

# Preparation of Lincomycin- $\beta$ -Cyclodextrin Complex by Ultrasonic Method

Xiangqun XU<sup>1\*</sup>, Jie Yang<sup>1</sup>, Youquan Zhong<sup>1</sup>, Huayu Wang<sup>1</sup>, Nian Hong<sup>1</sup>, Lin Cheng<sup>1\*</sup>

<sup>1</sup> Department of Pharmacy, JiangXi University of Traditional Chinese Medicine, JiangXi 330004, China

**Abstract.** To study the best process conditions for preparing ultrasonic lincomycin  $\beta$ -cyclodextrin inclusion. Method: Choose the usage ration of Lincomycin hydrochloride with  $\beta$ -cyclodextrin, the inclusion temperature and the time of reaction as the main factors, and use the inclusion yield as evaluated indicators and the process condition to conduct the L<sub>9</sub> (3<sup>4</sup>) orthogonal experiment Optimization Pack lincomycin hydrochloride. Outcome: The optimum inclusion process condition: molar ratio of the Lincomycin hydrochloride with  $\beta$ -cyclodextrin is 1:3, inclusion temperature is 30°C, inclusion time is 80 minutes. And use infrared spectrophotometry, microscopy imaging to identify the lincomycin hydrochloride  $\beta$ -cyclodextrin inclusion complex has been formed. Conclusion: The process condition of using  $\beta$ -cyclodextrin inclusion to inconclude lincomycin hydrochloride is feasible, effective, and of applicative value.

## 1 Introduction

Lincomycin hydrochloride is one of the drugs commonly used against infections, which belongs to narrow-spectrum antibiotics, and the role of which is similar to erythromycin. It mainly used in clinical strains caused by various infections, such as pneumonia, meningitis, endocarditis, tonsillitis and urinary tract infections and so forth. It slightly smells, with special odor and bitter taste. Although there are a variety of lincomycin hydrochloride dosage forms in market, such as injection, eye drops, tablets, oral liquid, etc., nothing can solve its special smell problem. Clinical trials suggest that the current side effects of this drug are more obvious either, after taking the drug, there are patients will be troubled by nausea, vomiting, loss of appetite, stomach discomfort or other bad reactions, and this has seriously impacted the clinical use of this drugs.  $\beta$ -cyclodextrin has the cyclic structure of a hollow cylinder, and inside of the cylinder is a hydrophobic region, which enables the hydrophobic drug molecule or a functional group with suitable shape and size can be embedded, and then form inclusion complexes. This study aims at concealing the special odor of the drug by making lincomycin  $\beta$ -cyclodextrin inclusion, so as to broaden the prospect of the drug in clinical application and explore the best technical condition of making the inclusion compound. With literature consulting,

## 2 The Experimental Part

### 2.1 Instruments and Drugs

Fu Liye infrared spectrum analyzer (Tianjin Light Optical Instrument Co. Ltd); UV9100 visible spectrophotometer; KQ 300CDE Numerical control ultrasonic generator (Kunshan ultrasonic instruments Co., Ltd.); Electronic balance. AG135 (METTLER TOLEDO). Electron microscope (1.0nm at 30kV, 1.5nm at 15kV; Shenzhen Delong Technology Co., Ltd)

Lincomycin Hydrochloride Standard (Chinese food and drug identification mechanism, Batch number: 130432-201109); Lincomycin hydrochloride samples (Jiangxi pharmaceutical factory);  $\beta$ -cyclodextrin (Shanghai Shan P

u Co. Ltd., purity 98%); KBr: HPLC grade (Tianjin Kermel Chemical Reagent Co., Ltd); Other reagents were of analytical grade.

### 2.2 Inclusion Compound [1-4]

Took appropriate  $\beta$ -cyclodextrin and added it into a certain amount of distilled water, dissolved it in the ultrasonic sonicator, and then added a certain amount of dissolved lincomycin hydrochloride, at a certain temperature, and after ultrasound reflecting of specified time, 24h of freezing in a 40°C refrigerator, then conducted vacuum filtration, respectively washed and dried it with a small amount of distilled water and a small amount of ethanol, and the inclusion compound was done.

### 2.3 Package and Process [5,6]

The vital impact factors of making the lincomycin  $\beta$ -cyclodextrin inclusion compound is the feed ratio selection, inclusion temperature and inclusion time, each factor were taken three level to conduct orthogonal experiment, the design of the factor level is in form factors Table 1.

**Table 1.** Factors in the table

	A (Molar ratio)	B	C
	Lincomycin: Cyclodextrin	Inclusion temperature /°C	Inclusion time /min
1	1:1	30	60
2	1:2	40	80
3	1:3	50	100

## 3 Results and Discussion

### 3.1 Orthogonal

Analysing from the numbers of Table 2, the optimum conditions for the inclusion is A<sub>3</sub>B<sub>1</sub>C<sub>2</sub>, the degree of influence of each factor is B > A > C. Through analysis of variance (Table 3), it can be found that in the ultrasonic method of inclusion process, factor A and B were

significant. With the analysis of the ultrasonic method, we can see the optimal inclusion conditions is that the molar ratio of Lincomycin hydrochloride with  $\beta$ -cyclodextrin is 1:3, the inclusion temperature is 30 °C, and the inclusion time is 80 min.

**Table 2.** Lincomycin inclusion compound orthogonal experiment

	A	B	C	D	Inclusion yield %
1	1	1	1	1	8.3
2	1	2	2	2	21.3
3	1	3	3	3	47.1
4	2	1	2	3	5.5
5	2	2	3	1	1.6
6	2	3	1	2	34.4
7	3	1	3	2	5.5
8	3	2	1	3	36.1
9	3	3	2	1	52.9
K1	25.6	6.4	26.3	K1	25.6
K2	13.8	19.7	26.6	K2	13.8
K3	31.5	44.8	18.1	K3	31.5
R	17.7	38.4	8.5	R	17.7

**Table 3.** Analysis of variance table

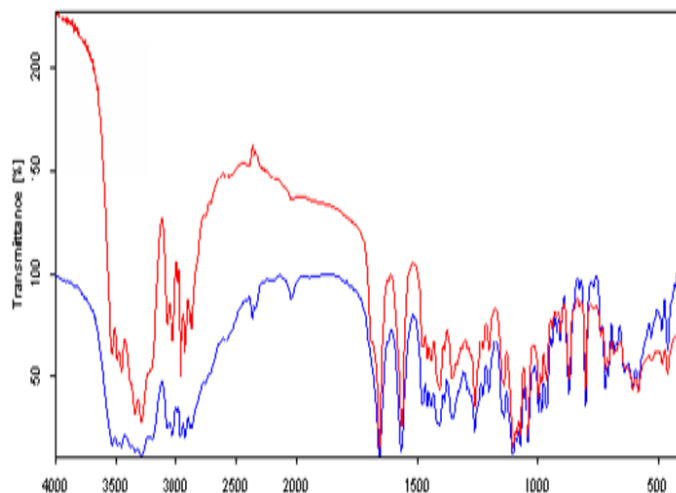
Source of variance	Squares	Freedom	Mean square	F	P
A	2278.81	2	1139.41	14.27	>0.05
B	484.99	2	242.50	3.04	>0.05
C	139.58	2	69.79	0.87	>0.05
deviation	159.66	2	79.83		

## 4 Inclusion Detection

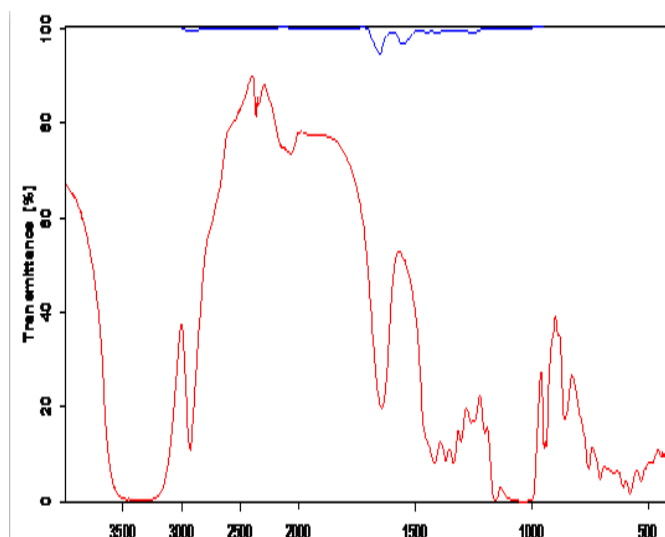
### 4.1 Infrared Spectroscopy

Respectively analyze the lincomycin hydrochloride ,  $\beta$ -cyclodextrin and their mixtures , and the four samples of inclusion compound by infrared spectroscopy .

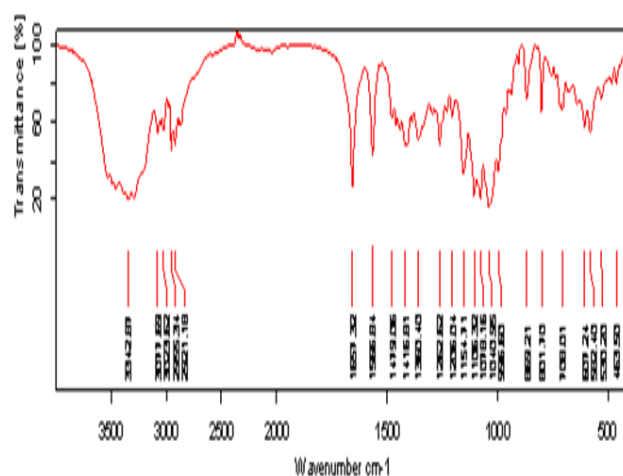
Figure 1 and Figure 2 shows that : The maximum absorption peak of Lincomycin hydrochloride is at  $2400\text{cm}^{-1}$ ; Figure 3 and Figure 4 shows that: the inclusion compound disappeared at the maximum absorption peak in  $2400\text{cm}^{-1}$ , which indicating that lincomycin hydrochloride has been included by  $\beta$ -cyclodextrin.



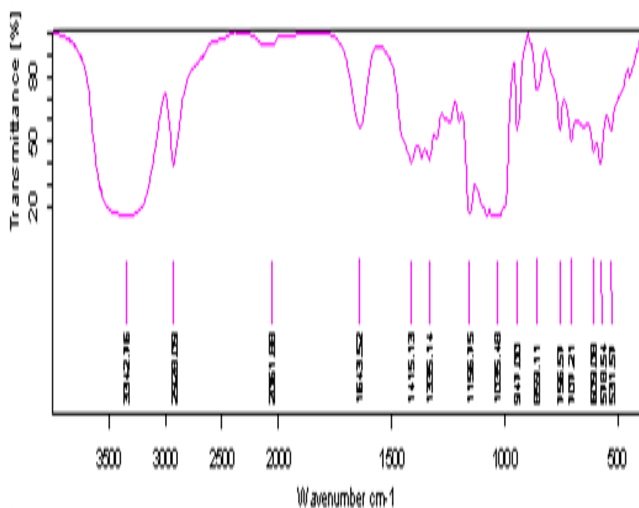
**Figure 1.** Lincomycin hydrochloride



**Figure 2.**  $\beta$ -cyclodextrin



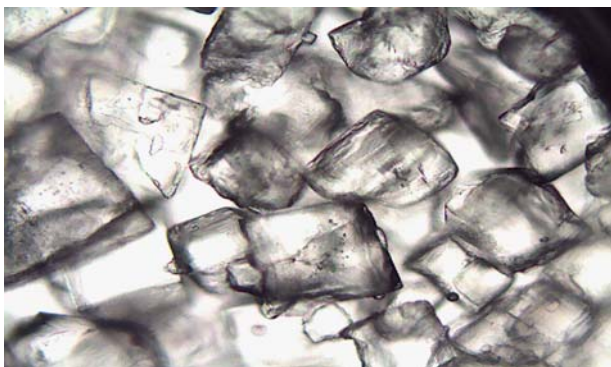
**Figure 3.** Lincomycin hydrochloride and a mixture of  $\beta$ -cyclodextrin



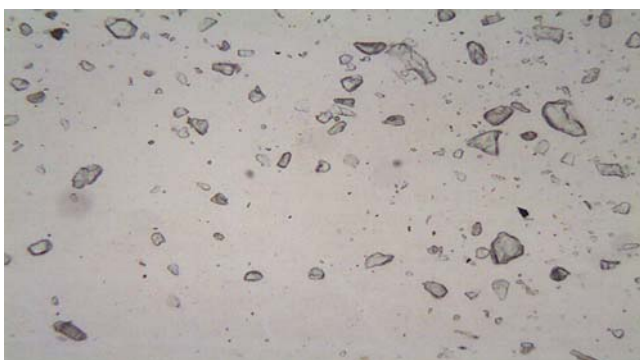
**Figure 4.** Lincomycin hydrochloride and B-cyclodextrin inclusion complex

#### 4.2 Microscopic Identification

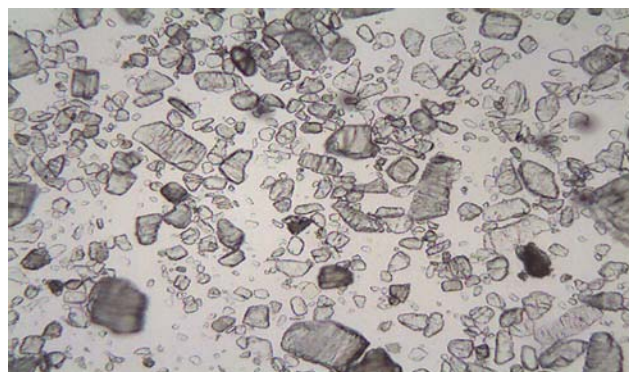
Under the inverted microscope it can be observed that the  $\beta$ -cyclodextrin inclusion complex shape compared with  $\beta$ -cyclodextrin itself undergone significant changes, transforming from translucent prismatic crystals (shown in Figure 5 and Figure 6) to an angular opaque bulk crystal (shown in Figure 7 and Figure 8), which proved that lincomycin hydrochloride has been included by  $\beta$ -cyclodextrin clathrate.



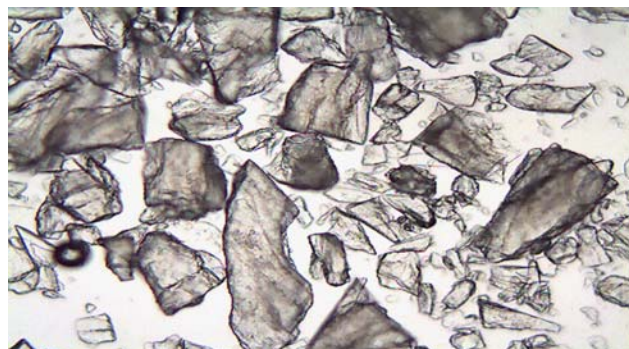
**Figure 5.** lincomycin hydrochloride crystal morphology



**Figure 6.**  $\beta$ -cyclodextrin crystal morphology



**Figure 7.** lincomycin- $\beta$ -cyclodextrin mechanical mixture



**Figure 8.** lincomycin- $\beta$ -cyclodextrin inclusion morphology

## 5 Results and Discussion

$\beta$ -CD is oral non-toxic, and can be easily absorbed by the body as a kind of carbohydrate. Also with the topless special cone-shaped cavity structure, it is easy to form complexes with drug molecules, on the medical application fully shows its excellent "embedding" effect, such as disguise odor of drugs, prevention of drug volatilization, hydrolysis, and increasing solubility, improved bioavailability, improve drug efficiency, lowering drug irritation, toxicity, and the drug can be powdered or made into granules, tablets, capsules and so on.

By now the experiments with  $\beta$ -cyclodextrin lincomycin has not been reported yet. Through experiments, we found that the choice and the usage of inclusion washing liquid will affect the experimental data. In this study, we used ultrasonic method and orthogonal design method and initially obtained the optimal preparation of  $\beta$ -cyclodextrin lincomycin hydrochloride, and the optimal inclusion process condition is: Lincomycin hydrochloride with  $\beta$ -cyclodextrin fine molar ratio of 1:3, inclusion temperature 30 °C, inclusion time was 80 min.

Infrared spectroscopy, microscopic identification, UV-visible spectrophotometry and other methods have all proved the formation of the inclusion compound. The experimental results showed that: The formation of the Lincomycin hydrochloride  $\beta$ -cyclodextrin inclusion complex is of great meaning in improving the effect of the drug.

## Acknowledgement

This research was supported by the Jiangxi University of Traditional Chinese Medicine Foundation(No. 2012ZR025) and the health department of Jiangxi Province Traditional Chinese medicine scientific Foundation (No. 2013A191) and Undergraduate Training Programs for Innovation and Entrepreneurship (No. 201310412042)

## References

- [1] Ye Sufang. Journal of chemical engineering, **2**(2002)
- [2] Chinese pharmacopoeia. the second version (2010)
- [3] Y.P.Ye, X.M.Wei, Central South Pharmacy, **2**, 3 (2004).
- [4] Y.Tong,L.K.Du, Practical Journal of Cardiac Cerebral Vascular Disease, **14** ,6 (2006).
- [5] X.B.Liu,X.J.Lv, Chinese Journal of Clinical Pharmacology. **21**, 6 (2005).
- [6] A.M.He,J.P.Fan,S.M.Lin, Fuqing Branch of Fujian Normal University, **5** (2010).