Original Research Paper

Development and evaluation of taste-masked dry suspension of cefuroxime axetil for enhancement of oral bioavailability

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\textbf{A B S T R A C T}

Cefuroxime axetil (CA) is an ester prodrug of cefuroxime with an unpleasant taste when administrated orally. This work was to mask the bitter taste of CA and enhance its oral bioavailability. Dry suspensions were prepared by means of wet granulation method and solid dispersion method. Binders, suspending agents and other compositions involved in the formulation were optimized. The differential scanning calorimetry (DSC) analysis indicated that CA was amorphous in the solid dispersion with stearic acid as the carrier, which contributed to an improvement of the dissolution rate. Taste evaluation was performed by three volunteers and taste masking was successfully achieved by the methods mentioned above. A pH 7.0 phosphate buffer was adopted to study the in vitro dissolution performance of the three formulations, i.e., two self-made dry suspensions and the commercial one. With a better release characteristic and a satisfying taste masking ability, the solid dispersion suspension was selected as the optimal formulation for the further pharmacokinetic study in beagle dogs. The values of $C_{\text{max}}$ and $\text{AUC}_{0\text{-}12}$ for the solid dispersion suspension were about 1.78-fold and 2.17-fold higher than these of reference suspension, respectively. The obtained results demonstrated that the solid dispersion can efficiently mask the bitter taste of CA and significantly enhance its oral bioavailability.

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1. \textbf{Introduction}

Cefuroxime axetil (CA) is an ester prodrug of cefuroxime, a second generation semi-synthetic cephalosporin antibiotic. Cefuroxime is stable to $\beta$-lactamase and demonstrates a broad-spectrum antibacterial activity against both Gram-positive and Gram-negative microorganism by inhibiting the synthesis of the bacterial cell walls. Cefuroxime is hardly...
absorbed when administrated orally, whereas with a 1-acetyloxethyl ester modification, the prodrug CA displays antibacterial activity in oral delivery[1,2]. After oral administration, CA is absorbed, and then rapidly hydrolyzed by the non-specific esterases which is distributed in the intestinal mucosa and portal blood, and ultimately transformed into the pharmacological active molecule cefuroxime [3]. The chemical structure of CA is shown in Fig. 1. The esterification has no impact on the antibacterial efficiency of cefuroxime. But like other water-insoluble drugs, CA has a limited solubility and dissolution rate in the gastrointestinal tract [4,5]. Furthermore, CA has an unpleasant taste which is likely to result in poor patient compliance, especially in the case of children and infants. Hence, taste masking and improving oral bioavailability are the key issues in the present work.

Oral administration is preferred among the various drug delivery systems, due to these advantages, such as safety, convenience, good patient compliance and so on. However, for the medicinal agents having unpleasant taste, oral delivery tends to be unfavorable. It is reported that the bitter substances interact with the taste buds and thus causing a negative sensory response [6]. Besides the conventional incorporation of flavors and sweeteners, there have been various approaches to solve this problem by employing various of dosage platforms such as fast dissolving platform, physical barriers, chemical or soluble modification and solid dispersion technology [6,7]. Among the above methods, solid dispersion gains great interest because it cannot only mask the bitter taste, but also enhance the dissolution rate for water-insoluble drug and consequently increase the oral bioavailability [8].

The commercial formulations available now include tablet, capsules, dispersible tablet and granules. In this work, we attempt to develop a taste masked dosage form of CA by employing dry suspension. Oral suspension is preferred to many patients because of the ease of swallowing and the flexibility in the administration. It is particularly advantageous for children, the elderly and infants, in the meantime, the unpleasant taste of the bitter medicinal agents can be overcome by administrating as undissolved particles. Dry powders for suspension are more desired due to their stability and convenience [9].

Dry suspension of CA was well prepared with wet granulation method and solid dispersion method in the present work. A simple and most used method for the preparation of solid dispersion, melting method [8] was adopted to prepare the solid dispersion. The in vitro and in vivo characteristics of the two self-made dry suspensions and its commercial formulation were evaluated.

2. Materials and methods

2.1. Materials

Cefuroxime axetil and the cefuroxime axetil commercial dry suspension (Yuntai®, NO. 20100503) were purchased from Shandong Lukang Pharmaceutical Group Co., Ltd. (China). Micronization silica gel, orange flavor concentration were purchased from Beijing Fengli Jingqiu Commerce and Trade Co., Ltd. (China). PVP K30 and microcrystalline cellulose were kindly supplied by BASF Co., Ltd. (Shanghai, China) and Anhui Sunhere Pharmaceutical Excipients Co., Ltd. (China), respectively. Stearic acid and HPMC E5 were purchased from Huzhou Zhanwang Pharmaceutical Factory (China). Pregelatinized starch was purchased from Shanxi Huaqi Commerce and Trade Co., Ltd. (China). Xanthan gum was purchased from Deosen Biochemical, Ltd. (Shandong, China). Xylitol was purchased from Futaste Co., Ltd. (Shandong, China). Aspartame was purchased from Changzhou Niutang Chemical Co., Ltd. (China). Acesulfame potassium was purchased from Beijing Weiduo Chemical Co., Ltd. (China). PEG6000 was purchased from Tianjin Kermel Chemical Reagent Co. Ltd. (Tianjin, China). Methanol and acetonitrile of chromatographic grade were purchased from Concord Technology Co., Ltd. (Tianjin, China). Cefuroxime Standard (91.6%, NO. 130943–200704) and glimepiride Reference Standard (99.9%) were purchased from National institutes for food and drug control. Deionized-distilled water was used throughout this study.

2.2. Preparation of cefuroxime axetil suspension by wet granulation method

Accurately weighed amounts of cefuroxime axetil and micronization silica gel (passed through 100-mesh sieve, respectively) were mixed together until uniform. Certain amounts of PVP K30, pregelatinized starch and powdered sucrose according to the formular were prepared in the same way. After the two mixtures being blended homogeneous, a liquid binder was added to facilitate the powder particles adhesion and prepared the damp mass. The resultant wet mass was screened into granules through a 60-mesh sieve, and then be dried in thermostatically controlled oven at 60 ℃. After drying, the granules were sized by passing through a 60-mesh screen. Other excipients including microcrystalline cellulose, xylitol, aspartame, acesulfame potassium, and orange flavor concentrate were passed through a 80-mesh screen and mixed well with the prepared granulation. The final dry suspension was sub-packaged for further evaluation.

2.3. Optimization of binders and suspending agents

Different concentration of PVP K30 and hydroxypropylmethylcellulose (3%, 5%, 10%) as binders both in aqueous and alcohol solution were investigated when preparing the wet damp mass. Optimal binder and the proper
concentration were judged by the granule hardness and particle size uniformity.

Suspending agent was optimized using single factor method. Arabic gum, xanthan gum, sodium alginate and hydroxypropylmethylcellulose were investigated for the ability of suspending using relative sediment volume as the evaluation index.

2.4. Preparation of cefuroxime axetil suspension by solid dispersion method

A melting method was adopted to prepare the solid dispersion. Firstly, accurately weighted amounts of 12.5 g CA and proper sucrose (1, 1.5, 2 times relative to the weight of CA) were passed through a 100-mesh screen and mixed. Carriers were heated at 70 °C to melt entirely, then the mixture of CA and sucrose were slowly added to the carriers with stirring until dissolved. After totally dispersed, the resultant mixture was quickly poured into the precooled evaporation pan, and then cooled in an ice bath under stirring to form a solid dispersion for another 1 h. After dried in thermostatically controlled oven to constant weight, the solid were pulverized and passed through a 40-mesh screen and then a 80-mesh screen, particles with diameters between the two sizes were selected for further use. PEG6000, arabic gum, Poloxamer 188, stearic acid and glyceryl monostearate were evaluated, and a series of solid dispersion were prepared with the final drug-carrier weight ratio of 1:4, 1:5 and 1:6. Other excipients including powdered sucrose, xylitol, aspartame, acesulfame potassium, xanthan gum, and orange flavor concentrate were passed through a 80-mesh screen and mixed well with the prepared solid dispersion powders. The final dry suspension was sub-packaged for further evaluation.

2.5. Differential scanning calorimetry analysis

The thermal properties of stearic acid, raw cefuroxime axetil, powdered sucrose, physical mixture, and the solid dispersion of the three substances were characterized using a differential scanning calorimetry (DSC 60, Shimadzu) instrument. Samples each weighing 10 mg were placed in hermetical aluminum pans, with Al2O3 as a reference. The temperature increased with a heating rate of 10 °C/min from 30 °C to 250 °C under a nitrogen gas flow.

2.6. Quality control

2.6.1. Physicochemical properties of the suspensions

The physical properties of the two dry suspensions made by different methods were evaluated after reconstitution, including color, pH, relative sediment volume, dispersibility and viscosity. Taste evaluation was performed by oral administration of the reconstituted suspensions to identify whether the formulations were taste masked, and three volunteers were involved in this experiment. Formulations were classified into four degrees: 1. Tasteless, or taste masked; 2. Slightly bitter, or accepted taste; 3. Bitter; 4. Very bitter. The raw CA was used as the reference with intervals of 2 h during each experiment, and volunteers were supplied with sufficient drinking water [10,11].

2.6.2. Assay of the drug content

The content of CA in the suspensions was determined by using a HPLC method. The HPLC system was equipped with a LC-10A VP HPLC pump and a SPD-10A VP UV–VIS detector. A VP-ODS C18 column (5 μm, 150 × 4.6 mm) was used with a mobile phase of methanol–water (40:60, v/v) at a flow rate of 1 ml/min. The UV detector was operated at 278 nm, and the retention time of CA was 12.6 min.

Solutions of dry suspensions and the CA Standard were prepared at a concentration of about 0.1 mg/ml of CA with methanol as the solvent, respectively. Perform the test with 20 μl of the two solutions. The content was calculated by the external standard method.

2.6.3. Primary stability study of the suspensions

Primary stability study of the suspensions was investigated at temperatures of 40 °C and 60 °C, at relative humidities of 75% and 92.5%, and exposed to light of 4500 lx for 5 d and 10 d.

2.7. In vitro dissolution tests

In vitro dissolution behaviors of the two kinds of CA dry suspensions and its commercial dry suspension were investigated using a ChP2010 Type2 dissolution apparatus (paddle method), and all the tests were carried out in triplicate. A volume of 900 ml pH 7.0 phosphate buffer was used as the release medium and the temperature was maintained at 37 ± 0.5 °C with a paddle speed of 50 r/min. A certain amount of dry suspensions equivalent to 125 mg CA were used in all of the dissolution tests. At pre-determined time intervals (5, 10, 20, 30, 45, 60 min), an aliquot of 5 ml of the release medium was withdrawn and passed through a 0.22 μm filter immediately. An equal volume of fresh medium was replaced. The concentration of CA in filtrate was determined using a UV spectrophotometer (Beijing Rayleigh Analytical Instrument Co.) at 280 nm.

2.8. Pharmacokinetic study in beagle dogs

2.8.1. Animals and dosing

The pharmacokinetic tests were in accordance with the Guide for Care and Use of Laboratory Animals of Shenyang Pharmaceutical University. Six male beagle dogs weighing 12–18 kg were used and were randomly divided into two groups. A cross-over design was adopted with a washout period of seven days. All of six dogs were fasted overnight for 12 h with free access to water. The solid dispersion dry suspension and the commercial dry suspension were administered orally at a single dose equivalent of 125 mg of CA. 3 ml of venous blood were collected from the dog's foreleg after oral administration at predefined time intervals (pre-dose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10 and 12 h post dose). The plasma was separated from the blood sample immediately by centrifuging at 3500 r/min for 10 min and stored at −20 °C until analysis.

2.8.2. Determination of cefuroxime in plasma

The concentration of cefuroxime in plasma was determined by a validated HPLC–MS/MS method with glimepiride as the internal standard. A solid phase extraction was employed.
[12,13]. Briefly, 300 μl 5 mM ammonium acetate solution, 50 μl mixture of methanol–water (50:50, v/v) and 50 μl internal standard solution were added to 200 μl plasma, the mixture was mixed for 2 min before a centrifugation of 10 min at 13,000 r/min. The supernatant was then loaded on a solid phase extraction column (preconditioned with 1 ml of methanol and then 1 ml of ultrapure water). After washing by 2 ml of water twice, the analytes were eluted by 2 ml methanol. Then the eluent was evaporated to dryness under a nitrogen flow and then be reconstituted by 100 μl mobile phase. 10 μl of the sample was used for analysis. The chromatographic separations were carried out on an ACQUITY UPLC system (Waters Corp., Milford, MA) and BEH C18 column (50 mm x 2.1 mm, 1.7 μm; Waters Corp.) using acetonitrile-5 mM ammonium acetate–formic acid (60:40:0.01) as the mobile phase with a flow rate of 0.2 ml/min. The compounds were analyzed by multiple reaction monitoring (MRM) of the transitions of m/z 423→207 for cefuroxime and m/z 491.13→352.24 for glimepiride, respectively.

2.8.3. Data analysis
The maximum plasma concentration of cefuroxime (C_{max}) and the time to reach C_{max} (T_{max}) were noted directly from the drug concentration–time profiles. The pharmacokinetic parameters such as area under curve (AUC), and the half life of the preparation (T_{1/2}) were calculated by DAS 2.1 software using a noncompartmental model. All data were shown as their mean ± S.D. (standard deviation). The t-test was used for statistical analysis, and the differences were considered significant at p < 0.05. The relative bioavailability value (F) was calculated using the following formula with the commercial dry suspension as a reference:

\[ F_r = \left( \frac{AUC_{t_{0}-t}}{AUC_{0}-t_{k}} \right) \times 100\% \]

3. Results and discussion
3.1. Preparation of cefuroxime axetil suspension
In the present study, we prepared two formulations to mask the unpleasant taste of CA, i.e., the wet granulation dry suspension and solid dispersion dry suspension. In the wet granulation method, the porous carrier micronization silica gel can sufficiently decrease the drug concentration in mouth cavity and prevent the CA from precipitating by a mechanism of absorption. Polymers were also added to the dry suspensions, which made the suspension viscous after hydration. The thick liquid restrained the drug molecular from diffusing to interact with the taste buds. Solid dispersion also plays an important role in taste masking technology except its remarkable achievements in improving the dissolution and bioavailability of water-insoluble drugs [8].

3.1.1. Effect of different binders
In the process of preparing the damp mass, different concentrations of PVP K30 and hydroxypropylmethylcellulose (3%, 5%, 10%) as binder, in their aqueous and alcohol solutions were investigated by judging the optimal binder from the granule hardness and the particle size uniformity. A liquid binder is often added to facilitate the powder particles adhesion and prepared the damp mass in wet granulation method. The binding agents usually used are 10–20% corn starch aqueous preparation, povidone, 25–50% glucose solution, 3% methylcellulose, PVP K30, hydroxypropylmethylcellulose and so on. A good binder results in proper granule hardness and don’t impact on the drug dissolution. For these reasons we choose three different concentrations of the two binders both in there aqueous and alcohol solution. The amounts of the binders used are according to the practice experience, i.e., the resultant wet mass should be squeezed in the hand. If the granules are too hard, it would be difficult for the loading drug to release, in contrast, if they are too soft, the granules tend to be crushed causing the particles break into fine powders and have a wide range of particle size distribution. An alcohol preparation of PVP K30 (5%) was selected as the optimal binder after experiments for it offering the granules appropriate hardness and a narrow range of particle size distribution.

3.1.2. Influence of different suspending agents
A suspending agent is needed in the dry suspension system in the case of reconstitution. Upon dilution and agitation with a specified quantity of vehicle, the dispersed particles have a tendency to settle to the bottom of the container because they have a greater density then that of the dispersion medium. According to the equation of Stocks’ law, an increase of the viscosity of the dispersion medium can decrease the rate of particle sedimentation. By adding suspending agent to the dry suspension, we can expect a slower rate of descent of the particles when the dry powders of suspension are reconstituted. In this study, arabic gum, xanthan gum, sodium alginate and hydroxypropylmethylcellulose were investigated for the ability of suspending using relative sediment volume as the evaluation index. The relative sediment volume was shown in Table 1. The nonionic polymer, xanthan gum can be completely absorbed on the particles as a hydrodynamic layer to prevent the aggregation and settlement due to steric hindrance between the particles and make the suspension easily redispersible. Meanwhile, the polymer restrained the drug diffusion hence exerting a synergistic effect on taste masking. So xanthan gum was selected as the optimal suspending agent for its excellent suspending ability in all the experiments. The final formula of wet granulation was shown in Table 2.

<table>
<thead>
<tr>
<th>Table 1 – The relative sediment volume of suspensions made up of different suspending agents.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspending agents</td>
</tr>
<tr>
<td>Relative sediment volume</td>
</tr>
</tbody>
</table>
3.1.3. Selection of the carriers in solid dispersion method

Solid dispersion is a process in which drugs are distributed or dispersed throughout a solid carrier. It was used to be a widely accepted platform in the field of taste masking. Several methods have been developed to prepare solid dispersion such as melting method, hot melt extrusion, solvent evaporation method, spray drying, supercritical fluid precipitation and so on [14,15]. We choose the simple melting method in this work. In the process, the active medicinal substance is allowed to be dissolved or dispersed in the melted solid carriers. Through cooling and pulverizing the molten mixture, we can get the solidified granules. Five classic polymers having a low melting point including PEG6000, arabic gum, Poloxamer 188, stearic acid and glyceryl monostearate were investigated in the experiment. Upon the addition of CA, the clear and transparent molten carriers became yellow in terms of PEG6000, arabic gum and Poloxamer 188 which indicated a potential change in physicochemical characteristics. Although glyceryl monostearate didn’t undergo a color transformation, it produced a disgusting smell. Therefore, stearic acid was selected as the optimal carrier and final drug-carrier weight ratios of 1:4, 1:5 and 1:6 were evaluated. To further strengthening the taste masking ability and accelerating the drug release from the lipophilic stearic acid, sucrose, a water-soluble sweetener was added to the drug-carrier mixture. Overall, when CA, sucrose, stearic acid mixed at a weight ratio of 1:2:4, the resulting powders had a good dispersibility and showed excellent taste masking ability. The optimal formula was shown in Table 3.

### Table 3 - Formulation of dry suspension by solid dispersion method.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Quantity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA–Sucrose–Stearic-acid solid dispersion</td>
<td>70.00</td>
</tr>
<tr>
<td>(1:2:4, w/w/w)</td>
<td></td>
</tr>
<tr>
<td>Sucrose</td>
<td>12.00</td>
</tr>
<tr>
<td>Xylitol</td>
<td>6.00</td>
</tr>
<tr>
<td>Aspartame</td>
<td>2.00</td>
</tr>
<tr>
<td>Acesulfame potassium</td>
<td>3.00</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>6.00</td>
</tr>
<tr>
<td>Orange flavor concentrate</td>
<td>1.00</td>
</tr>
</tbody>
</table>

3.2. Differential scanning calorimetry analysis

DSC curves of stearic acid, raw cefuroxime axetil, powdered sucrose, the physical mixture, and the solid dispersion were shown in Fig. 2. As can be seen from the curves, the raw cefuroxime axetil showed decalescence peaks and the melting points were about 86.68 °C and 179.01 °C, which indicates the pure drug was polymorphs. The stearic acid and powdered sucrose showed endothermic peaks at 61.37 °C and 185.40 °C, respectively. The physical mixture just showed the above four decalescence peaks. In the curve of the solid dispersion, the two endothermic peaks of stearic acid and powdered sucrose can be easily identified while the endothermic peaks of CA disappeared totally, indicating that CA was amorphous incorporated in solid dispersion and powdered sucrose was not incorporated in solid dispersion for its hydrophilicity.

3.3. Physicochemical properties of the suspension

Physicochemical properties of the self-made dry suspensions after reconstitution including color, pH, relative sediment volume, dispersibility, viscosity and drug loading were evaluated for quality control. All the properties generally met the requirements for suspension and all the evaluation parameters were shown in Table 4. When the dry suspensions...
were made into liquid form of suspensions, they had a white color and a good redispersibility with no sedimentation during 24 h. The relative sediment volume was calculated by the ratio of the volume after sedimentation and the original volume. The higher the value is, the more stable the suspension will be. The suspensions showed a very low viscosity which also benefits to the redispersion, and the drug loading test revealed that the suspension had a drug content of 99.02 ± 0.34% and 99.13 ± 0.64% for wet granulation suspension and solid dispersion suspension, respectively.

For oral drug delivery system, taste is an important issue for the administration of bitter drugs. Solving this problem is the main purpose of this study. Taste evaluation was performed by oral administration of the reconstituted suspensions, and three volunteers were involved in this experiment. The results showed that each volunteer classified the two self-made formulations to the first rank, while the raw CA was belonging to the third rank. Taste evaluation indicates that the taste of CA was successfully masked by both formulations.

### Table 5 – Primary stability of the suspensions.

<table>
<thead>
<tr>
<th>Storage conditions</th>
<th>Appearance</th>
<th>Content (%)</th>
<th>pH</th>
<th>Weight gain (%)</th>
<th>Appearance</th>
<th>Content (%)</th>
<th>pH</th>
<th>Weight gain (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beginning</td>
<td>White powder</td>
<td>100±0.02</td>
<td>5.60±0.31</td>
<td>0</td>
<td>White powder</td>
<td>99.9±0.34</td>
<td>5.24±0.02</td>
<td>0</td>
</tr>
<tr>
<td>40 °C 5 d</td>
<td>White powder</td>
<td>101.7±0.78</td>
<td>5.55±0.54</td>
<td>–</td>
<td>White powder</td>
<td>100.22±0.37</td>
<td>5.10±0.51</td>
<td>–</td>
</tr>
<tr>
<td>10 d 60 °C</td>
<td>White powder</td>
<td>96.93±0.66</td>
<td>5.55±0.32</td>
<td>–</td>
<td>White powder</td>
<td>98.41±0.98</td>
<td>5.13±0.20</td>
<td>–</td>
</tr>
<tr>
<td>5 d RH75%</td>
<td>Light yellow powder</td>
<td>96.50±0.65</td>
<td>4.46±0.20</td>
<td>–</td>
<td>Light yellow powder</td>
<td>94.21±0.46</td>
<td>4.51±0.03</td>
<td>–</td>
</tr>
<tr>
<td>10 d RH92.5%</td>
<td>Light yellow powder</td>
<td>96.11±0.36</td>
<td>4.22±0.37</td>
<td>–</td>
<td>Yellow powder</td>
<td>93.32±0.88</td>
<td>4.32±0.15</td>
<td>–</td>
</tr>
<tr>
<td>5 d 4500 lx</td>
<td>White powder</td>
<td>99.83±0.78</td>
<td>5.57±0.43</td>
<td>0.97±0.71</td>
<td>White powder</td>
<td>98.43±0.91</td>
<td>5.07±0.08</td>
<td>1.21±0.03</td>
</tr>
<tr>
<td>10 d</td>
<td>White powder</td>
<td>98.32±0.69</td>
<td>5.54±0.89</td>
<td>1.03±0.04</td>
<td>White powder</td>
<td>97.67±1.01</td>
<td>5.00±0.10</td>
<td>1.78±0.35</td>
</tr>
</tbody>
</table>

Formulation 1 is referred to solid dispersion suspension.
Formulation 2 is referred to wet granulation suspension.

Fig. 3 – Dissolution profiles of two formulations of cefuroxime axetil dry suspension and its commercial dry suspension in pH 7.0 phosphate buffer (means ± SD, n = 3).
Formulation 1: Solid dispersion suspension; Formulation 2: Wet granulation suspension.

Fig. 4 – Average drug concentration–time profiles after a single oral dose of cefuroxime axetil dry suspension and the reference suspension (means ± SD, n = 6).
In the primary stability study, properties of appearance, drug content, pH and weight gain (%) were investigated. According to the results shown in Table 5, both of the formulations showed a decreased pH under the high temperature of 60 °C, and a slight weight gain under the high relative humidity of 70% and 92.5%. So the samples used in the current experiment were stored in sealed containers away from heat, light and humidity to keep its properties unchanged.

3.4. In vitro dissolution test

The dissolution of commercial dry suspension and dry suspensions prepared by wet granulation method and solid dispersion method were performed in pH 7.0 phosphate buffer and the corresponding profiles are shown in Fig. 3. Both formulations showed a higher and faster release than that of the commercial suspension. The solid dispersion suspension displayed a significant improvement in dissolution rate with more than 70% of the drug dissolved within 20 min, owing to the amorphous state of drug in the solid dispersion. In comparison with the self-made formulations, the commercial dry suspension showed a lower and slower release, and only around 50% of the drug dissolved within 20 min.

3.5. Pharmacokinetic study

A sensitive and accurate liquid chromatography—dual mass spectrometry analysis method and a solid phase extraction process were well validated. The in vivo pharmacokinetic behaviors of solid dispersion suspension and commercial dry suspension were well validated. The in vivo pharmacokinetic behaviors of solid dispersion suspension and commercial dry suspension were investigated following a single oral dose of 125 mg CA to six beagle dogs. The mean drug concentration—time profiles of the test and reference formulations are presented in Fig. 4. The main pharmacokinetic parameters are listed in Table 6. The Cmax and AUC0–12 values of the solid dispersion suspension were about 1.78-fold and 2.17-fold greater than those of the reference suspension with significant difference, respectively. The Tmax decreases by half an hour, which indicated a rapid dissolution and absorption of the drug, but there were no significant difference between the Tmax of the two formulations. The relative bioavailability (F) of test formulation was 274.0 ± 188.9%, which illustrated that the test formulation can improve the oral bioavailability significantly compared with the reference suspension.

Bioavailability refers to the rate and amount of a drug entering the systemic circulation after administration, and the bioavailability of the intravenous route of administration was considered to be 100%. For other routes of drug delivery, bioavailability was determined by drug solubility and permeability, and many other diverse factors involved in the manufacturing process, such as particle size, crystal form, physicochemical properties of excipients. For drugs with poor dissolution and limited permeability, their bioavailability is often incomplete [14]. The enhanced oral bioavailability of the self-made solid dispersion suspension is probably attributed to the amorphous state of CA in solid dispersion, making the loading drug dissolved and absorbed more effectively in the gastrointestinal tract. The same result was obtained in other research that the bioavailability was improved after administration of amorphous CA in nanoparticles [16]. Drugs are observed amorphous when they are prepared into solid dispersion, and they can be incorporated at a molecular level or as the particles throughout the carriers. The particles dispersed in the solid dispersion are usually at a nanoscopic level [17,18], which results in an increased dissolution rate according to the Noyes–Whitney equation. Moreover, the amorphous drug has a higher apparent solubility than the crystalline form [19]. And more importantly, the amorphous form didn’t undergo crystal transition and showed sufficient stability for a long time, which is essential for transportation and storage of the pharmaceutical dosage forms [20]. In this regard, we can better understand why solid dispersion suspension had a significant improvement of the oral bioavailability.

4. Conclusion

Taste masked dry suspensions of a bitter drug, cefuroxime axetil, were successfully prepared using wet granulation method and solid dispersion method. Several important parameters involved in the formulation procedure were optimized. The DSC analysis indicated that CA was amorphous in the solid dispersion, resulting in an enhancement of the dissolution rate and extent. As the optimal formulation, the solid dispersion suspension was selected for the further pharmacokinetic study in beagle dogs. The Cmax and AUC0–12 values of the solid dispersion suspension were about 1.78-fold and 2.17-fold greater than these of reference suspension, respectively. The obtained results demonstrated that the solid dispersion suspension can efficiently mask the bitter taste of CA and significantly enhance its oral bioavailability.

Acknowledgments

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