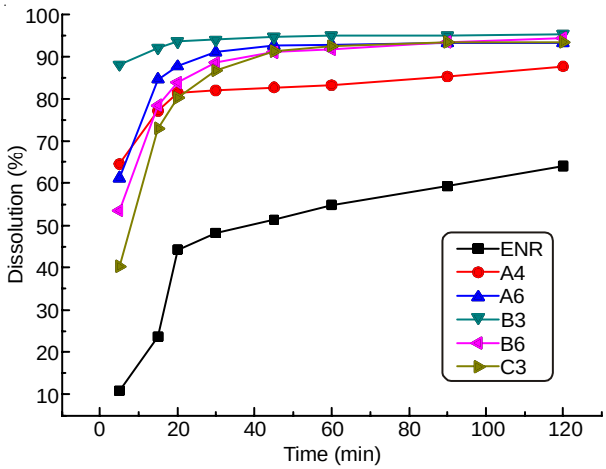

Fig. 5. Dissolution profiles of enrofloxacin (ENR), ENR/SBE$_7$-β-CD inclusion complex (A4), ENR/SBE$_7$-β-CD/HPMC inclusion complex (A6), ENR/PVP K30 1:9 solid dispersion(B3), ENR/PVP K30/EC solid dispersion (B6) and ENR/RESIN complex (C3) in pH 6.8 phosphate buffer

The dissolution profiles of ENR/PVP K30 and ENR/PVP K30/EC are shown in Fig. 5. Solid dispersions in all PVP K30 exhibited faster dissolution rates than pure drugs and eventually dissolubility are above 90 %. The ENR/PVP K30 had the best solubility for it arrive 87 % at 5 min. The enhanced dissolution rate of enrofloxacin from solid dispersions might be due to drug wettability increased, particle size reduced and interactions between drug and auxiliary material. Compared with ENR/PVP K30, dissolubility of ENR/PVP K30/EC solid dispersion was significantly slow in the first 20 min, indicating that EC prevent drug dissolving out. As a result of these studies, the best dissolution rate is obtained with PVP K30 alone. Due to low solubility of enrofloxacin, its solubility after formulation of solid dispersions was investigated. These results indicate higher solubility of enrofloxacin from 1:9 ENR/PVP K30 solid dispersion than corresponding 1:8:1 ENR/PVP K30/EC solid dispersion.

Fig 5 demonstrates the drug release studies of the ion-exchange resin complex, which exhibited faster dissolution rates than pure drugs. At 5 min, drug release rate of ion-exchange resin complex is 40 %, while the pure drug is 11 %. Eventually dissolubility of ion-exchange resin complex arrive 93 %, the pure drug just 64 %. Explanation from X-ray diffraction, enrofloxacin crystals were transformed to an amorphous in resin, distributing in resin as molecular. enrofloxacin was easily exchanged by ion in the dissolution medium. The ion exchange mechanism was the prime cause of drug release, then diffusing into the solution. The drug release rate increased due to the increased surface area of resin complex.

From above observations, it was concluded that all formulations showed faster dissolution as compared to pure drug. Dissolution rate of pure enrofloxacin is less because of its hydrophobic nature. The rapid dissolution of enrofloxacin from formulations may be attributed to drug dispersed in hydrophilic carrier matrix.

The drug in inclusion complexes showed superior performance in dissolution properties than solid dispersions and ion-exchange complex. This may be due to increased proportion of water soluble carriers in inclusion complex. As soluble

TABLE-2
RESULTS FOR THE THRESHOLD OF BITTER TASTE OF ENROFLOXACIN

	Enrofloxacin (mg/mL)								
Volunteer	0.125	0.25	0.5	1.0	2	4	8	16	25
1	0	0.5	1.0	1.5	2.0	2.0	2.5	3.0	3.0+
2	0	0.5	1.0	1.5	2.0	2.5	2.5	3.0	3.0+
3	0	0.5	1.0	1.5	2.0	2.0	2.5	3.0	3.0+
4	0	0	0.5	1.0	1.5	2.0	2.5	3.0	3.0+
5	0	0	0.5	1.0	2.0	2.5	2.5	3.0	3.0+
6	0	0.5	1.0	1.5	2.0	2.5	2.5	3.0	3.0+

carrier dissolution, the insoluble drug gets exposed to dissolution medium in the form of very fine particles for quick dissolution.

Taste perception test: Bitterness evaluation is listed in Tables 2 and 3. The mean bitter score of 1 mg/mL enrofloxacin is 1.33. The results demonstrated that the bitterness recognition threshold was 1 mg/mL. Thus 1 mg/mL was selected as the suitable amount for this study. To evaluate the taste masking ability among the samples, volunteers were ordered to taste the samples, the formulations equivalent to 1 mg/mL enrofloxacin and rate them on the numerical scale.

TABLE-3
RESULTS FOR THE BITTER TASTE SCORES OF ENROFLOXACIN PREPARATIONS

Volunteer	Score				
	A4	A6	B3	B6	C3
1	1.0	1.5	2.5	1.5	0
2	1.0	1.5	2.5	2.0	0
3	1.5	1.5	2.5	1.5	0
4	1.5	1.5	2.5	1.5	0
5	1.5	1.5	2.5	1.5	0
6	1.5	1.5	2.5	2.0	0

The mean score of ENR/PVP K30 solid dispersion (B3) indicates that the formulation sufficiently promoted the bitterness of enrofloxacin. Compared with a mean score of other formulations, this contributes to the higher solubility of enrofloxacin in ENR/PVP K30 solid dispersion. While in ENR/PVP K30/EC solid dispersion (B6), with the addition of ethyl cellulose, the solubility of enrofloxacin decreased, consequently the bitter score of enrofloxacin is quite smaller than the solid dispersion without ethyl cellulose. Indicating that add some ethyl cellulose could decrease the gustatory sensation.

The bitter tastes of binary (A4) and ternary inclusion complexes (A6) are similar to reference suspension, maybe contribute to the solubility of enrofloxacin in inclusion complex change lightly.

It is worthy to mention that ENR/ion-exchange resin complex (C3) shows no bitter taste, indicating dissolution of the drug content is extremely low, totally inhibited the bitter taste. Although in former dissolution test, enrofloxacin/ion-exchange resin complex shows better dissolution performance than enrofloxacin. The bitter taste inhibited maybe contribute to ion-exchange resin enwraps the bitter tasting drug, impeding its interaction with the buds. The result is that enrofloxacin of ion-exchange resin dose not attach to the taste-dud receptors in mouth cavity and thus reduces bitterness.

Conclusion

The increase in dissolution rate of enrofloxacin might be achieved with all of these formulations. The results of dissolution study showed that enrofloxacin/PVP K30 solid dispersion had the fastest dissolution rate than other formulations and enrofloxacin itself. While ion-exchange resin complex has the best effect on taste masking. The experiment results indicate that SBE_7-β-CD in binary and ternary system have lightly changed solubility and taste masking. Inclusion technique improved the dissolution rate in phosphate buffer, indicating that inclusion complex may promote enrofloxacin absorption use, has biology effect.

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