

TIZANIDINE LIQUID PREPARATION AND USE THEREOF

[0001] This application claims the priority of Chinese Patent Application No. 202110577512.4, filed with the China National Intellectual Property Administration on May 26, 2021, and titled
5 with “TIZANIDINE LIQUID PREPARATION AND USE THEREOF”, which is hereby incorporated by reference.

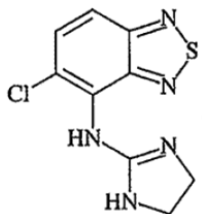
FIELD

[0002] The present disclosure relates to the field of medicine, and in particular to a tizanidine
10 liquid preparation and use thereof.

BACKGROUND

[0003] Tizanidine is a central α -2 adrenergic agonist used to treat muscle spasm.

[0004] The chemical structure of tizanidine is shown as follows:



15 [0005]

[0006] Tizanidine is currently marketed under the trademark Zanaflex® for the treatment of muscle spasm caused by spinal cord injury or multiple sclerosis.

[0007] The elderly population accounts for the largest proportion of tizanidine formula drug users. According to the Medical Expenditure Panel Survey (MEPS) of American Agency for
20 Healthcare Research and Quality (AHRQ), about 2.06 million people are prescribed tizanidine. According to some prescription drug use data from MEDICARED in the United States, about 1.46 million elderly/disabled/severely ill patients were prescribed tizanidine in 2018. It can be estimated that the elderly accounted for more than 60%.

[0008] Elderly people with neurological diseases are more likely to suffer from dysphagia:

dysphagia is a common clinical symptom, and central nervous system diseases are common diseases that cause dysphagia. In foreign countries, the incidence of dysphagia in acute stroke patients is 37%-78%; in China, the incidence of dysphagia in acute stroke patients is 51%-73%. Although most patients recovered swallowing function 1 month after stroke, some patients still have dysphagia 6 months after stroke. The overall prevalence of dysphagia in MS patients is about 33-43%, the incidence of dysphagia with acute cervical spinal cord injury is about 30.9%, and the incidence of dysphagia with brain injury is 27-30%.

[0009] Solid oral dosage forms play the largest and most important role in the overall pharmaceutical preparation. At present, most of the tizanidine dosage forms on the market are ordinary tablets, and there are also capsule preparations. Because drinking water is generally needed to help swallowing when taking the drugs in ordinary tablets/capsule preparations, tizanidine hydrochloride ordinary tablets/capsule preparations have poor compliance for some special groups such as young children, the elderly, patients with dysphagia, patients with certain mental illnesses, and patients who have difficulty in changing their position in bed, which cannot meet the needs of clinical medication. In clinical practice, tablets are often crushed or capsules are often opened and then administered to patients with dysphagia. Crushing/opening/mixing with other drugs for administration may cause risks of adverse reactions and medical errors. Since a large number of patients have difficulty in swallowing solid oral dosage forms, various solid forms of oral drugs such as buccal tablets, sublingual tablets, effervescent tablets, chewable tablets, orally disintegrating tablets, and soluble tablets have been developed in medicine.

[0010] There are certain limitations in the dose titration process of oral solid preparations: 1) the dose division is inaccurate; 2) multiple specifications need to be developed, and the cost of preparation development for enterprises becomes high; 3) during the dose titration process according to the change of patient's condition, the changes of specifications required can easily lead to waste. However, liquid preparations do not have the above problems during the dose titration process.

[0011] It can be seen that, compared with oral solid preparations, the development of tizanidine liquid preparations has the advantage of more convenient adjustment of dose titration, and it is also easy to improve compliance of taking medicine for those such as young children, the elderly, patients with dysphagia, patients with certain mental illnesses, and patients who have difficulty in

changing their position in bed, thereby meeting the clinical needs.

[0012] It is well known that liquid active pharmaceutical preparations are more susceptible to chemical instability than solid active pharmaceutical preparations. Although liquid active pharmaceutical preparations have obvious clinical advantages, preparation developers are often discouraged due to their stability problem.

[0013] The impurity detection of related substances in the drug is an important indicator to measure the chemical stability of drugs. The higher the impurity content of the related substances is, the worse the chemical stability is. The chemical stability of liquid preparations greatly affects its clinical promotion and use, and the impurity content of the related substances affects the safety of medication, wherein the more impurities are, the greater the possible medication risk is.

[0014] Since there is no marketed product of tizanidine liquid preparations on the market at present, the Pharmacopoeia has not made relevant specifications on the related substances of tizanidine liquid preparations. Therefore, the related substances of tizanidine liquid preparations should be referred to the relevant regulations on the related substances of tizanidine tablets in the Chinese Pharmacopoeia - the total impurity amount of the related substances in tizanidine tablets shall not exceed 0.5%.

[0015] At present, the ordinary tablets and capsule preparations of tizanidine on the market have a high probability of adverse reactions after being administered to human body. Taking Zanaflex® (tizanidine hydrochloride) tablets and capsules as an example, it is stated in their instructions that under single-dose administration, among the adverse reactions in patients, the incidence of 'somnolence' alone is as high as 78% (single dose of 8 mg)/92% (single dose of 16 mg). Adverse reaction of drug refers to the reaction generated during the use of drug with normal usage and dosage, which is irrelevant to the purpose of the drug use or harmful to the body, not only referring to the side effect of the drug. The quality, dosage form, impurities, excipients, content and the like of drugs are all factors that cause drug adverse reactions. The adverse reactions of tizanidine ordinary tablets and capsule preparations greatly affect the safety of tizanidine drug use. Meanwhile, the high incidence of somnolence among its adverse reactions also affects the normal life of the patients taking the medicine to a certain extent, and greatly reduces the compliance of patients taking the medicine. Therefore, how to reduce the incidence of

adverse reactions in normal use of tizanidine drugs is of great significance to enhance the safety of drug use and the compliance of patients taking the medicine.

[0016] Moreover, for muscle spasm, the faster the drug acts, the more quickly the pain of patients can be relieved. For oral drugs, food often has a great impact on the speed of drug action, and the drug peak time of the existing tizanidine ordinary tablets and capsule preparations under a post-prandial condition is significantly prolonged, which is not conducive to quickly reducing the pain of patients. Therefore, how to reduce the impact of food on the peak time of the drug and speed up the drug action of tizanidine under a post-prandial condition is also one of the problems to be solved.

[0017] In addition to consideration of the factors such as stability, adverse reactions and drug action speed in the development of new liquid drug dosage form of tizanidine, the influence of changes of dosage form on drug efficacy is also a factor that must be considered. The dosage form of the drug determines the route and method of administration, which directly affects the degree of drug absorption, thereby affecting the drug efficacy. The physical and chemical properties of the drug will directly affect the release of the drug, thereby affecting the therapeutic effect of the drug. The selection of excipients in the drug preparation not only affects the production process and the appearance and physical properties of the preparation, but also will change the bioavailability of the preparation, thereby affecting the efficacy of the preparation.

[0018] Therefore, it is an urgent problem to be solved to develop a tizanidine liquid preparation with low content of impurities, strong stability, low adverse reaction rate, little effect of food on the drug action speed, fast drug action speed under a post-prandial condition, and equivalent bioavailability to solid preparations.

SUMMARY

[0019] In view of this, the object of the present disclosure is to provide a tizanidine liquid preparation, which has low content of impurity and strong stability; compared to tizanidine solid preparations, it has low adverse reaction rate, little effect of food on the drug action speed, fast drug action speed under a post-prandial condition, and equivalent bioavailability to solid preparations.

[0020] In the present disclosure, the tizanidine liquid preparation comprises an active ingredient, disodium EDTA and other pharmaceutical excipients; wherein the active ingredient is one or more of tizanidine or a pharmaceutically acceptable salt, solvate and hydrate thereof.

[0021] Preferably, the pH value of the tizanidine liquid preparation is greater than 3.5 and smaller than 6.5.

[0022] Preferably, the pH value of the tizanidine liquid preparation is 4.0-6.1.

[0023] Preferably, the tizanidine liquid preparation comprises solvent, and the solvent is water.

[0024] Preferably, the other pharmaceutical excipient is one or more of a pH adjusting agent, a preservative, a co-solvent, a thickening agent, an aromatic agent, a sweetening agent and a coloring agent.

[0025] Preferably, the pH adjusting agent is one or more of citric acid, ascorbic acid, acetic acid, tartaric acid, trisodium citrate, sodium citrate, potassium citrate, sodium phosphate, tricalcium phosphate, calcium carbonate, sodium bicarbonate, calcium phosphate, calcium carbonate, magnesium hydroxide, hydrochloric acid and sodium hydroxide;

[0026] The co-solvent is one or more of sorbitol, maltitol, mannitol, isomaltose, xylitol, glucose and fructose;

[0027] The preservative is one or more of sodium benzoate, ethylparaben, propylparaben, sodium methylparaben, sodium ethylparaben, sodium propylparaben, benzoic acid, potassium phenylpropionate, sorbic acid, sodium sorbate, calcium sorbate, potassium sorbate, dehydroacetic acid, sodium diacetate, and calcium propionate;

[0028] The thickening agent is one or more of hypromellose, hydroxypropyl cellulose, colloidal silicon dioxide, methyl cellulose, sodium carboxymethyl cellulose, sodium alginate, and cyclodextrin;

[0029] The aromatic agent is one or more of strawberry aromatic agent, orange aromatic agent, banana aromatic agent, cherry aromatic agent, lemon aromatic agent, cardamom aromatic agent, fennel aromatic agent, mint aromatic agent, menthol aromatic agent and vanillin aromatic agent;

[0030] The sweetening agent is one or more of sucralose, glycerin, sodium saccharin, glucose, stevia, stevioside, aspartame, sodium cyclamate, acesulfame potassium, alitame, and neotame;

- [0031] The coloring agent is one or more of amaranth red, carmine, erythrosine, new red, lemon yellow, sunset yellow, indigo, beet red, shellac red, bilberry red, capsicum red, and red rice red.
- [0032] Preferably, the pH adjusting agent is a mixture of citric acid and sodium citrate;
- 5 [0033] The preservative is a mixture of sodium methylparaben and sodium propylparaben, or sodium benzoate;
- [0034] The co-solvent is sorbitol;
- [0035] The thickening agent is a mixture of hydroxypropyl cellulose and colloidal silicon dioxide, or hydroxypropyl cellulose;
- 10 [0036] The aromatic agent is strawberry aromatic agent;
- [0037] The sweetening agent is sucralose.
- [0038] Preferably, each 100 mL of the liquid preparation comprises the following components: 0.02-1 g of active ingredient, 0-0.2 g of disodium EDTA; wherein the content of disodium EDTA is not 0.
- 15 [0039] Preferably, each 100mL liquid preparation comprises the following components:
- [0040] Tizanidine 0.02-1g
- [0041] Disodium EDTA 0.005-0.2g.
- [0042] Preferably, each 100mL liquid preparation comprises the following components:
- [0043] Tizanidine 0.02-1g
- 20 [0044] Disodium EDTA 0.005-0.2g
- [0045] Citric acid 0.01-0.2g
- [0046] Sodium citrate 0.01-0.1g.
- [0047] Preferably, each 100mL liquid preparation comprises the following components:
- [0048] Tizanidine 0.04-0.09g
- 25 [0049] Disodium EDTA 0.008-0.12g

[0050] Citric acid 0.06-0.14g

[0051] Sodium citrate 0.02-0.06g.

[0052] Preferably, the tizanidine liquid preparation comprises the following components:

[0053] Tizanidine, sodium methylparaben, sodium propylparaben, disodium EDTA, sucralose,
5 citric acid, sodium citrate, strawberry aromatic agent and water; or

[0054] tizanidine, sodium methylparaben, sodium propylparaben, sorbitol, disodium EDTA,
sucralose, citric acid, sodium citrate, strawberry aromatic agent and water; or

[0055] tizanidine, hydroxypropyl cellulose, sodium methylparaben, sodium propylparaben,
sorbitol, disodium EDTA, sucralose, citric acid, sodium citrate, strawberry aromatic agent and
10 water; or

[0056] tizanidine, hydroxypropyl cellulose, colloidal silicon dioxide, sodium methylparaben,
sodium propylparaben, sorbitol, disodium EDTA, sucralose, citric acid, sodium citrate,
strawberry aromatic agent and water; or

[0057] tizanidine, hydroxypropyl cellulose, sodium benzoate, glycerin, sorbitol, disodium
15 EDTA, sucralose, strawberry aromatic agent and water.

[0058] Preferably, each 100mL liquid preparation comprises the following components:

[0059] Tizanidine hydrochloride 0.046g, sodium methylparaben, 0.1g, sodium propylparaben
0.01g, disodium EDTA 0.1g, sucralose 0.05g, citric acid 0.083g, sodium citrate 0.042g,
strawberry aromatic agent 0.05g, and the remainder water; or

[0060] tizanidine hydrochloride 0.046g, sodium methylparaben 0.1g, sodium propylparaben
20 0.01g, 70% sorbitol solution 25g, disodium EDTA 0.1g, sucralose 0.05g, citric acid 0.09g,
sodium citrate 0.035g, strawberry aromatic agent 0.05g, and the remainder water; or

[0061] tizanidine hydrochloride 0.046g, hydroxypropyl cellulose 2.5g, sodium methylparaben
0.1g, sodium propylparaben 0.01g, 70% sorbitol solution 15g, disodium EDTA 0.1g, sucralose
25 0.05g, citric acid 0.09g, sodium citrate 0.046g, strawberry aromatic agent 0.05g, and the
remainder water; or

[0062] tizanidine hydrochloride 0.046g, hydroxypropyl cellulose 2.5g, colloidal silicon dioxide

0.5g, sodium methylparaben 0.1g, sodium propylparaben 0.01g, 70% sorbitol solution 15g, disodium EDTA 0.1g, sucralose 0.05g, citric acid 0.09g, sodium citrate 0.04g, strawberry aromatic agent 0.05g, and the remainder water; or

[0063] tizanidine hydrochloride 0.046g, hydroxypropyl cellulose 5g, sodium benzoate 0.1g, glycerin 15g, 70% sorbitol solution 25g, disodium EDTA 0.1g, sucralose 0.05g, strawberry aromatic agent 0.05g, and the remainder water.

[0064] The active pharmaceutical ingredient in the tizanidine liquid preparation of the present disclosure is preferably tizanidine hydrochloride, in which the content of the active pharmaceutical ingredient tizanidine hydrochloride is 0.046g/100mL, and the liquid preparation of the present disclosure also comprises disodium EDTA; when the liquid preparation is stored at room temperature, the total impurity amount of its related substances is $\leq 0.2\%$, and/or after the liquid preparation is administered, the mean value of C_{max} , mean value of AUC_{0-t} and/or mean value of $AUC_{0-\infty}$ of tizanidine thereof are respectively within the range of 80%-120% of the mean value of C_{max} , mean value of AUC_{0-t} and/or mean value of $AUC_{0-\infty}$ of the tizanidine in the following liquid preparations after being administered in equivalent doses with respect to tizanidine:

[0065] (1) Each 100mL liquid preparation comprises tizanidine hydrochloride 0.046g, sodium methylparaben 0.1g, sodium propylparaben 0.01g, disodium EDTA 0.1g, sucralose 0.05g, citric acid 0.083g, sodium citrate 0.042g, strawberry aromatic agent 0.05g, and the remainder water; or

[0066] (2) Each 100mL liquid preparation comprises tizanidine hydrochloride 0.046g, sodium methylparaben 0.1g, sodium propylparaben 0.01g, 70% sorbitol solution 25g, disodium EDTA 0.1g, sucralose 0.05g, citric acid 0.09g, sodium citrate 0.035g, strawberry aromatic agent 0.05g, and the remainder water; or

[0067] (3) Each 100mL liquid preparation comprises tizanidine hydrochloride 0.046g, hydroxypropyl cellulose 2.5g, sodium methylparaben 0.1g, sodium propylparaben 0.01g, 70% sorbitol solution 15g, disodium EDTA 0.1g, sucralose 0.05g, citric acid 0.09g, sodium citrate 0.046g, strawberry aromatic agent 0.05g, and the remainder water; or

[0068] (4) Each 100mL liquid preparation comprises tizanidine hydrochloride 0.046g, hydroxypropyl cellulose 2.5g, colloidal silicon dioxide 0.5g, sodium methylparaben 0.1g, sodium

propylparaben 0.01g, 70% sorbitol solution 15g, disodium EDTA 0.1g, sucralose 0.05g, citric acid 0.09g, sodium citrate 0.04g, strawberry aromatic agent 0.05g, and the remainder water; or

[0069] (5) Each 100mL liquid preparation comprises tizanidine hydrochloride 0.046g, hydroxypropyl cellulose 5g, sodium benzoate 0.1g, glycerin 15g, 70% sorbitol solution 25g, disodium EDTA 0.1g, sucralose 0.05g, strawberry aromatic agent 0.05g, and the remainder water.

[0070] When the tizanidine liquid preparation of the present disclosure is hermetically stored under the condition of 40°C/75%RH for 0-3 months, the total impurity amount of its related substances is $\leq 0.2\%$, and/or when the tizanidine liquid preparation of the present disclosure is hermetically stored under the condition of 25°C/60%RH for 0-6 months, the total impurity amount of its related substances is $\leq 0.2\%$.

[0071] The pre-prandial and post-prandial bioavailability of the liquid preparation of the present disclosure is equivalent with that of Zanaflex® tizanidine tablets, and/or the pre-prandial and post-prandial bioavailability of the liquid preparation of the present disclosure is equivalent with that of Zanaflex® tizanidine capsules.

[0072] The evaluation criteria for the bioavailability equivalence of the liquid preparation of the present disclosure and tizanidine tablets/capsules under a post-prandial condition are:

[0073] The upper limit of the one-sided 95% confidence interval for $C_{\max}$ is ≤ 0 ;

[0074] The 90% confidence interval for AUC_{0-t} is between 80% -125%;

[0075] The 90% confidence interval for $AUC_{0-\infty}$ is between 80%-125%.

[0076] The mean value of $T_{\max}$ of the tizanidine liquid preparation of the present disclosure under the post-prandial condition is smaller than the mean value of $T_{\max}$ of the tizanidine tablets/capsules under the post-prandial condition.

[0077] Under the condition that the tizanidine liquid preparation of the present disclosure is administered in the same dose with respect to tizanidine, the incidence of adverse reactions of the present disclosure is smaller than the incidence of adverse reactions of the tizanidine tablets/capsules.

[0078] More specifically, under the condition that the tizanidine liquid preparation of the present disclosure is administered in the same dose with respect to tizanidine, the incidence of the

pre-prandial adverse reaction item-drowsiness of the liquid preparation of the present disclosure is smaller than that of the tizanidine tablets/capsules; and/or

[0079] the incidence of post-prandial adverse reaction item-drowsiness of the liquid preparation of the present disclosure is smaller than that of the tizanidine tablets/capsules; and/or

5 **[0080]** the incidence of post-prandial adverse reaction item-headache of the liquid preparation of the present disclosure is smaller than that of the tizanidine tablets/capsules; and/or

[0081] the incidence of post-prandial adverse reaction item-vomiting of the liquid preparation of the present disclosure is smaller than that of the tizanidine capsules.

10 **[0082]** Use of a tizanidine liquid preparation in preparing a medicament for treating muscle spasm.

[0083] There are many factors that affect the chemical stability of medicines, among which temperature is one of the important factors affecting the stability of pharmaceutical preparations. Generally speaking, as the temperature increases, the degradation reaction speed is accelerated. Light is also a reason that may affect the stability of pharmaceutical preparations, wherein light
15 may induce chain reactions, which can accelerate the degradation rate. The presence of oxygen may also accelerate the oxidation reaction, which can affect the stability of the drug. Other factors such as environmental humidity, packaging materials, pH value, excipients and the like may also affect the chemical stability of the drug. The stability of different drugs can be affected by different factors.

20 **[0084]** In the research process, the preparation researchers of the present disclosure found that the metal ions in the solution have an impact on the chemical stability of the tizanidine solution, in which the presence of the metal ions has the effect of accelerating the degradation of tizanidine related substances. The present disclosure uses disodium EDTA as a chelating agent, which can combine with metal ions in the tizanidine solution to prepare a tizanidine liquid preparation with
25 strong chemical stability and an impurity content of the related substances in compliance with the Pharmacopoeia. Disodium EDTA can combine and maintain with minerals and metal ions such as chromium, iron, lead, mercury, copper, aluminum, nickel, zinc, calcium, cobalt, manganese and magnesium after being dissolved in water. When these minerals and metal ions are combined, they no longer have an impact on the chemical stability of the tizanidine solution, which ensures

the chemical stability of the tizanidine liquid preparation of the present disclosure to a great extent.

[0085] The tizanidine liquid preparation of the present disclosure has good chemical stability in both glass bottles and polyester bottles which are conventional storage containers for liquid medicines. It can be seen that the present disclosure does not have strict requirements on storage containers, and storage containers can be selected according to actual needs during storage and transportation. The medicinal solution of the present disclosure can be stored at room temperature, which is conducive to reducing the costs of storage and transportation.

[0086] The tizanidine liquid preparation of the present disclosure has a clear appearance, and does not appear precipitation, turbidity or other phenomena after being placed for a long time, which has strong physical stability. The impurity content of its related substances is far lower than the limit specified by the Pharmacopoeia for the impurity content of the related substances in tizanidine products, which meets the requirements of drug application and can be promoted and applied in clinical practice.

[0087] Compared with the existing tizanidine solid preparations on the market, the tizanidine liquid preparation prepared by the present disclosure has less adverse reactions in the human body, improving the use safety of the tizanidine drug and the compliance of patients taking the medicine.

[0088] The liquid preparation of the present disclosure is administered via oral cavity, preferably orally administered. It has the advantages of accurate dose titration and convenient administration for young children, the elderly, patients with dysphagia, patients with certain mental illnesses and patients who have difficulty in changing their position in bed.

[0089] Meanwhile, compared with the existing tablets and capsules, the tizanidine liquid preparation prepared by the present disclosure achieves the pre-prandial and post-prandial bioavailability equivalence in human body, and has efficacy which is not smaller than that of the existing solid preparations. Moreover, the impact of food on the action speed of the liquid preparation of the present disclosure is smaller than its impact on the existing solid preparations. Compared with the existing solid preparations, the present disclosure has a faster onset of drug action under a post-prandial condition, and can relieve the pain of patients more quickly.

[0090] To sum up, the present disclosure obtains a tizanidine liquid preparation with few impurities, strong chemical and physical stability, and few adverse reactions, which achieves pre-prandial and post-prandial bioavailability equivalence with the existing tizanidine solid preparations. Meanwhile, compared with the existing tizanidine solid preparations, the liquid preparation of the present disclosure has a faster onset of drug action under a post-prandial condition, and meets the market demand for tizanidine oral pharmaceutical dosage forms and the clinical needs.

DETAILED DESCRIPTION

[0091] The technical solutions of the present disclosure will be clearly and completely described below with reference to the embodiments of the present disclosure. Obviously, the described embodiments are only a part of the preferred embodiments of the present disclosure, rather than all the embodiments. Based on the embodiments of the present disclosure, all other embodiments obtained by those of ordinary skill in the art without creative efforts shall fall within the protection scope of the present disclosure.

[0092] The present disclosure provides a stable tizanidine liquid preparation, wherein the active pharmaceutical ingredient of the liquid preparation is one or more of tizanidine or a pharmaceutically acceptable salt, solvate and hydrate thereof. The term stable according to the present disclosure refers to chemically stable and/or physically stable.

[0093] Regardless of the presenting form of the active pharmaceutical ingredient of the present disclosure, after it is dissolved, it is the tizanidine dissolved in the drug solution that produces the medicinal effect. In order to facilitate data comparison, in the embodiments of the present disclosure, tizanidine hydrochloride was preferably used as the bulk drug to investigate various aspects.

[0094] The range of pH value of bulk drug solution of tizanidine hydrochloride was investigated:

[0095] Experimental method:

[0096] (1) 0.323 g of tizanidine hydrochloride was weighed and dissolved in 400 mL of

purified water;

[0097] (2) The solution of the previous step was divided into four equal parts, and the pH was adjusted to 3.5, 4.5, 5.5 and 6.5 using 0.1N HCl and 0.1N NaOH;

[0098] (3) Freezing and thawing test—four sample solutions were stored at 2-8°C, room temperature, and 40°C/75% RH respectively for 24 hours, which was repeated 3 times.

[0099] The changes in the pH and appearance of the tizanidine hydrochloride bulk drug solution and the detection of the related substances in the freezing and thawing test are shown in the following table:

[00100] Table 1 Table of investigation of effect of pH on tizanidine hydrochloride bulk drug solution

Sample	pH value	Appearance	Increment of the total impurity of the related substances % ($\pm$)
1	3.5	Clear colorless solution	0.79%
2	4.5	Clear colorless solution	0.21%
3	5.5	Clear colorless solution	0.34%
4	6.5	Clear pale yellow solution	0.22%

[00101] Physical observation showed that when the pH was 6.5, the color of the solution changed from colorless to pale yellow.

[00102] In the above table, the sample solution No. 1 showed the largest difference in the total impurity change of the related substances before and after the freezing and thawing test, of which the total impurity change of the related substances before and after the freezing and thawing test was 0.79%.

[00103] From the appearance change of the tizanidine hydrochloride bulk drug solution and the difference of total impurity change of the related substances before and after the freezing and thawing test, it can be seen that the tizanidine hydrochloride bulk drug solution has better stability when its pH value is within the range of greater than 3.5 and smaller than 6.5.

[00104] Therefore, the pH value of the present disclosure is preferably selected to be greater

than 3.5 and smaller than 6.5.

[00105] Next, the stability of the tizanidine liquid preparation of the present disclosure is investigated through specific examples.

[00106] Glass bottle/polyester bottle is one of the inner packagings commonly used for solid tablets or liquid preparations. The glass bottle has excellent properties such as good heat resistance and uneasy adsorption, but it is relatively brittle, easy to be broken, and cannot be pressed, which brings inconvenience to the production and transportation, and the trace amount of metal ions contained in glass may affect the stability of drugs. The polyester bottle is not easy to be broken, has zero breakage rate, low price, and low cost of production and transportation, but its heat resistance is poor, and more additives are added in the production process thereof, easily leading to changes in the quality of drugs. Moreover, the polyester bottle also has disadvantages of breathability, easy adsorption and the like, which can also accelerate the speed of oxidative deterioration of drugs and cause drug deterioration.

[00107] Therefore, during the stability investigation process of the present disclosure, the tizanidine liquid preparation was stored in a glass bottle and a polyester bottle, which are two commonly used medicine storage containers, to detect the related substances.

[00108] The test method of stability investigation of the present disclosure is:

[00109] a Accelerated test steps:

[00110] (1) In the stability test chamber, the temperature was set to 40°C and the relative humidity was set to 75%;

[00111] (2) The liquid preparations sealed into a glass bottle and the liquid preparations sealed into a polyester bottle were taken and placed in a preset stability test chamber;

[00112] (3) The samples after placement were taken to detect the related substances.

[00113] b Normal temperature test steps:

[00114] (1) In the stability test chamber, the temperature was set to 25°C and the relative humidity was set to 60%;

[00115] (2) The liquid preparations sealed into a glass bottle and the liquid preparations sealed

into a polyester bottle were taken and placed in a preset stability test chamber;

[00116] (3) The samples after placement were taken to detect the related substances.

[00117] This method was adopted for the test methods of the accelerated test and the normal temperature test in all the examples of the present disclosure.

5 [00118] **Example 1**

[00119] In addition to the tizanidine bulk drug, the liquid preparation of the present disclosure also comprises disodium EDTA and one or more other pharmaceutically acceptable excipients. Therefore, after the relevant excipients were added to make the tizanidine hydrochloride liquid preparation, the stability and range of pH value of the liquid preparation were studied:

10 [00120] (I) Experimental formula:

[00121] Table 2 Formula table

Material name	1	2	3
	Unit measurement (g/1000mL)	Unit measurement (g/1000mL)	Unit measurement (g/1000mL)
Tizanidine hydrochloride	0.46	0.46	0.46
Sodium methylparaben	1.00	1.00	1.00
Sodium propylparaben	0.10	0.10	0.10
Disodium EDTA	1.00	1.00	1.00
Sucralose	0.50	0.50	0.50
Citric acid	0.83	0.83	0.83
Sodium citrate	0.42	0.42	0.42
Strawberry aromatic agent	0.50	0.50	0.50
0.1N HCl	Adjusting pH to about 4.0	-	-
0.1N NaOH	-	-	Adjusting pH to about 6.0
Purified water (appropriate amount)	Making up to 1000mL	Making up to 1000mL	Making up to 1000mL

[00122] With regard to the formula table of the present application, it should be understood that the invention disclosed in the present application is not limited to a specific preparation volume. In the case where the concentration of each component of the liquid preparation is determined, the preparation volume can be changed according to the requirements of production and test.

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[00123] Descriptions of liquid preparation volumes provided throughout this application are given for the purpose of describing particular embodiments or concentration of each component only, and are not intended to limit the scope of the present disclosure.

[00124] (II) Process:

5 **[00125]** The materials were weighed according to the prescribed amount for use;

[00126] (1) Disodium EDTA was dissolved in an appropriate amount of water and stirred well;

[00127] (2) Sucralose was dissolved in an appropriate amount of water, added to the solution obtained in step (1), and stirred evenly;

10 **[00128]** (3) Sodium methylparaben was dissolved in an appropriate amount of water, and the mixture was added to the solution obtained in step (2), and stirred evenly;

[00129] (4) Sodium propylparaben was dissolved in an appropriate amount of water, and the mixture was added to the solution obtained in step (3), and stirred evenly;

[00130] (5) Citric acid was dissolved in an appropriate amount of water, and the mixture was added to the solution obtained in step (4), and stirred evenly;

15 **[00131]** (6) Sodium citrate was dissolved in an appropriate amount of water, and the mixture was added to the solution obtained in step (5), and stirred evenly;

[00132] (7) Tizanidine hydrochloride was dissolved in an appropriate amount of water, and the mixture was added to the solution obtained in step (6), and stirred evenly;

20 **[00133]** (8) The pH of the solution in step (7) was adjusted to about 4.0 or 6.0 using 0.1N HCl or 0.1N NaOH or no pH adjustment was performed.

[00134] (9) Strawberry aromatic agent was added to the solution obtained in step (8) under stirring, and stirred evenly;

[00135] (10) Water was added to adjust the volume to 1000 mL, and the obtained solution was filtered to obtain a tizanidine hydrochloride liquid preparation.

25 **[00136]** (III) Detection methods for the related substances:

[00137] The related substances were determined using high performance liquid chromatography.

[00138] Test solution: About 10g of tizanidine hydrochloride liquid preparation was taken, accurately weighed (corresponding to about 4mg of tizanidine), and put in a 100mL volumetric flask. The preparation was diluted to the mark by adding a diluent [a mixture of mobile phase A and mobile phase B according to a certain ratio]. The mixture was shaken well, and filtered to take the filtrate.

[00139] Control solution: 1.0mL of the test solution was precisely measured, put in a 100mL volumetric flask. The test solution was diluted to the mark by adding a diluent. The mixture was shaken well.

[00140] The chromatographic column was an octadecylsilane-bonded silica gel column C18 (4.6×250mm, 5μm). Gradient elution was performed according to Table 3 in which the sodium pentanesulfonate solution (3.5g of sodium pentanesulfonate was taken and dissolved in 1000mL of water. and the pH was adjusted to 3.0 using phosphoric acid solution or sodium hydroxide test solution) was used as mobile phase A, and acetonitrile was used as mobile phase B; the flow rate was 1.0 mL/min; the detection wavelength was 230 nm; the injection volume was 50 μL; the column temperature was 30 °C.

[00141] Table 3 Gradient elution procedure

Time (min)	Mobile phase A (%)	Mobile phase B (%)
0	94	6
5	94	6
20	80	20
25	78	28
45	72	45
50	55	50
55	50	50
60	94	6
0	94	6

[00142] Limit: If there are impurity peaks in the chromatogram of the test solution, the total area of the impurity peaks shall not be greater than 0.5 times of the main peak area of the control solution (i.e., the total impurity amount of the related substances shall not exceed 0.5%).

[00143] This detection method can be used for the detection of the related substances in all the examples in the present specification, but the detection method of the related substances of the present disclosure is not limited to this detection method; those skilled in the art can also partly

adjust the detection method/detection parameters by conventional means to detect the related substances of the present disclosure.

[00144] Table 4 Detection results of the related substances of tizanidine hydrochloride liquid preparations with different pH in the accelerated test

Sample	Condition	0 day	Accelerated for 1 month-40°C /75%RH		Accelerated for 3 months-40°C /75%RH	
			Glass bottle	Polyester bottle	Glass bottle	Polyester bottle
1	pH	4.0	-	-	4.05	4.04
	Content %	101.1	101.1	102.1	101.2	101.3
	Total impurity of the related substances%	Undetected	0.02	0.03	0.05	0.05
2	pH	5.0	-	-	5.18	5.17
	Content %	100.5	101.3	101.8	100.8	102.8
	Total impurity of the related substances%	0.02	0.03	0.02	0.05	0.04
3	pH	6.1	-	-	6.08	6.06
	Content %	100.4	100.8	100.5	100.1	99.8
	Total impurity of the related substances%	Undetected	0.08	0.04	0.14	0.14

[00145] The results in Table 4 show that under the accelerated condition, when the pH was 4.0/5.0/6.1, the total impurity content of the related substances in tizanidine liquid preparations for 0 day, 1 month, and 3 months were all less than 0.2%, which was far less than the 0.5% stipulated in the Pharmacopoeia; meanwhile, no turbidity or precipitation occurred in liquid preparations with different pH values. It can be seen that when the pH of the tizanidine liquid preparation of the present disclosure changes within the range of 4.0-6.1, the pH value has no substantial effect on the physical and chemical stability of the preparation, and will not affect the marketing and use of the drug.

[00146] In order to further verify the long-term stability of the liquid preparation in this example, the tizanidine liquid preparation prepared in this example was subjected to a normal temperature test. In order to save resources, only the No. 2 formula without HCl or NaOH added in Table 2

was investigated in this investigation.

[00147] Table 5 Detection results of the related substances of tizanidine hydrochloride liquid preparation of No. 2 formula in normal temperature test

Condition	Room temperature for 6 months-25°C /60%RH	
	Glass bottle	Polyester bottle
Content %	98.6	102.5
Total impurity of the related substances%	0.03	0.03

[00148] The total impurities of the related substances in the liquid preparation of this example which was placed at room temperature for 6 months were 0.03% (glass bottle) and 0.03% (polyester bottle), wherein the total impurity content of the related substances were both less than 0.2%, far less than the limit of 0.5% stipulated in the Pharmacopoeia, indicating that the liquid preparation of this example had good chemical stability.

[00149] There was no big difference in the detection results of the related substances in the liquid preparation of this example stored in the glass bottle and the polyester bottle. It can be seen that the liquid preparation of this example did not have strict requirements on storage containers, and storage containers can be selected according to actual needs during storage and transportation.

[00150] Meanwhile, whether in the accelerated test or in the normal temperature test, the tizanidine liquid preparation of this example did not appear precipitation, turbidity or other phenomena, indicating that the liquid preparation of this example had good physical stability under both accelerated conditions and normal temperature conditions for a long-term storage.

[00151] It can be seen that the liquid preparation of this example not only had low impurity content, but also had good chemical/physical stability, which meets the specifications of the Pharmacopoeia and the requirements for drug marketing, and has strong durability to storage containers, providing a variety of storage options clinically.

[00152] Example 2

[00153] In this example, an excipient-co-solvent was added to the formula to investigate the stability.

[00154] (I) Experimental formula

[00155]

Table 6 Formula table

Material name	Role in formula	Unit measurement (g/1000mL)
Tizanidine hydrochloride	Active ingredient	0.46
Sodium methylparaben	Preservative	1.00
Sodium propylparaben	Preservative	0.10
70% sorbitol	Co-solvent	250.00
Disodium EDTA	Chelating agent	1.00
Sucralose	Sweetening agent	0.50
Citric acid	pH adjusting agent	0.90
Sodium citrate	pH adjusting agent	0.35
Strawberry aromatic agent	Aromatic agent	0.50
Purified water (appropriate amount)	Diluent	Making up to 1000mL

[00156] (II) Process:

[00157] The materials were weighed according to the prescribed amount for use;

[00158] (1) Disodium EDTA was dissolved in an appropriate amount of water and stirred well;

5 [00159] (2) Sucralose was dissolved in an appropriate amount of water, and the mixture was added to the solution obtained in step (1);

[00160] (3) Under stirring, sorbitol with a concentration of 70% was added to the solution obtained in step (2);

10 [00161] (4) Sodium methylparaben and sodium propylparaben were dissolved in water, and the mixture was added to the solution obtained in step (3) under stirring;

[00162] (5) Citric acid and sodium citrate were added to the solution obtained in step (4) under stirring;

[00163] (6) Tizanidine hydrochloride was dissolved in water alone, then the mixture was added to the solution obtained in step (5) under continuous stirring;

15 [00164] (7) Strawberry aromatic agent was added to the solution obtained in step (6) under stirring;

[00165] (10) Water was added to adjust the volume to 1000 mL, and the obtained solution was filtered to obtain a tizanidine hydrochloride liquid preparation.

[00166] (III) Stability investigation

[00167] The liquid preparations prepared in this example were subjected to accelerated test.

[00168] Table 7 Detection results of the related substances in accelerated test

Condition	0 day	Accelerated for 1 month-40°C /75%RH		Accelerated for 3 months-40°C /75%RH	
		Glass bottle	Polyester bottle	Glass bottle	Polyester bottle
Content %	101.4	101.5	104.8	101.4	101.7
Total impurity of the related substances%	Undetected	Undetected	Undetected	0.15	0.16

[00169] At 0 day, the pH value of the liquid preparation of this example was measured to be 5.0.

- 5 Since when the pH value of the tizanidine liquid preparation of the present disclosure changes within the range of 4.0-6.1, the stability of the present disclosure is not substantially affected, the pH value was not investigated in this example.

[00170] Under accelerated conditions, the total impurity content of the related substances in the liquid preparation of this example in 0, 1, and 3 months was all less than 0.2%, far less than the
10 limit of 0.5% specified by the Pharmacopoeia, indicating the liquid preparation of this example had good chemical stability, and complied with regulations of the Pharmacopoeia.

[00171] In order to further verify the long-term stability of the liquid preparation of this example, the tizanidine liquid preparations prepared in this example were subjected to normal temperature test.

15 [00172] Table 8 Detection results of the related substances in normal temperature test

Condition	Room temperature for 6 months-25°C/60%RH	
	Glass bottle	Polyester bottle
Content %	102.3	106.0
Total impurity of the related substances%	0.15	0.19

[00173] The total impurities of the related substances in the liquid preparation of this example placed at room temperature for 6 months were 0.15% (glass bottle) and 0.19% (polyester bottle), which were both less than 0.2%, far less than the limit of 0.5% specified in the Pharmacopoeia, indicating that the liquid preparation of this example had good chemical stability, and complied

with regulations of the Pharmacopoeia.

[00174] There was no big difference in the detection results of the total impurity of the related substances in the liquid preparation of this example stored in the glass bottle and the polyester bottle. It can be seen that the liquid preparation of this example did not have strict requirements on storage containers, and storage containers can be selected according to actual needs during storage and transportation.

[00175] Meanwhile, whether in the accelerated test or in the normal temperature test, the tizanidine liquid preparation of this example did not appear precipitation, turbidity or other phenomena, indicating that the liquid preparation of this example had good physical stability under both accelerated conditions and normal temperature conditions for a long-term storage.

[00176] The liquid preparation of this example not only had low impurity content, but also had good long-term stability, which meets the requirements of the Pharmacopoeia and the requirements for drug marketing.

[00177] Compared with Example 1, in this example, a co-solvent was added to the formula of the liquid preparation. It can be seen that the addition of the co-solvent has no substantial effect on the physical and chemical stability of the liquid preparation of the present disclosure, and will not affect the marketing and use of the drug.

[00178] Example 3

[00179] In this example, an excipient-thickening agent was added to the formula, and the addition amount of the co-solvent was adjusted to investigate the stability.

[00180] (I) Experimental formula

[00181] Table 9 Formula table

Material name	Role in formula	Unit measurement (g/1000mL)
Tizanidine hydrochloride	Active ingredient	0.46
Hydroxypropyl cellulose	Thickening agent	25.00
Sodium methylparaben	Preservative	1.00
Sodium propylparaben	Preservative	0.10
70% sorbitol	Co-solvent	150.00
Disodium EDTA	Chelating agent	1.00

Sucralose	Sweetening agent	0.50
Citric acid	pH adjusting agent	0.90
Sodium citrate	pH adjusting agent	0.46
Strawberry aromatic agent	Aromatic agent	0.50
Purified water (appropriate amount)	Diluent	Making up to 1000mL

[00182] (II) Process

[00183] The materials were weighed according to the prescribed amount for use;

[00184] (1) Hydroxypropyl cellulose was added to an appropriate amount of water to disperse, and stirred until the solution became clear.

5 **[00185]** (2) Disodium EDTA was dissolved in water and the mixture was added to the solution obtained in step (1) under stirring.

[00186] (3) Sorbitol with a concentration of 70% was added to the solution obtained in step (2) under stirring, and stirred until the solution became clear.

10 **[00187]** (4) Sodium methylparaben and sodium propylparaben were dissolved in water, and the mixture was added to the solution obtained in step (3) under stirring.

[00188] (5) Citric acid and sodium citrate were added to the solution obtained in step (4) with stirring.

[00189] (6) Sucralose was dissolved in water, and the mixture was added to the solution obtained in step (5) under stirring.

15 **[00190]** (7) Tizanidine hydrochloride was dissolved in water alone, then the mixture was added to the solution obtained in step (6) under continuous stirring.

[00191] (8) Strawberry aromatic agent was added to the solution obtained in step (7) under continuous stirring.

20 **[00192]** (9) Water was added to adjust the volume to 1000 mL, and the obtained solution was filtered to obtain a tizanidine hydrochloride liquid preparation.

[00193] (III) Stability investigation

[00194] The liquid preparations prepared in this example were subjected to accelerated test.

[00195] Table 10 Detection results of the related substances in accelerated test

Condition	0 day	Accelerated for 1 month-40°C /75%RH		Accelerated for 3 months-40°C /75%RH	
		Glass bottle	Polyester bottle	Glass bottle	Polyester bottle
Content %	103.8	100.7	101.5	102.5	102.4
Total impurity of the related substances%	Undetected	Undetected	Undetected	0.12	0.10

[00196] At 0 day, the pH value of the liquid preparation of this example was measured to be 5.2. Since when the pH value of the tizanidine liquid preparation of the present disclosure changes within the range of 4.0-6.1, the stability of the present disclosure is not substantially affected, the pH value was not investigated in this example.

5 **[00197]** Under accelerated conditions, the total impurity content of the related substances in the liquid preparation of this example in 0, 1, and 3 months was all less than 0.2%, far less than the limit of 0.5% specified by the Pharmacopoeia, indicating the liquid preparation of this example had good chemical stability, and complied with regulations of the Pharmacopoeia.

10 **[00198]** In order to further verify the long-term stability of the liquid preparation of this example, the tizanidine liquid preparation prepared in this example was subjected to normal temperature test.

[00199] Table 11 Detection results of the related substances in normal temperature test

Condition	Room temperature for 6 months-25°C /60%RH	
	Glass bottle	Polyester bottle
Content %	104.3	104.3
Total impurity of the related substances%	0.06	0.06

15 **[00200]** The total impurities of the related substances in the liquid preparation of this example placed at room temperature for 6 months were 0.06% (glass bottle) and 0.06% (polyester bottle), which were both less than 0.2%, far less than the limit of 0.5% specified in the Pharmacopoeia, indicating that the liquid preparation of this example had good chemical stability, and complied with regulations of the Pharmacopoeia.

20 **[00201]** There was no big difference in the detection results of the total impurity of the related substances in the liquid preparation of this example stored in the glass bottle and the polyester bottle. It can be seen that the liquid preparation of this example did not have strict requirements

on storage containers, and storage containers can be selected according to actual needs during storage and transportation.

[00202] Meanwhile, whether in the accelerated test or in the normal temperature test, the tizanidine liquid preparation of this example did not appear precipitation, turbidity or other phenomena, indicating that the liquid preparation of this example had good physical stability under both accelerated conditions and normal temperature conditions for a long-term storage.

[00203] The liquid preparation of this example not only had low impurity content, but also had good long-term stability, which meets the specifications of the Pharmacopoeia and the requirements for drug marketing.

[00204] Compared with Example 2, in this example, a thickening agent was added, and the addition amount of the co-solvent was reduced. It can be seen that the changes of the viscosity of the liquid preparation and the adjustment of the addition amount of the co-solvent in the present disclosure have no substantial effect on the physical and chemical stability of the liquid preparation of the present disclosure, and will not affect the marketing and use of the drug.

[00205] Example 4

[00206] In this example, the type and addition amount of the thickening agent in the formula were adjusted to investigate the stability.

[00207] (1) Experimental formula

[00208] Table 12 Formula table

Material name	Role in formula	Unit measurement (g/1000mL)
Tizanidine hydrochloride	Active ingredient	0.46
Hydroxypropyl cellulose	Thickening agent	25.00
Colloidal silicon dioxide	Thickening agent	5.0
Sodium methylparaben	Preservative	1.0
Sodium propylparaben	Preservative	0.1
70% sorbitol	Co-solvent	150.00
Disodium EDTA	Chelating agent	1.00
Sucralose	Sweetening agent	0.50
Citric acid	pH adjusting agent	0.90
Sodium citrate	pH adjusting agent	0.40
Strawberry aromatic agent	Aromatic agent	0.50

Purified water (appropriate amount)	Diluent	Making up to 1000mL
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[00209] (II) Process

[00210] The materials were weighed according to the prescribed amount for use;

[00211] (1) Hydroxypropyl cellulose was added to an appropriate amount of water to disperse, and stirred until the solution became clear.

5 **[00212]** (2) Disodium EDTA was dissolved in water and the mixture was added to the solution obtained in step (1) under stirring, and stirred until the solution became clear.

[00213] (3) Sorbitol with a concentration of 70% was added to the solution obtained in step (2) under stirring, and stirred until the solution became clear.

10 **[00214]** (4) Sodium methylparaben and sodium propylparaben were dissolved in water, and the mixture was added to the solution obtained in step (3) under stirring.

[00215] (5) Citric acid and sodium citrate were dissolved in water, and the mixture was added to the solution obtained in step (4) with stirring.

[00216] (6) Sucralose was dissolved in water, and the mixture was added to the solution obtained in step (5).

15 **[00217]** (7) Colloidal silicon dioxide was dispersed in water and the mixture was added to the solution obtained in step (6) with stirring.

[00218] (8) Tizanidine hydrochloride was dissolved in water alone, then the mixture was added to the solution obtained in step (7) under continuous stirring.

20 **[00219]** (9) Strawberry aromatic agent was added to the solution obtained in step (8) under continuous stirring.

[00220] (10) Water was added to adjust the volume to 1000 mL, and the obtained solution was filtered to obtain a tizanidine hydrochloride liquid preparation.

[00221] (III) Stability investigation

[00222] The liquid preparations prepared in this example were subjected to accelerated test.

25 **[00223]** Table 13 Detection results of the related substances in accelerated test

Condition	0 day	Accelerated for 1 month-40°C /75%RH		Accelerated for 3 months-40°C /75%RH	
		Glass bottle	Polyester bottle	Glass bottle	Polyester bottle
Content %	102.2	101.2	101.4	102.9	101.7
Total impurity of the related substances%	Undetected	Undetected	Undetected	0.08	0.09

[00224] At 0 day, the pH value of the liquid preparation of this example was measured to be 5.1. Since when the pH value of the tizanidine liquid preparation of the present disclosure changes within the range of 4.0-6.1, the stability of the present disclosure is not substantially affected, the pH value was not investigated in this example.

5 **[00225]** Under accelerated conditions, the total impurity content of the related substances in the liquid preparation of this example in 0, 1, and 3 months was all less than 0.2%, far less than the limit of 0.5% specified by the Pharmacopoeia, indicating the liquid preparation of this example had good chemical stability, and complied with regulations of the Pharmacopoeia.

10 **[00226]** On the basis of Example 3, the formula of this example was added with colloidal silicon dioxide to adjust the formula of the thickening agent. According to the comparison of the detection results of the total impurities of the related substances in Table 10 and Table 13, it can be seen that the changes of the formula of the thickening agent had no substantial effect on the chemical stability of the present disclosure; and according to the comparison results of Table 7/Table 10 and Table 13, it can be seen that the chemical stability of the tizanidine liquid preparation of this example was obviously not lower than that of the tizanidine liquid preparation of Example 2/Example 3. Under accelerated conditions, the impurity content of the related substances of the tizanidine liquid preparation of this example in 0-3 months complied with the regulations of the Pharmacopoeia.

20 **[00227]** There was no big difference in the detection results of the related substances in the liquid preparation of this example stored in the glass bottle and the polyester bottle. It can be seen that the liquid preparation of this example did not have strict requirements on storage containers, and storage containers can be selected according to actual needs during storage and transportation.

[00228] Meanwhile, the liquid preparation of this example did not appear precipitation, turbidity

or other phenomena, which had good physical stability.

[00229] It can be seen that the adjustment of the formula of the thickening agent has no substantial effect on the physical and chemical stability of the liquid preparation of the present disclosure, and will not affect the marketing and use of the drug.

5 [00230] **Example 5**

[00231] In this example, the adjustment of excipients was intensified to investigate the stability.

[00232] (I) Experimental formula

[00233] Table 14 Formula table

Material name	Role in formula	Unit measurement (g/1000mL)
Tizanidine hydrochloride	Active ingredient	0.46
Hydroxypropyl cellulose	Thickening agent	50.0
Sodium benzoate	Preservative	1.0
Glycerin	Sweetening agent	150.0
70% sorbitol	Co-solvent	250.0
Disodium EDTA	Chelating agent	1.0
Sucralose	Sweetening agent	0.5
Strawberry aromatic agent	Aromatic agent	0.5
Purified water (appropriate amount)	Diluent	Making up to 1000mL

[00234] (II) Process

10 [00235] The materials were weighed according to the prescribed amount for use;

[00236] (1) Hydroxypropyl cellulose was added to an appropriate amount of water to disperse, and stirred until the solution became clear.

[00237] (2) Sodium benzoate was dissolved in water and the mixture was added to the solution obtained in step (1).

15 [00238] (3) Then disodium EDTA was dissolved in water and the mixture was added to the solution obtained in step (2) under stirring.

[00239] (4) Sucralose was added to the solution obtained in step (3) and stirred evenly.

[00240] (5) Glycerin was added to the solution obtained in step (4).

[00241] (6) Sorbitol with a concentration of 70% was added to the solution obtained in step (5)

under stirring.

[00242] (7) Tizanidine hydrochloride was dissolved in water alone, then the mixture was added to the solution obtained in step (6) under continuous stirring.

5 [00243] (8) Strawberry aromatic agent was added to the solution obtained in step (7) under continuous stirring.

[00244] (9) Water was added to adjust the volume to 1000 mL, and the obtained solution was filtered to obtain a tizanidine hydrochloride liquid preparation.

[00245] (III) Stability investigation

[00246] The liquid preparations prepared in this example were subjected to accelerated test.

10 [00247] Table 15 Detection results of the related substances in accelerated test

Condition	0 day	Accelerated for 1 month-40°C /75%RH		Accelerated for 3 months-40°C /75%RH	
		Glass bottle	Polyester bottle	Glass bottle	Polyester bottle
Content %	97.9	97.8	98.5	101.8	101.4
Total impurity of the related substances%	Undetected	Undetected	Undetected	Undetected	Undetected

15 [00248] Under accelerated conditions, the total impurities of the related substances in this example were not detected in 0, 1, and 3 months. The total impurity content was all less than 0.2%, far less than the limit of 0.5% stipulated in the Pharmacopoeia, indicating the liquid preparation of this example had good chemical stability, and complied with regulations of the Pharmacopoeia.

[00249] There was no difference in the detection results of the related substances of this example stored in the glass bottle and the polyester bottle. It can be seen that this example did not have strict requirements on the storage containers, and the storage containers can be selected according to actual needs during storage and transportation.

20 [00250] Meanwhile, the tizanidine liquid preparation of this example did not appear precipitation, turbidity or other phenomena, which had good physical stability.

[00251] Compared with the formula of Example 2, the pH value adjusting agent was deleted in

this example. The pH value of the medicinal solution in this example was detected to be 4.9 at 0 day, which was within the pH value range of 4.0-6.1. According to the comparison results of the total impurities of the related substances in this example and Example 2 under the accelerated test (comparing Table 15 with Table 7), it can be seen that the deletion of the pH value adjusting agent had no substantial effect on the physical and chemical stability of the liquid preparation of the present disclosure, and will not affect the marketing and use of the drug.

[00252] In this example, the preservative in the formula of Example 2 was replaced with sodium benzoate. According to the comparison results of the total impurities of the related substances in this example and Example 2 under the accelerated test (comparing Table 15 with Table 7), it can be seen that the replacement of the preservative had no substantial impact on the physical and chemical stability of the liquid preparation of the present disclosure, and will not affect the marketing and use of the drug.

[00253] Compared with the formula of Example 2, glycerin was added as a sweetening agent in this example. According to the comparison results of the total impurities of the related substances in this example and Example 2 under the accelerated test (comparing Table 15 with Table 7), it can be seen that the change of the sweetening agent formula had no substantial impact on the physical and chemical stability of the liquid preparation of the present disclosure, and will not affect the marketing and use of the drug.

[00254] Compared with the formula of Example 2, hydroxypropyl cellulose was added as a thickening agent in this example. According to the comparison results of the total impurities of the related substances in this example and Example 2 under the accelerated test (comparing Table 15 with Table 7), it can be seen that the addition of the thickening agent had no substantial impact on the physical and chemical stability of the liquid preparation of the present disclosure, and will not affect the marketing and use of the drug.

[00255] Compared with the formula of Example 2, in the formula of this example, in addition to the active substance tizanidine hydrochloride, only the excipients sorbitol, disodium EDTA, and sucralose and strawberry aromatic agent which only play a role in correcting the taste were retained, the rest of the excipients were all different. It can be seen that in addition to sorbitol and disodium EDTA, corresponding changes and deletions of other excipients within the scope of

knowledge of those skilled in the art have no substantial impact on the physical and chemical stability of the liquid preparation of the present disclosure, and will not affect the marketing and use of the drug.

[00256] Meanwhile, according to the comparison between Example 1 and Example 2, it can be seen that the addition of co-solvent-sorbitol had no substantial effect on the physical and chemical stability of the liquid preparation of the present disclosure, and will not affect the marketing and use of the drug.

[00257] It can be seen that the changes and deletions of other excipients other than disodium EDTA in the present disclosure will not have a substantial impact on the physical and chemical stability of the present disclosure. The other excipients comprise but are not limited to:

[00258] a pH adjusting agent (citric acid, ascorbic acid, acetic acid, tartaric acid, trisodium citrate, sodium citrate, potassium citrate, sodium phosphate, tricalcium phosphate, calcium carbonate, sodium bicarbonate, calcium phosphate, calcium carbonate, magnesium hydroxide, hydrochloric acid, sodium hydroxide, etc.); and/or

[00259] a co-solvent (sorbitol, maltitol, mannitol, isomaltose, xylitol, glucose, fructose, etc.); and/or

[00260] a preservative (sodium benzoate, ethylparaben, propylparaben, sodium methylparaben, sodium ethylparaben, sodium propylparaben, benzoic acid, potassium phenylpropionate, sorbic acid, sodium sorbate, calcium sorbate, potassium sorbate, dehydroacetic acid, sodium diacetate, calcium propionate, etc.); and/or

[00261] a thickening agent (hypromellose, hydroxypropyl cellulose, colloidal silicon dioxide, methylcellulose, sodium carboxymethylcellulose, sodium alginate, cyclodextrin, etc.); and/or

[00262] an aromatic agent (strawberry aromatic agent, orange aromatic agent, banana aromatic agent, cherry aromatic agent, lemon aromatic agent, cardamom aromatic agent, fennel aromatic agent, mint aromatic agent, menthol aromatic agent, vanillin aromatic agent, etc.); and/or

[00263] a sweetening agent (sucralose, glycerin, sodium saccharin, glucose, stevia, stevioside, aspartame, cyclamate, acesulfame potassium, alitame, neotame, etc.); and/or

[00264] a coloring agent for color-enhancing effect only (amaranth red, carmine, erythrosine,

new red, lemon yellow, sunset yellow, indigo, beet red, shellac red, bilberry red, capsicum red, red rice red, etc.).

5 [00265] The investigation time designed for the stability research of the tizanidine liquid preparation of the present disclosure was 24 months or longer. At present, the data of the 0-3 month accelerated test and the 0-6 month normal temperature test of the tizanidine liquid preparation of the present disclosure show that the impurity content of the related substances thereof was all less than 0.2% at 40°C /75%RH and 25°C /60%RH, which was far less than the limit of 0.5% stipulated in the Pharmacopoeia. This shows that the stability of the liquid preparation of the present disclosure under the medicine storage conditions can be expected to be
10 comparable to the stability obtained in the above-described stability test.

[00266] The tizanidine liquid preparation of the present disclosure was added with a preservative to investigate the efficacy of the preservative and the stability of 24 months or longer. It can be expected that the microbial indicators of the liquid preparation of the present disclosure meet the quality standards of medicines.

15 [00267] In the present disclosure, the human pharmacokinetic test under a pre-prandial (i.e., fasting) or a post-prandial condition through clinical trials was performed below, and meanwhile the incidence of adverse reactions was investigated:

[00268] Experimental sample:

[00269] i. The tizanidine hydrochloride liquid preparation prepared in Example 1;

20 [00270] ii. The tizanidine hydrochloride liquid preparation prepared in Example 2;

[00271] iii. Zanaflex® (tizanidine hydrochloride) 4mg tablet (standard 1);

[00272] iv. Zanaflex® (tizanidine hydrochloride) 4mg capsule (standard 2).

[00273] Pre-prandial (fasting) bioequivalence test method and test results:

25 [00274] This test was conducted in 25 healthy adult subjects under a pre-prandial condition, using a randomized, open-label, crossover, single-dose (4 mg as calculated in tizanidine), 5-cycle and 5-sequence crossover test design. The cycle washout period was 2 days. The subjects were fasted for at least 10 hours before administration, prohibited from drinking water one hour before and one hour after administration (except for 240 mL of water during administration), and

provided with standard meals 4 hours and 8 hours after administration. The subjects were not allowed to eat food or beverages containing caffeine and/or xanthine (e.g., coffee, tea, soda water containing caffeine, cola, etc.), and were prohibited from eating grapefruit and/or grapefruit juice, and food containing poppy during the first 48 hours of each cycle and throughout the test period.

5 [00275] Administration method:

[00276] The administration method of the liquid preparation was as follows: the subject maintained a sitting position, and 10mL of i/ii was injected into the subject's mouth with an oral syringe, which was swallowed together with 50mL of water by the subject. The syringe was rinsed by 10mL of water, and the washing water was injected into the subject's mouth, which was
10 repeated three times. Then the subject was provided with water to ensure that the total amount of water provided to the subject during the medicine taking was 240 mL. The subject kept a sitting position within two hours after taking the medicine.

[00277] The administration method of tablets/capsules was as follows: the subject maintained a sitting position, a single dose of iii/iv was placed in the subject's mouth, and swallowed in
15 entirety with 240 mL of water (the subject was not allowed to chew or crush the tablets/capsules). The subject kept a sitting position within two hours after taking the medicine.

[00278] 2.5 mL of blood samples of subjects in each cycle were collected before administration (0.00h) and 0.08h, 0.16h, 0.25h, 0.33h, 0.50h, 0.67h, 0.83h, 1.00h, 1.25h, 1.50h, 1.75h, 2.00 h, 2.50 h, 3.00 h, 4.00 h, 6.00 h, 8.00 h, 10.00 h and 12.00 h after administration, respectively. The
20 relevant pharmacokinetic parameters were calculated.

[00279] $T_{\max}$ is the peak time of the drug.

[00280] $C_{\max}$ is the peak concentration, i.e., the maximum blood concentration measured.

[00281] AUC_{0-t} was calculated by the linear trapezoidal method.

[00282] $AUC_{0-\infty} = AUC_{0-t} + Ct/\lambda_z$. t is the sample collecting time of the last measurable blood
25 drug concentration; Ct is the drug concentration of the last measurable sample, and λ_z is the terminal elimination rate constant.

[00283] Table 16 Results of human pharmacokinetic test under a pre-prandial condition

Parameter (mean value)	i	ii	iii	iv
$C_{\max}$ (pg/mL)	6891.0570	6700.6869	6214.9907	6884.0184
AUC_{0-t} (pg·hr/mL)	16452.1907	16750.9623	15326.0384	15937.0213
$AUC_{0-\infty}$ (pg·hr/mL)	16770.7496	17017.0368	15570.9400	16190.1320
$T_{\max}$ (hr)	0.80	0.71	0.87	0.87

[00284] Table 17 Results of bioequivalence evaluation of i and iii under a pre-prandial condition

Parameter	Lower 90% CI	Upper 90% CI	90% CI equivalent range	Result
$C_{\max}$	84.51%	125.59%	69.56–143.76 %	Equivalent
AUC_{0-t}	84.98%	118.93%	73.50–136.06%	Equivalent
$AUC_{0-\infty}$	85.75%	117.62%	74.87–133.57%	Equivalent

[00285] Table 18 Results of bioequivalence evaluation of i and iv under a pre-prandial condition

Parameter	Lower 90% CI	Upper 90% CI	90% CI equivalent range	Result
$C_{\max}$	86.83 %	128.34%	69.56–143.76 %	Equivalent
AUC_{0-t}	92.29%	128.55%	73.50–136.06%	Equivalent
$AUC_{0-\infty}$	91.72%	125.24%	74.87–133.57%	Equivalent

[00286] Table 19 Results of bioequivalence evaluation of ii and iii under a pre-prandial condition

Parameter	Lower 90% CI	Upper 90% CI	90% CI equivalent range	Result
$C_{\max}$	86.42%	128.38%	69.56–143.76 %	Equivalent
AUC_{0-t}	87.94%	123.02%	73.50–136.06%	Equivalent
$AUC_{0-\infty}$	89.03%	122.07%	74.87–133.57%	Equivalent

5 **[00287]** Table 20 Results of bioequivalence evaluation of ii and iv under a pre-prandial condition

Parameter	Lower 90% CI	Upper 90% CI	90% CI equivalent range	Result
$C_{\max}$	88.78%	131.22 %	69.56–143.76 %	Equivalent
AUC_{0-t}	95.47%	132.99 %	73.50–136.06%	Equivalent
$AUC_{0-\infty}$	95.20%	130.00 %	74.87–133.57%	Equivalent

[00288] Conclusion: The tizanidine liquid preparation prepared by the present disclosure can achieve bioequivalence with the existing commercial standard product-Zanaflex® (tizanidine hydrochloride) 4 mg tablet/capsule under a pre-prandial condition.

[00289] Investigation test and test results of pre-prandial (fasting) adverse reaction:

[00290] During the pre-prandial bioequivalence test, the adverse reactions of the subjects during the whole experiment were recorded by means of observation, interview and active reporting.

[00291] Table 21 Investigation results of adverse reactions and the incidence thereof under a pre-prandial condition

Sample	i	ii	iii	iv
Drowsiness	None	8.00%	40.00%	16.00%
Headache	None	None	None	None
Asthenia	None	None	None	None
Vertigo	None	4.00%	None	None
Incidence of adverse reactions	0	12.00%	40.00%	16.00%

[00292] As can be seen from the experimental results in the above table, the incidence of pre-prandial adverse reactions (drowsiness, headache, asthenia, vertigo) in Example 1/Example 2 of the present disclosure was 0/12.00%, while the incidence of the adverse reactions (drowsiness, headache, asthenia, vertigo) of tablets/capsules was 40.00%/16.00%. It can be seen that under a pre-prandial condition, the incidence of adverse reactions (drowsiness, headache, asthenia, vertigo) of the tizanidine liquid preparation of the present disclosure was smaller than that of the existing solid preparations.

[00293] Post-prandial bioequivalence test method and test results:

[00294] The test was conducted in 27 healthy adult subjects under a post-prandial condition using a randomized, open-label, crossover, single-dose (tizanidine 4 mg), 6-cycle and 3-sequence partially replicated test design. The cycle washout period was 2 days. The subjects were fasted for at least 10 hours before administration, prohibited from drinking water one hour before and one hour after administration (except for 240 mL of water during administration), then provided with a high-calorie, high-fat, non-vegetable standard meal at 0.5h before administration, administered within 0.5 h after the meal, and provided with a high-calorie, high-fat, non-vegetable standard meal at 4, 8, and 12 h after administration. The subjects were not allowed to eat food or beverages containing caffeine and/or xanthine (e.g., coffee, tea, soda water containing caffeine, cola, etc.), and were prohibited from eating grapefruit and/or grapefruit juice, and food containing poppy during the first 48 hours of each cycle and throughout the test period.

[00295] Administration method:

[00296] The administration method of the liquid preparation was as follows: the subject maintained a sitting position, and 10mL of i/ii was injected into the subject's mouth with an oral syringe, which was swallowed together with 50mL of water by the subject. The syringe was rinsed by 10mL of water, and the washing water was injected into the subject's mouth, which was repeated three times. Then the subject was provided with water to ensure that the total amount of water provided to the subject during the medicine taking was 240 mL. The subject kept a sitting position within two hours after taking the medicine.

[00297] The administration method of tablets/capsules was as follows: the subject maintained a sitting position, a single dose of iii/iv was placed in the subject's mouth, and swallowed in entirety with 240 mL of water (the subject was not allowed to chew or crush the tablets/capsules). The subject kept a sitting position within two hours after taking the medicine.

[00298] 2.5 mL of blood samples of subjects in each cycle were collected before administration (0.00h) and 0.08h, 0.16h, 0.25h, 0.33h, 0.50h, 0.67h, 0.83h, 1.00h, 1.25h, 1.50h, 1.75h, 2.00 h, 2.50 h, 3.00 h, 4.00 h, 6.00 h, 8.00 h, 10.00 h and 12.00 h after administration, respectively. The relevant pharmacokinetic parameters were calculated.

[00299] $C_{\max}$ is the peak concentration, i.e., the maximum blood concentration measured.

[00300] AUC_{0-t} was calculated by the linear trapezoidal method.

[00301] $AUC_{0-\infty} = AUC_{0-t} + C_t / \lambda_z$. t is the sample collecting time of the last measurable blood drug concentration; C_t is the drug concentration of the last measurable sample, and λ_z is the terminal elimination rate constant.

[00302] Table 22 Results of human pharmacokinetic test under a post-prandial condition

Parameter (mean value)	i	ii	iii	iv
$C_{\max}$ (pg/mL)	4879.123	4852.799	5395.440	4832.833
AUC_{0-t} (pg·hr/mL)	14551.615	14810.490	14943.559	15267.928
$AUC_{0-\infty}$ (pg·hr/mL)	14783.945	15051.702	15180.678	15557.618
$T_{\max}$ (hr)	0.94	1.00	1.74	2.02

[00303] In the above table, the T_{max} of the tizanidine hydrochloride liquid preparation of Example 1/Example 2 of the present disclosure was 0.94/1.00 hour; whereas the T_{max} of the existing (tizanidine hydrochloride) tablet/capsule was 1.74/2.02 hour. It can be seen that under the post-prandial condition, the T_{max} of the liquid preparation of the present disclosure was significantly lower than that of the existing solid preparation, indicating that the drug action was obviously accelerated.

[00304] According to the comparison results of Table 16 and Table 22, it can be seen that the T_{max} of the tizanidine hydrochloride liquid preparation of Example 1/Example 2 of the present disclosure under the post-prandial condition was only 0.14/0.29 hours longer than that under the pre-prandial condition, while the T_{max} of the existing tablet/capsule under the post-prandial condition was 0.87/1.15 hours longer than that under the pre-prandial condition. It can be seen that the impact of food on the T_{max} of the present disclosure is less than its impact on the existing solid preparations.

[00305] It can be seen that the effect of food on the drug action speed of the tizanidine hydrochloride liquid preparation of the present disclosure is less than its effect on the existing solid preparation; under the post-prandial condition, the present disclosure has a faster drug action than the existing solid preparations.

[00306] Since the post-prandial bioequivalence test method used a partially replicated test design, it is well known to those skilled in the art that if the S_{WR} (intra-individual standard deviation) ≥ 0.294 (i.e., $ISCV\% \geq 30\%$), the RSABE method can be used for equivalence evaluation (applying to any or all of AUC_{0-t} , $AUC_{0-\infty}$, C_{max}). The standard for determining whether the pharmacokinetic parameters (AUC_{0-t} , $AUC_{0-\infty}$, or C_{max}) of the test preparation and reference preparation are bioequivalently equivalent by using RSABE method is: the point estimate of the geometric mean ratio of the calculated parameter (hereinafter referred to as the point estimate) is within the range of 80%-125%, and meanwhile, the upper limit of the one-sided 95% confidence interval of the calculated parameter (abbreviated as 95% confidence upper limit) ≤ 0 . If $S_{WR} < 0.294$ (i.e., $ISCV\% < 30\%$), the ABE method should be used to evaluate the bioequivalence.

[00307] Table 23-1 Results of C_{max} bioequivalence evaluation of i and iii under a post-prandial

condition

Parameter	ISCV%	Point estimate (%)	95% confidence upper limit	Result
$C_{\max}$	51.62%	98.60%	-0.1251	Equivalent

[00308] Table 23-2 Results of AUC_{0-t} and $AUC_{0-\infty}$ bioequivalence evaluation of i and iii under a post-prandial condition

Parameter	ISCV%	Lower 90% CI	Upper 90% CI	90% CI equivalent range	Result
AUC_{0-t}	25.75%	94.27%	115.44%	80.00-125.00%	Equivalent
$AUC_{0-\infty}$	25.62%	94.48%	115.54%	80.00-125.00%	Equivalent

[00309] Table 24-1 Results of $C_{\max}$ bioequivalence evaluation of i and iv under a post-prandial condition

Parameter	ISCV%	Point estimate (%)	95% confidence upper limit	Result
$C_{\max}$	33.64%	108.39%	-0.0241	Equivalent

[00310] Table 24-2 Results of AUC_{0-t} and $AUC_{0-\infty}$ bioequivalence evaluation of i and iv under a post-prandial condition

Parameter	ISCV%	Lower 90% CI	Upper 90% CI	90% CI equivalent range	Result
AUC_{0-t}	26.04%	92.62%	116.22%	80.00-125.00%	Equivalent
$AUC_{0-\infty}$	25.46%	92.50%	115.82%	80.00-125.00%	Equivalent

[00311] Table 25-1 Results of $C_{\max}$ bioequivalence evaluation of ii and iii under a post-prandial condition

Parameter	ISCV%	Point estimate (%)	95% confidence upper limit	Result
$C_{\max}$	51.62%	103.73%	-0.122	Equivalent

[00312] Table 25-2 Results of AUC_{0-t} and $AUC_{0-\infty}$ bioequivalence evaluation of ii and iii under a post-prandial condition

Parameter	ISCV%	Lower 90% CI	Upper 90% CI	90% CI equivalent range	Result
AUC_{0-t}	25.97%	104.12%	123.69%	80.00-125.00%	Equivalent
$AUC_{0-\infty}$	25.74%	104.30%	123.74%	80.00-125.00%	Equivalent

[00313] Table 26-1 Results of $C_{\max}$ bioequivalence evaluation of ii and iv under a post-prandial condition

Parameter	ISCV%	Point estimate (%)	95% confidence upper	Result
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			limit	
C_{max}	33.64%	114.46%	-0.0041	Equivalent

[00314] Table 26-2 Results of AUC_{0-t} and $AUC_{0-\infty}$ bioequivalence evaluation of ii and iv under a post-prandial condition

Parameter	ISCV%	Lower 90% CI	Upper 90% CI	90% CI equivalent range	Result
AUC_{0-t}	25.85%	103.32%	122.33%	80.00-125.00%	Equivalent
$AUC_{0-\infty}$	25.30%	103.10%	121.88%	80.00-125.00%	Equivalent

[00315] Conclusion: The tizanidine liquid preparation prepared by the present disclosure can achieve bioequivalence with the existing commercial standard product-Zanaflex® (tizanidine hydrochloride) 4 mg tablet/capsule under a post-prandial condition.

[00316] Investigation test and test results of post-prandial adverse reaction:

[00317] During the post-prandial bioequivalence test, the adverse reactions of the subjects during the whole experiment were recorded by means of observation, interview and active reporting.

[00318] Table 27 Investigation results of adverse reactions and the incidence thereof under a post-prandial condition

Sample	i	ii	iii	iv
Drowsiness	3.70%	3.70%	25.92%	22.22%
Vomiting	None	None	None	1.85%
Headache	None	None	3.70%	1.85%
Incidence of adverse reactions	3.70%	3.70%	29.62%	25.92%

[00319] As can be seen from the experimental results in the above table, the incidence of post-prandial adverse reactions (drowsiness, vomiting, headache) in Example 1/Example 2 of the present disclosure was 3.70%/3.70%, whereas the incidence of the adverse reactions (drowsiness, vomiting, headache) of tablets/capsules was 29.62%/25.92%. It can be seen that under a post-prandial condition, the incidence of adverse reactions (drowsiness, vomiting, headache) of the tizanidine liquid preparation of the present disclosure was smaller than that of the existing solid preparations.

[00320] From the investigation results of the adverse reactions and the incidence thereof in Table 21 and Table 27, it can be seen that the incidence of the adverse reaction item-drowsiness

of the tizanidine liquid preparation of the present disclosure under the pre-prandial/post-prandial conditions was both smaller than that of the solid preparations (i.e. tablet and capsule preparations); the incidence of the adverse reaction item-headache under the post-prandial condition was smaller than that of the solid preparations (i.e. tablet and capsule preparations); and the incidence of the adverse reaction item-vomiting under the post-prandial condition was smaller than that of the capsule preparation.

[00321] It can be seen that the incidence of adverse reactions of the tizanidine liquid preparation of the present disclosure is smaller than that of the existing solid preparations, no matter under the pre-prandial or post-prandial conditions. The liquid preparation of the present disclosure changes the pharmaceutical dosage form of tizanidine and the related excipients, thereby significantly reducing the drug adverse reactions, which is unexpected by those skilled in the art. The reduction of the adverse reaction rate of the medicine of the present disclosure improves the safety of the drug use and the compliance of patients taking the medicine in the present disclosure.

[00322] To sum up, the tizanidine liquid preparation of the present disclosure has low impurity content and strong stability. Compared with the existing tizanidine solid preparations, the tizanidine liquid preparation has low adverse reaction rate, little effect of food on the drug action speed, fast drug action speed under a post-prandial condition, and equivalent bioavailability to the existing solid preparations, which satisfies the clinical needs.

[00323] The above description of the disclosed embodiments enables those skilled in the art to realize or use the present disclosure. Various modifications to these embodiments will be readily obvious to those skilled in the art, and the generic principles defined herein may be realized in other embodiments without departing from the spirit or scope of the present disclosure. Thus, the present disclosure is not intended to be limited to the embodiments shown herein, but is to be accorded the widest scope consistent with the principles and novel features disclosed herein.

CLAIMS

1. A tizanidine liquid preparation, comprising an active ingredient, disodium EDTA and other pharmaceutical excipients; the active ingredient is one or more of tizanidine or a pharmaceutically acceptable salt, solvate and hydrate thereof.

2. The tizanidine liquid preparation according to claim 1, wherein the pH value of the liquid preparation is greater than 3.5 and smaller than 6.5.

3. The tizanidine liquid preparation according to claim 1, wherein the pH value of the liquid preparation is 4.0-6.1.

4. The tizanidine liquid preparation according to claim 1, wherein the liquid preparation comprises solvent, and the solvent is water.

5. The tizanidine liquid preparation according to claim 1, wherein the other pharmaceutical excipient is one or more of a pH adjusting agent, a preservative, a co-solvent, a thickening agent, an aromatic agent, a sweetening agent and a coloring agent.

6. The tizanidine liquid preparation according to claim 5, wherein the pH adjusting agent is one or more of citric acid, ascorbic acid, acetic acid, tartaric acid, trisodium citrate, sodium citrate, potassium citrate, sodium phosphate, tricalcium phosphate, calcium carbonate, sodium bicarbonate, calcium phosphate, calcium carbonate, magnesium hydroxide, hydrochloric acid and sodium hydroxide;

the co-solvent is one or more of sorbitol, maltitol, mannitol, isomaltose, xylitol, glucose and fructose;

the preservative is one or more of sodium benzoate, ethylparaben, propylparaben, sodium methylparaben, sodium ethylparaben, sodium propylparaben, benzoic acid, potassium phenylpropionate, sorbic acid, sodium sorbate, calcium sorbate, potassium sorbate, dehydroacetic acid, sodium diacetate, and calcium propionate;

the thickening agent is one or more of hypromellose, hydroxypropyl cellulose, colloidal silicon dioxide, methyl cellulose, sodium carboxymethyl cellulose, sodium alginate, and cyclodextrin;

the aromatic agent is one or more of strawberry aromatic agent, orange aromatic agent, banana aromatic agent, cherry aromatic agent, lemon aromatic agent, cardamom aromatic agent, fennel aromatic agent, mint aromatic agent, menthol aromatic agent and vanillin aromatic agent;

the sweetening agent is one or more of sucralose, glycerin, sodium saccharin, glucose, stevia, stevioside, aspartame, sodium cyclamate, acesulfame potassium, alitame, and neotame;

the coloring agent is one or more of amaranth red, carmine, erythrosine, new red, lemon yellow, sunset yellow, indigo, beet red, shellac red, bilberry red, capsicum red, and red rice red.

7. The tizanidine liquid preparation according to claim 5, wherein the pH adjusting agent is a mixture of citric acid and sodium citrate;

the preservative is a mixture of sodium methylparaben and sodium propylparaben, or sodium benzoate;

the co-solvent is sorbitol;

the thickening agent is a mixture of hydroxypropyl cellulose and colloidal silicon dioxide, or hydroxypropyl cellulose;

the aromatic agent is strawberry aromatic agent;

the sweetening agent is sucralose.

8. The tizanidine liquid preparation according to claim 6, wherein each 100 mL of the liquid preparation comprises the following components:

0.02-1 g of active ingredient, 0-0.2 g of disodium EDTA; wherein the content of disodium EDTA is not 0.

9. The tizanidine liquid preparation according to claim 6, wherein each 100mL liquid preparation comprises the following components:

tizanidine	0.02-1g
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disodium EDTA	0.005-0.2g.
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10. The tizanidine liquid preparation according to claim 6, wherein each 100mL liquid preparation comprises the following components:

tizanidine	0.02-1g
disodium EDTA	0.005-0.2g
citric acid	0.01-0.2g
sodium citrate	0.01-0.1g.

5 11. The tizanidine liquid preparation according to claim 6, wherein each 100mL liquid preparation comprises the following components:

tizanidine	0.04-0.09g
disodium EDTA	0.008-0.12g
citric acid	0.06-0.14g
10 sodium citrate	0.02-0.06g.

12. The tizanidine liquid preparation according to claim 6, wherein the liquid preparation comprises the following components:

tizanidine, sodium methylparaben, sodium propylparaben, disodium EDTA, sucralose, citric acid, sodium citrate, strawberry aromatic agent and water; or

15 tizanidine, sodium methylparaben, sodium propylparaben, sorbitol, disodium EDTA, sucralose, citric acid, sodium citrate, strawberry aromatic agent and water; or

tizanidine, hydroxypropyl cellulose, sodium methylparaben, sodium propylparaben, sorbitol, disodium EDTA, sucralose, citric acid, sodium citrate, strawberry aromatic agent and water; or

20 tizanidine, hydroxypropyl cellulose, colloidal silicon dioxide, sodium methylparaben, sodium propylparaben, sorbitol, disodium EDTA, sucralose, citric acid, sodium citrate, strawberry aromatic agent and water; or

tizanidine, hydroxypropyl cellulose, sodium benzoate, glycerin, sorbitol, disodium EDTA, sucralose, strawberry aromatic agent and water.

25 13. The tizanidine liquid preparation according to claim 12, wherein each 100 mL of the liquid preparation comprises the following components:

tizanidine hydrochloride 0.046g, sodium methylparaben 0.1g, sodium propylparaben 0.01g,

disodium EDTA 0.1g, sucralose 0.05g, citric acid 0.083g, sodium citrate 0.042g, strawberry aromatic agent 0.05g, and the remainder water; or

tizanidine hydrochloride 0.046g, sodium methylparaben 0.1g, sodium propylparaben 0.01g, 70% sorbitol solution 25g, disodium EDTA 0.1g, sucralose 0.05g, citric acid 0.09g, sodium citrate 0.035g, strawberry aromatic agent 0.05g, and the remainder water; or

tizanidine hydrochloride 0.046g, hydroxypropyl cellulose 2.5g, sodium methylparaben 0.1g, sodium propylparaben 0.01g, 70% sorbitol solution 15g, disodium EDTA 0.1g, sucralose 0.05g, citric acid 0.09g, sodium citrate 0.046g, strawberry aromatic agent 0.05g, and the remainder water; or

tizanidine hydrochloride 0.046g, hydroxypropyl cellulose 2.5g, colloidal silicon dioxide 0.5g, sodium methylparaben 0.1g, sodium propylparaben 0.01g, 70% sorbitol solution 15g, disodium EDTA 0.1g, sucralose 0.05g, citric acid 0.09g, sodium citrate 0.04g, strawberry aromatic agent 0.05g, and the remainder water; or

tizanidine hydrochloride 0.046g, hydroxypropyl cellulose 5g, sodium benzoate 0.1g, glycerin 15g, 70% sorbitol solution 25g, disodium EDTA 0.1g, sucralose 0.05g, strawberry aromatic agent 0.05g, and the remainder water.

14. The tizanidine liquid preparation according to any of claims 1-13, wherein the content of tizanidine hydrochloride in the liquid preparation is 0.046g/100mL, and the liquid preparation also comprises disodium EDTA; when the liquid preparation is stored at room temperature, the total impurity amount of its related substances is $\leq 0.2\%$, and/or, after the liquid preparation is administered, the mean value of $C_{\max}$, mean value of AUC_{0-t} and/or mean value of $AUC_{0-\infty}$ of tizanidine thereof are respectively within the range of 80%-120% of the mean value of $C_{\max}$, mean value of AUC_{0-t} and/or mean value of $AUC_{0-\infty}$ of the tizanidine in the following liquid preparations after being administrated in equivalent doses with respect to tizanidine:

(1) each 100mL liquid preparation comprises tizanidine hydrochloride 0.046g, sodium methylparaben 0.1g, sodium propylparaben 0.01g, disodium EDTA 0.1g, sucralose 0.05g, citric acid 0.083g, sodium citrate 0.042g, strawberry aromatic agent 0.05g, and the remainder water; or

(2) each 100mL liquid preparation comprises tizanidine hydrochloride 0.046g, sodium

methylparaben 0.1g, sodium propylparaben 0.01g, 70% sorbitol solution 25g, disodium EDTA 0.1g, sucralose 0.05g, citric acid 0.09g, sodium citrate 0.035g, strawberry aromatic agent 0.05g, and the remainder water; or,

5 (3) each 100mL liquid preparation comprises tizanidine hydrochloride 0.046g, hydroxypropyl cellulose 2.5g, sodium methylparaben 0.1g, sodium propylparaben 0.01g, 70% sorbitol solution 15g, disodium EDTA 0.1g, sucralose 0.05g, citric acid 0.09g, sodium citrate 0.046g, strawberry aromatic agent 0.05g, and the remainder water; or

10 (4) each 100mL liquid preparation comprises tizanidine hydrochloride 0.046g, hydroxypropyl cellulose 2.5g, colloidal silicon dioxide 0.5g, sodium methylparaben 0.1g, sodium propylparaben 0.01g, 70% sorbitol solution 15g, disodium EDTA 0.1g, sucralose 0.05g, citric acid 0.09g, sodium citrate 0.04g, strawberry aromatic agent 0.05g, and the remainder water; or

(5) each 100mL liquid preparation comprises tizanidine hydrochloride 0.046g, hydroxypropyl cellulose 5g, sodium benzoate 0.1g, glycerin 15g, 70% sorbitol solution 25g, disodium EDTA 0.1g, sucralose 0.05g, strawberry aromatic agent 0.05g, and the remainder water.

15 15. The tizanidine liquid preparation according to any of claims 1-13, wherein when the liquid preparation is hermetically stored under the condition of 40°C/75%RH for 0-3 months, the total impurity amount of its related substances is $\leq 0.2\%$; and/or

when the liquid preparation is hermetically stored under the condition of 25°C/60%RH for 0-6 months, the total impurity amount of its related substances is $\leq 0.2\%$.

20 16. The tizanidine liquid preparation according to any of claims 1-13, wherein the pre-prandial and post-prandial bioavailability of the liquid preparation is equivalent with that of Zanaflex® tizanidine tablets; and/or

the pre-prandial and post-prandial bioavailability of the liquid preparation is equivalent with that of Zanaflex® tizanidine capsules.

25 17. The tizanidine liquid preparation according to claim 16, wherein under a post-prandial condition, the evaluation criteria for the bioavailability equivalence are:

the upper limit of the one-sided 95% confidence interval for $C_{\max}$ is ≤ 0 ;

the 90% confidence interval for AUC_{0-t} is between 80% -125%;

the 90% confidence interval for $AUC_{0-\infty}$ is between 80%-125%.

18. The tizanidine liquid preparation according to any of claims 1-13, wherein the mean value of T_{max} of the liquid preparation under the post-prandial condition is smaller than the mean value of T_{max} of the tizanidine tablets/capsules under the post-prandial condition.

5 19. The tizanidine liquid preparation according to any of claims 1-13, wherein under the condition of administering the same dose with respect to tizanidine:

the incidence of adverse reactions of the liquid preparation is smaller than the incidence of adverse reactions of the tizanidine tablets/capsules.

10 20. The tizanidine liquid preparation according to any of claims 1-13, wherein under the condition of administering the same dose with respect to tizanidine:

the incidence of the pre-prandial adverse reaction item-drowsiness of the liquid preparation is smaller than that of the tizanidine tablets/capsules; and/or

the incidence of post-prandial adverse reaction item-drowsiness of the liquid preparation is smaller than that of the tizanidine tablets/capsules; and/or

15 the incidence of post-prandial adverse reaction item-headache of the liquid preparation is smaller than that of the tizanidine tablets/capsules; and/or

the incidence of post-prandial adverse reaction item-vomiting of the liquid preparation is smaller than that of the tizanidine capsules.

20 21. Use of the tizanidine liquid preparation according to any of claims 1-20 in the preparation of a medicament for treating muscle spasm.