Study on Preparation and Stability of Sultamicillin Tosilate-β-Cyclodextrin

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Abstract. Preparation of sultamicillin tosilate β-cyclodextrin inclusion to study the stablility. Method: the contents of the inclusion compound of the mixture were determined by the method of saturated aqueous solution. The content of the mixture was determined by UV spectrophotometry and the content of the mixture was studied by using the method of determining the content of the mixture. Outcome: the results show that the inclusion complex was formed by the observation of microscope and infrared spectrum analysis. Its inclusion in high temperature, strong light and high humidity, Sultamicillinic tosilate concentration change is relatively large. So sultamicillin tosilate β-cyclodextrin inclusion should be kept in the dark, cool, dry conditions .

1 Introduction

Sultamicillin tosilate is formed by sulbactam and ampicillin connected to the double ester [1] .most commonly used to treat various diseases in respiratory tract infection [2].after oral administration in the intestinal wall by enterolactone enzymatic hydrolysis into sulbactam and ampicillin to play a role. sulbactam and ampicillin exist at the same time, not only protect the ampicillin from hydrolysis of beta lactamases destruction, but also expanded the spectrum antibiotic ampicillin, on Staphylococcus aureus strains, Acinetobacter and Bacteroides fragilis and other bacteria also has good antibacterial activity. But the bitter taste[3]is one of the major shortcomings, and drag the west of sultamicillin tosilate slightly soluble in water, and itself has a strong hydrophobic drug release speed is slow, so that the curative effect.

β- cyclodextrin (β-CD) is a seven glucose molecules, the compound 4- glycosidic linkage is made of a hollow cylinder having a slightly tapered dimensional cyclic structure. In its hollow structure, the outer upper end (the larger open end) by the C2 and C3 constitute a secondary hydroxyl group, lower (smaller open end) constituted by a primary hydroxyl C6, hydrophilic, while the cavity due to the C-H bond the shielding effect of the hydrophobic region is formed, the drug molecules can be entrapped within the structure in which the hole is formed clathrate [4,5]. β-CD by inclusion of the drug, using its own hydrophilic properties, thereby increasing the solubility of poorly soluble drugs, the application of some poorly soluble drugs made for the liquid formulation provides a good solution. This experiment try [6] preparation sultamicillin tosilate with β-cyclodextrin (β-CD) inclusion compound by saturated aqueous solution method to to cover the bitterness and improve the utilization rate of the target. At the same time, the stability of the inclusion complex in the high temperature, high temperature and high humidity conditions was investigated.

2 The Experiment

2.1 Instruments and Drugs

Fu Liye infrared spectrum analyzer(Tianjin Light Optical Instrument Co. Ltd) ; UV9100 visible spectrophotometer; Electronic balance.AG135 (METTLER TOLEDO). Electron microscope (Shenzhen Delong Technology Co., Ltd) ; GZX-9240 electric drying oven (Shanghai Boxun Industrial Co., Ltd. Medical Equipment Factory); SHZ-B circulating water pump (Linhai City Seiko Vacuum Equipment Factory);

Sultamicillin tosilate samples: analytical grade (Tianjin Damao Chemical Reagent Co., Ltd); β-cyclodextrin : analytical grade (Tianjin Damao Chemical Reagent Co., Ltd);KBr: HPLC grade (Tianjin Damao Chemical Reagent Co., Ltd); Other reagents were of analytical grade.

2.2 Inclusion Compound

Took appropriate β-cyclodextrin saturated solution made by adding distilled the saturated solution water. Then weigh a certain amount of sultamicillin tosilate, adding a small amount of ethanol, methanol dissolved. Then slowly added dropwise β-cyclodextrin saturated solution, at a certain temperature, the reaction to ultrasound specified time. 4℃ in the refrigerator and then vacuum filtration after 24h, respectively, and a small amount of distilled water and a small amount of anhydrous ethanol washing, drying, loose powder form clathrates.

2.3 The measurement of sultamicillin tosilate content

2.3.1 Preparation of sample solution

Precision according to take a certain amount by the stability after the experiment of drying sultamicillin tosilate-β-CD inclusion complex in 50 ml volumetric

flask, adding anhydrous alcohol to scale shake to mix evenly, as the sample solution.

2.3.2 Preparation of reference solution

Precision according to take a certain amount amount of fresh prepared drying sultamicillin tosilate-β-CD inclusion complex in 50 ml volumetric flask, adding anhydrous alcohol to scale shake to mix evenly, as the sample solution.

2.3.3 Measurement method

Sultamicillin tosilate standard curve：Precision weigh 0.0030g sultamicillin tosilate, with a mixture of methanol and ethanol as solvent, with 100ml solution. Respectively, 5, 10, 15, 20ml and then 50ml solution. The mixture of methanol and ethanol was blank, and the absorbance was measured at 205nm. Taking the absorbance as the vertical coordinate, the concentration is the horizontal coordinate and linear regression.

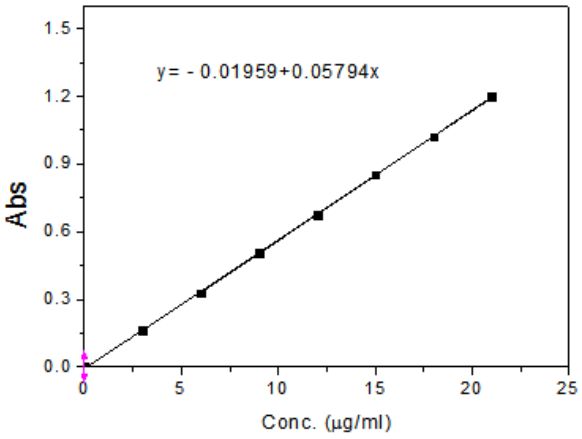

Figure 1. Standard curve

Measurement content：By UV Vis spectrophotometry, in Tosi acid Shu He Westwood - beta - cyclodextrin package peak 205 nm absorption maximum of determination of the corresponding absorbency. According to the equation of standard curve calculate.

3 Inclusion Detection

3.1 Infrared Spectroscopy

Measured using KBr pellets β-CD, sultamicillin tosilate, sultamicillin tosilate and β-CD mixture, and sultamicillin tosilate-β-CD inclusion complex infrared spectra with a resolution 2cm^{-1},4000-400cm^{-1} a full spectrum scan,results shown in Figure 2-5.

Figure 5 shows that : O-H stretching vibration unchanged at 3391cm-1 in the sultamicillin tosilate and β-CD mixture, the inclusion complex shift to lower wave number. In 1000-1900cm-1 wavelength, the mixture and sultamicillin tosilate-β-CD inclusion complex also have significant differences, indicating that the inclusion complex has formed a new phase. Can be judged accordingly sultamicillin tosilate-β-CD inclusion complex has been formed.

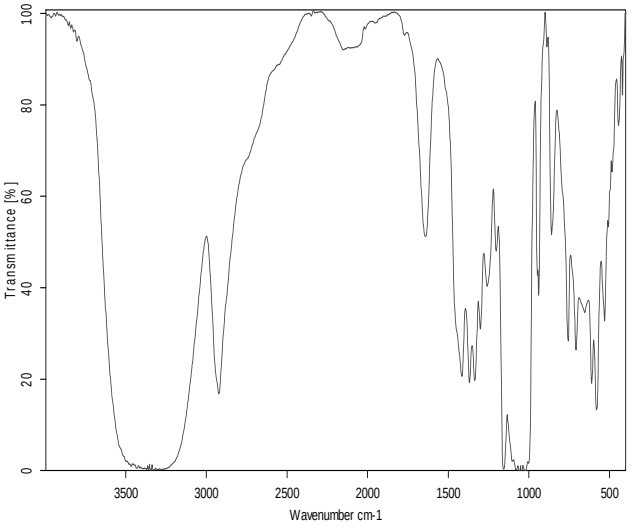

Figure 2. β-CD morphology

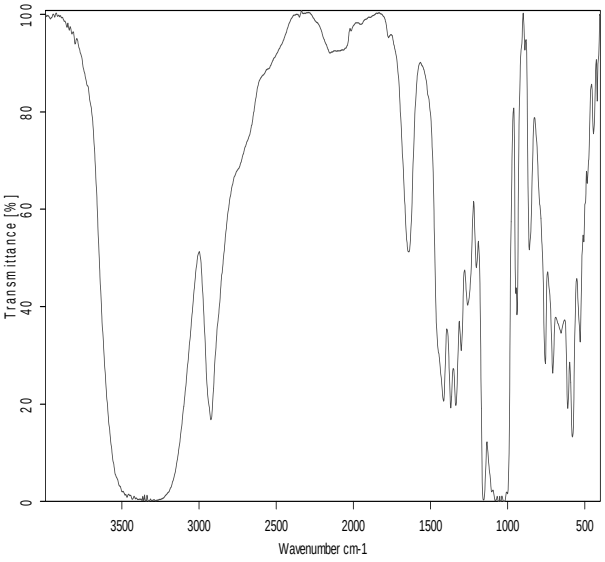

Figure 3. sultamicillin tosilate

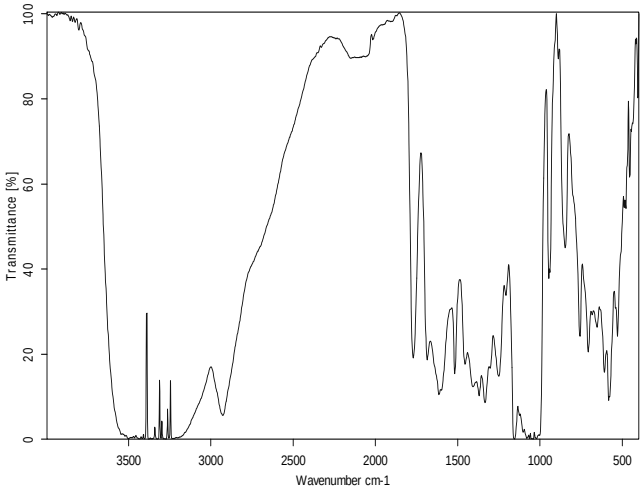

Figure 4. sultamicillin tosilate and β-CD mixture

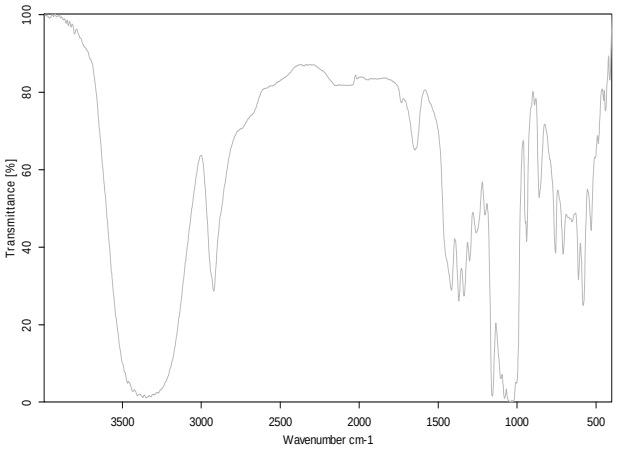

Figure 5. sultamicillin tosilate-β-CD inclusion complex

3.2 Microscopic Identification

The dried β-CD, sultamicillin tosilate, sultamicillin tosilate and β-CD mixture, and sultamicillin tosilate-β-CD inclusion complex were placed at 40 times the electron microscope and to obtain photos, results shown in Figure6-9.

From Figure 6, uncoated drug β-CD is translucent columnar crystals, the shape of the larger; known from Figure 7 sultamicillin tosilate semitransparent columnar crystals, more slender shape; Figure 8 known sultamicillin tosilate and β-CD mixture is mixed with their graphics, can distinguish their shape; and Figure 9 known sultamicillin tosilate-β-CD inclusion complex of β-CD has been included because of drugs so was opaque lumps, smaller shape. In the formation of the inclusion complex, the original β-CD semitransparent columnar crystal microstructure traits disappear. Clathrate surface and can not tell their basic shape, which determine the inclusion complex has formed. Compare their microstructure, can be determined sultamicillin tosilate has entered the cavity of β-CD, so as to be synthesized with the packet a physical mixture of different phase stable mixture

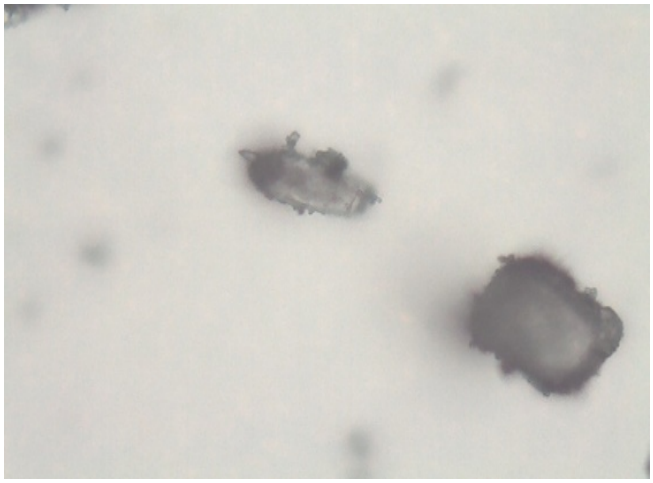

Figure 6. β-CD morphology

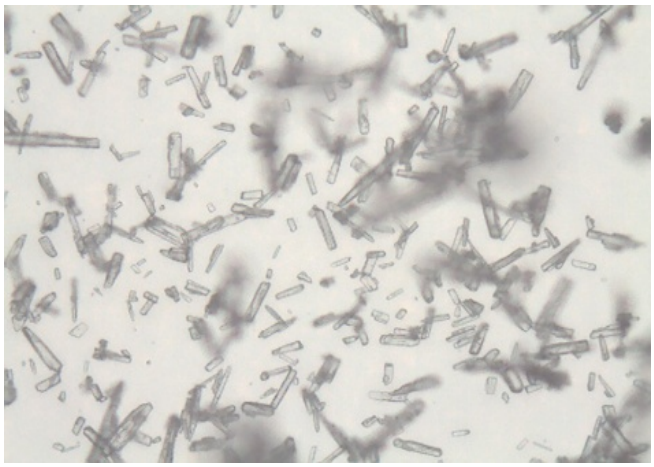

Figure 7. sultamicillin tosilate

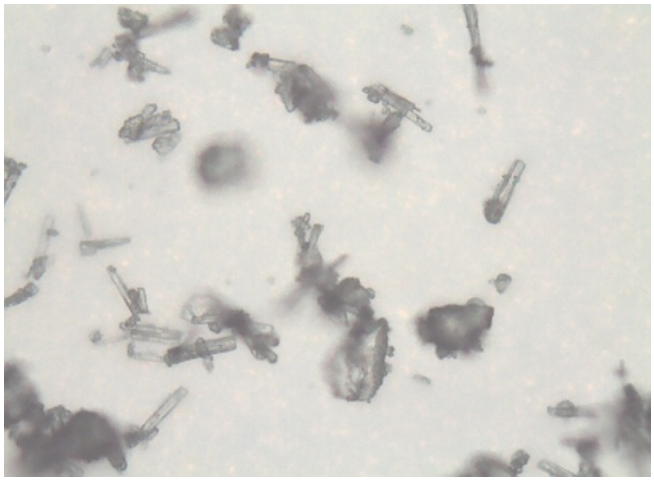

Figure 8. sultamicillin tosilate and β-CD mixture

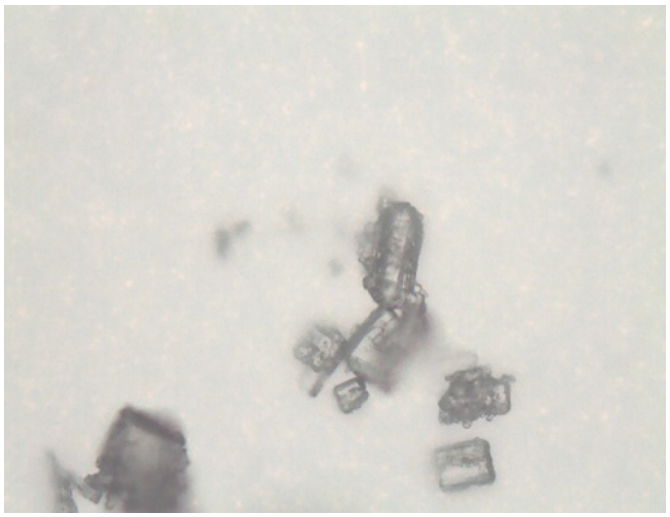

Figure 9. sultamicillin tosilate-β-CD inclusion complex

4 Stability of inclusion complexes

4.1 Stability experiment of sample light irradiation

Measured a certain amount of sultamicillin β-cyclodextrin inclusion complex encapsulated in the colorless glass jar, placing ultraviolet lamp (253 nm) irradiation, placing the 5 day.

4.2 Sample high humidity stability test

Precision Weigh a certain amount of clathrate, placed on a glass slide, and then placed into clathrate slide containing a saturated solution of potassium nitrate (25 ℃ , relative humidity of 92.5%) in the chromatography tank, at a temperature 25 ℃ placed, in the first 5 day checks. Results: The characters gradually changed by a milky cream, and medicines has been weight gain.

4.3 Sample temperature stability test

Weigh a certain amount of dry Tosi acid sultamicillin β-cyclodextrin inclusion complex in dry small beaker, placed in a vacuum oven, the temperature was raised to 60 ℃, after 5 day taken place.

Table 1. Stability results.

Experimental category	Before the experiment(ug/ml)	After the experiment(ug/ml)
light irradiation	2.8079	13.3835
high humidity	2.8079	11.2552
temperature	2.8079	2.8079

5 Results and Discussion

The experiment were prepared with a saturated aqueous legal sultamicillin tosilate-β-CD inclusion complex, aimed at increasing drag sultamicillin west acid soluble, improving the rate of drug release and conceal their bitterness, which can be further prepared lay the foundation for a variety of dosage forms. Experimental results show that the stability of the inclusion complex, at high temperatures, strong light and high humidity, Tosi acid sultamicillin relatively large concentration. Therefore sultamicillin tosilate-β-CD inclusion complex should be kept in the dark, cool, dry conditions.

Acknowledgement

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