Formulation Screening of Levetiracetam Sustained Release Tablets

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Abstract: Objective: To prepare the sustained-release preparation of levetiracetam. **Methods:** The sustained-release materials were selected for wet granulation and tablet pressing, and the best formula was determined. Levetiracetam sustained-release tablets were prepared and the influencing factors were investigated. **Results and Conclusions:** The formulation was reasonable, the preparation process was simple, and the quality was stable.

Keywords: Levetiracetam; Sustained release tablets; Release; Stability

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Author Introduction: Jing Zhou (1973.02 -), Female, Han nationality, Bachelor, Pharmaceutical engineer, Research direction: drug R & D.

1. Introduction

Levetiracetam, developed by Belgium's UCB company, is a new antiepileptic drug. It was named "Keppra" in April 2000® Approved by FDA and listed in the United States and the European Union. Levetiracetam sustained release tablets (trade name:Keppra XR)® [1] approved by FDA in February 2009. Levetiracetam is mainly used in the treatment of partial seizures in adults and children over 4 years old. It is a new antiepileptic drug used most in the treatment of epilepsy. Levetiracetam sustained-release tablets have the advantages of less medication times (once a day), convenient clinical medication,stable blood concentration and low toxic and side effects. It is the preferred dosage form for the clinical application of levetiracetam.

Refer to levetiracetam sustained release tablets [2] (trade name: Keppra XR) of UCB (youshibi) Company in Belgium®. To prepare levetiracetam sustained-release tablets [3] and investigate the influencing factors. The results are summarized as follows:

2. Raw and Auxiliary Materials and Instruments and Equipment

Levetiracetam (Shandong Ruihe Pharmaceutical Technology Co., Ltd.), hydroxypropyl methylcellulose (Dow Chemical Co., Ltd.), wet mixing granulator (Beijing Institute of Aeronautical Technology), rotary tablet press, high-efficiency coating machine (Shanghai Tianhe Pharmaceutical Machinery Factory), gas chromatograph, drug dissolution tester and high-performance liquid chromatograph (Shimadzu).

3. Methods and Results

3.1 Prescription Screening and Preparation Process

According to the formulation of the original preparation and the level of key quality attributes as the research and development objectives of the self-developed products, referring to the types of excipients used in the original levetiracetam sustained-release tablets (Keppra XR), the dosage of each excipient is based on ensuring that the particles have good fluidity, the plain tablets have low brittleness, and the tablet release behavior is consistent with that of the original product.

Because the main drug content in the prescription of this product is high, about 70%, and the compressibility of the main drug is poor, but because the main drug has good wet and thermal stability, it is decided to prepare this product by wet granulation process to improve the compressibility of the material.

According to the original formulation and the compatibility test results of raw and auxiliary materials, hydroxypropyl methylcellulose is selected as the slow-release material, polyethylene glycol 6000 as the adhesive, silica as the flow aid,magnesium stearate as the lubricant and stomach soluble film coating premix as the coating material.

Test results of different prescriptions are as follows:

Prescription 4 is the most consistent with the release behavior of the original preparation, so the hydroxypropyl methylcellulose of model K15M is determined as the sustained-release material of this product, and the dosage of hydroxypropyl methylcellulose is determined to be about 160 mg/tablet. The dosage of polyethylene glycol 6000 is 2%. The release curves of formula 4 and the original preparation in four release media were further determined and compared.

It can be seen from the determination results that the similarity factor F2 of formula 4 and the original preparation in the four release media is greater than 50, and the release behavior is consistent. Therefore, formula 4 is determined as the best formula.

Table 1. proportion of raw and auxiliary materials of different prescriptions (100 Tablets, g)

Raw and auxiliary materials		Prescription 1	Prescription 2	Prescription 3	Prescription 4	Prescription 5
Levetiracetam		50.0	50.0	50.0	50.0	50.0
Hydroxypropyl methylcellulose (K4M)		18.0	—	—	—	—
Hydroxypropyl methylcellulose (K15M)		—	18.0	—	18.0	18.0
Hydroxypropyl methylcellulose (K100M)		—	—	18.0	—	—
80%ethanol		31.4	30.5	30.4	32.1	31.2
Polyethylene glycol6000		0.8	0.8	0.8	1.4	2.1
Magnesium stearate		0.6	0.6	0.6	0.6	0.6
Silicon dioxide		0.6	0.6	0.6	0.6	0.6
Gastric soluble film coating premix		2.0	1.9	2.0	2.0	2.0
Detection index	Angle of repose (°)	34.7	33.4	34.6	33.7	34.2
	Brittleness (%)	0.45	0.42	0.53	0.23	0.10

Table 2. Comparison of each prescription and the original preparation at pH 6 Comparison of release results in 0 phosphate buffer

Time(h)	1	2	8	f_2
Prescription 1 (%)	35.9	52.3	93.9	82.0
Prescription 2 (%)	34.9	49.6	89.2	67.8
Prescription 3 (%)	33.0	47.1	86.9	61.0
Prescription 4 (%)	33.9	50.6	96.2	99.2
Prescription 5 (%)	32.9	48.8	89.5	68.2
Original preparation (%)	33.7	51.0	96.4	—

Table 3. comparison results of release curve between prescription 4 and the original preparation

	Time(hr)	1	2	4	6	8	12	f_2
pH6.0Phosphate buffer	Prescription 4 (%)	33.8	51.0	71.8	86.0	94.3	99.0	84.3
	Original preparation (%)	33.7	51.0	74.4	88.5	96.4	100.2	
Water	Prescription 4 (%)	34.7	50.0	72.5	83.9	93.7	98.2	85.4
	Original preparation (%)	32.5	49.0	70.7	85.4	93.3	98.7	
0.1mol/l hydrochloric acid solution	Prescription 4 (%)	34.7	51.7	73.6	87.5	96.2	99.1	90.7
	Original preparation (%)	33.2	50.0	73.4	87.0	94.1	99.9	
pH4. 5 acetate buffer	Prescription 4 (%)	32.2	49.3	72.1	84.3	93.1	98.9	84.6
	Original preparation (%)	32.7	49.2	70.9	87.6	94.9	102.9	

3.2 Sample Preparation: Produce 1000 Samples in One Batch According to the Determined Prescription 4

Weigh the prescription amount of levetiracetam and hydroxypropyl methylcellulose into the wet mixing granulator for dry mixing. After dry mixing, add 80% ethanol to make soft material. The prepared soft material is granulated with 20 mesh screen of swing granulator, and the wet particles are dried with blast at 55~65 ºC. The moisture control range of dry particles is 2.0%~4.0%. The dry particles are granulated through 20 mesh screen of swing granulator. Add the prescribed amount of magnesium stearate, silicon dioxide and polyethylene glycol 6000 into the whole dry particle, mix evenly, convert the standard tablet weight according to the intermediate content, press, coat and test.

3.3 Analysis and Detection of Levetiracetam Sustained Release Tablets

According to the Chinese Pharmacopoeia and the quality standard of levetiracetam sustained-release tablets [4], determination: 1) properties: it is a white film coated tablet, which appears white or almost white after removing the coating; 2) Hardness: 12-18 kg; 3) Brittleness: <0.5%; 4) Weight difference: meet the requirements.

Determination of related substances in levetiracetam sustained release tablets: calculated according to the impurity reference method: impurity B shall be≤0.2%, the peak area of other single unknown impurities shall not be greater than the peak area of levetiracetam in the reference solution (0.06%), and the total impurities shall be≤0.5%. Test results: impurity B is not detected, the maximum single impurity is 0.02%, and the total impurity is 0.1%.

Determination of release rate of levetiracetam sustained release tablets: the release amount of each tablet in 1 hour, 2 hours and 8 hours should be 21%~40%, 41%~60% and more than 80% of the marked amount respectively. The test results of samples were 35%, 53% and 93%.

Determination of levetiracetam R-isomer: not more than 0.5%. The test result of the sample is 0.0013%.

Determination of levetiracetam sustained release tablets [5]: The content of levetiracetam ($C_8H_{14}N_2O_2$) should be 95.0%~105.0% of the marked amount. The determination result of the sample is 99.5%.

3.4 Investigation of Influencing Factors

Placement conditions: high humidity rh92.5%, high temperature 60 ºC, light 4500lx±500lx. Investigation time: 5 days, 10 days and 30 days. Investigation items: properties, related substances, levetiracetam R-isomer, release degree and content. Results: the impurity B in the bare sample increased from 0.001% to 0.010%, with an increase of 0.009% during the investigation of levetiracetam sustained-release tablets at 60 ºC. The other largest single miscellaneous increased from 0.013% to 0.198%, with an increase of 0.185%, and the total miscellaneous increased from 0.024% to 0.279%, with an increase of 0.255%. There is no obvious change in the impurity level of the sample after packaging. Under the condition of high humidity, except for obvious moisture absorption and weight gain, other quality indexes of bare lofting products have no obvious change. There was no significant change in each quality index under light conditions.

4. Discussion

The formulation uses hydroxypropyl methylcellulose K15M as sustained-release material and polyethylene glycol 6000 as adhesive to jointly control the release rate of the drug. The properties, hardness, brittleness, weight difference, release, content and related substances of the prepared tablets are qualified. The investigation and research results of influencing factors show that the product quality is stable. It shows that nimesulide sustained-release tablets prepared according to this prescription and process have strong operability and controllable quality.

References

[1] Levetiracetam sustained release tablets (trade name Keppra XR)® FDA instructions.

[2] Import registration standard of levetiracetam tablets jx20070146.

[3] Usp38 “levetiracetam sustained release tablets”.

[4] Quality standard for clinical trial application of levetiracetam API.

[5] Release determination method of levetiracetam sustained release tablets published by FDA.