Research Article

Formulation study of duloxetine hydrochloride enteric-coated tablets

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Abstract
During storage, duloxetine hydrochloride may have an unexpected cross reaction with enteric coated acrylic resin, which may affect the product quality. Solve the problem of cross-reaction between the Duloxetine enteric-coated tablets core and coated enteric materials and improve the quality of the products. Duloxetine enteric-coated tablets' core formulation and isolation layer prescription were designed and compared with duloxetine enteric-coated tablets sold on the market. Then, we measured the dissolution rate, content, and releasing rate of prepared duloxetine enteric-coated tablets. In the formulation of tablets core, prescription 3 had advantages in particle mobility, disintegration time, and dissolution rate. Prescription 5 was stable during the coating process, and the dissolution residue in the cup was relatively good, showing obvious dissolution advantages. Thus, prescription 5 was selected as the isolation layer prescription. The most suitable adhesive for the preparation of Duloxetine hydrochloride enteric-coated tablets was povione K30 dissolved in ethanol solution with 1/2 of the prescription amount. When 1.3 g colloidal silica was added to the prescription and the dosage of magnesium stearate was 1.48 g, the dissolution rate of the drug could be relatively improved. The ratio of sucrose and talc was 138/8.7, which could effectively configure the coating solution with a solid content of 15–20% to make the coating smooth.

Keywords Duloxetine enteric-coated tablets · Tablet core · Coating material · Prescription process · Dissolution rate · Disintegration time

1 Introduction

Duloxetine hydrochloride was developed by Lilly and has been listed in the United States, the European Union, and other regions [1]. Duloxetine hydrochloride is a serotonin and norepinephrine reuptake inhibitor (SNRI) that has been used to treat severe adult depression, moderate to severe stress urinary incontinence, and diabetic peripheral neuropathic pain [2, 3]. The new indications in the United States for treating adult diabetic peripheral neuropathy pain made duloxetine the first drug officially approved by the FDA to treat this disease [4, 5].

Duloxetine Hydrochloride is used from 40 mg/day (20 mg twice a day) to 60 mg/day (once a day or 30 mg twice a day), in order to maintain the patient's blood concentration in a stable state, reduce adverse drug reactions and improve the patient's medication compliance, researchers have prepared the drug into a sustained release preparation. However, due to the stability problems mentioned previously, it is necessary to prepare

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enteric coated sustained release preparations during the development of drugs. For example, the patent Duloxetine hydrochloride enteric coated sustained-release granules and its preparation method, CN107412198A of Beijing Wanquan Dezhong Pharmaceutical Biotechnology Co., Ltd disclosed the preparation method of Duloxetine Hydrochloride enteric sustained-release preparation, which used ordinary sustained-release materials to prepare the drug into gel matrix sustained-release tablets, and then enteric coating [6]. The patent Duloxetine Hydrochloride Pharmaceutical Composition, CN102579403B of Tianjin Songrui Pharmaceutical Technology disclosed a preparation method of Duloxetine Hydrochloride Sustained Release Capsules. The blank pill core was prepared in advance, Duloxetine Hydrochloride was loaded outside the blank pill core, and the enteric coated sustained-release coating was coated outside the pill core [7]. The disclosed preparation method had complex steps and inconvenient operation.

Duloxetine hydrochloride enteric-coated tablet is a new type of SNRI drug. It was reported that duloxetine hydrochloride might have an unexpected cross-reaction with enteric-coated acrylic resin during storage, affecting product quality [8, 9]. Therefore, we studied and designed the tablet's core formulation process and the isolation layer formulation to improve product quality to solve this problem.

2 Materials and method

2.1 Reagents

Duloxetine hydrochloride was purchased from Wandai Pharm (Shanghai, China). Povidone K30, sucrose, lactose, crosslinked povidone, magnesium stearate, and colloidal silica were purchased from Chineway (Shanghai, China). Ethanol (95%), hydroxypropyl methylcellulose, talc, titania, acrylic resin, and triethyl citrate were purchased from Hongyuan Pharm (Jiangsu, China). Acetonitrile, trisodium phosphate, hydrochloric acid, dipotassium hydrogen phosphate, and potassium dihydrogen phosphate were purchased from Sino Pharm (Shanghai, China). Tablet press (ZP27A), Coating machine (WKY500) and Disintegrator (DT-50) were purchased from Tian Feng Pharmaceutical Equipment Co. LTD (Shanghai, China).

2.2 Tablets core prescription design

According to the shortcomings of the original prescription, a new prescription process was designed under the premise of improving product quality standards. The process had to reach the new product quality standard and retain the composition of, and compatibility with, the original prescription and excipients. The method of mixing duloxetine hydrochloride and excipients was used, and then adhesive (Povidone K30) was added to stir and granulate instead of dissolving duloxetine hydrochloride in ethanol. In addition, magnesium stearate that would affect the dissolution of the preparation in the original prescription was reduced, and colloidal silica was added as the lubricant. In the original formulation process, the dosage of magnesium stearate was 0.17 g/1000 tablets and colloidal silica was 0.03 g/1000 tablets. Magnesium stearate and colloidal silica were added after granulation. Screening tests are shown in Table 1.

2.3 Prescription design of isolation layer and enteric layer

Studies have shown that duloxetine hydrochloride might cross-react with enteric-coated acrylic resin, affecting the release of duloxetine hydrochloride enteric-coated tablets and reducing stability. Due to the presence of secondary amino in the structure of duloxetine hydrochloride, it reacts with many enteric-soluble materials containing carboxyl groups to form a coating that dissolves slowly or does not dissolve at all, which affects the release of drugs [10]. Therefore, the research showed that the most suitable adhesive for the Duloxetine hydrochloride enteric-coated tablets preparation. According to the technical scheme explored in a previous experiment, adding talc powder to

Table 1 Core composition (calculated as 1,000 tablets, unit: g)

Raw material	Prescription 1	Prescription 2	Prescription 3
Duloxetine hydrochloride	22.4	22.4	22.4
Povidone K30	3.5	3.5	3.5 (1/2within plus)
Sucrose	138	138	138
Lactose	80	80	80
Crosslinked povidone	2.5	2.5	2.5
Magnesium stearate	1.98	1.48	1.48
Colloidal silica	–	0.5	0.5
50% ethanol	Proper amount	Proper amount	Proper amount

the isolation layer could increase the compactness of the isolation layer and resist adhesion during drug dissolution. Furthermore, adding sucrose could improve the dissolution rate. The isolation layer was screened through comparative experiments, as shown in Table 2.

A tablet press was dedicated to pressing the core, which was then transferred by a drive to a die hole in the coating turntable (the die hole was filled with the coating material as the bottom layer). With the rotation of the turntable, the required coating material was added from the top of the sheet core, and then pressure was applied to make the sheet core pressed into the coating material to form a pressed coating tablet.

The method of pressing coating was used in this study. Two tablet presses were equipped into a set of machine. When coating operation was carried out, one tablet press was used to press the material into a core, and the internal transmission device transfered the core to the mold hole of the other tablet press. Some coating materials had been filled in the mold hole as the bottom layer, and then the core was placed on it. Then, the coating materials were added to fill the mold hole, and the second pressing was carried out to make coated tablets.

2.4 Measurement of angle, compressibility and disintegration

Angle of repose measurement is a test method based on the fall method. The powder or particle from a certain height of the funnel naturally dropped onto the horizontal plate, until no more test products fall in the funnel. The Angle θ between the formed cone and the horizontal plate is Calculated. The powder falls freely from the funnel to form a heap collective with radius r on the disk, and the heap collective height is fixed at h, then $\tan\theta = h/r$.

In this study, crystal lamination method was used. The drug particles can be crushed, screened and dried properly, and then added with the appropriate amount of disintegrant and lubricant to press into tablets.

Six coating tablets were taken from each pot of coating tablets at the exit of the coating machine, and were respectively put into the six tubes of the disintegrator, and the disintegrator was used to determine the disintegration time of the drug.

2.5 Release measurement

Following Appendix XD Second Method, Chinese Pharmacopoeia 2015 Edition, Vol. II, the dissolution measurement method was used to determine the dissolution of duloxetine hydrochloride. First, 750 mL of hydrochloric acid solution (9 → 1000) was used as the release medium; rotation speed was 100 revolutions per minute. After 2 h, no discoloration, cracks, or disintegration occurred in the six tablets. Then, 250 mL of 0.2 mol/L sodium phosphate solution preheated was added at 37 °C into a dissolution cup and mixed. After 45 min, the appropriate amount of solution was taken and centrifuged, and the supernatant was the test solution. In addition, an appropriate amount of duloxetine hydrochloride reference substance was accurately weighed, dissolved in 30% ethanol solution, and quantitatively diluted with the above phosphate buffer to prepare a solution containing about 22.4 μg duloxetine hydrochloride per mL as the reference solution. Take 10 μL from each of the above two solutions and determine according to the content determination method in pharmacopoeia. Finally, the release of each piece was calculated.

2.6 Determination of relating substances

An appropriate amount of the fine powder of the product (about 22.4 mg of duloxetine hydrochloride) was accurately weighed and placed in a 100 mL measuring bottle. Next, the mobile phase was added properly and shaken to dissolve duloxetine hydrochloride. Then, the mobile phase was added to dilute to scale, shaken, and filtered. The filtrate was used as a test solution. First, 1 mL of the test solution was precisely measured in a 100-mL volumetric flask,

Table 2 Composition of isolation layer and enteric layer (calculated as 1000 tablets, unit: g)

Raw material of isolation layer	Prescription 4	Prescription 5	Prescription 6
Hydroxypropyl methylcellulose	6.5	6.5	6.5
Sucrose	10.0	8.7	7.0
Talc	2.2	3.5	5.2
Titania	1.3	1.3	1.3
Purified water	Proper amount (solid content about 15%)		
Raw material of enteric layer	Prescription 7		
Acrylic resin	52.2		
Triethyl citrate	1.6		
Talc powder	2.6		
Purified water	Proper amount (solid content about 20%)		

adding a mobile phase to scale and shaken well, as a control solution. The detection wavelength was 230 nm, the flow rate was 1.0 mL/min. Next, the solution was injected into a liquid chromatography column, and the chromatogram was recorded. If there was a 1-naphthol peak, the peak area should be calculated by multiplying by 0.52, which could not be greater than 1/2 (0.5%) of the peak area of the reference. Thus, the total impurity peak area could not be greater than 80% (0.8%) of the main peak area of the reference substance.

2.7 Content determination

Ten tablets of this product were grind to fine powder and an appropriate amount was accurately weighed (about 22.4 mg duloxetine hydrochloride). Then, the powder was put in a 100-mL measuring bottle, and an appropriate amount of mobile phase was added. The duloxetine hydrochloride was dissolved using ultrasounds, diluted to the scale with the mobile phase, and shaken well. Subsequently, the solution was filtered, 1 mL of the filtrate was accurately measured and placed in a 10-mL measuring bottle, diluted to the scale with mobile phase, and shaken well. As a result, 10-µL was accurately measured and injected into the liquid chromatography column, and the chromatogram was recorded. In addition, a precise amount of duloxetine hydrochloride was weighed, dissolved in mobile phase, and quantitatively diluted to produce a solution containing about 22.4 µg of duloxetine hydrochloride per 1 mL, which was determined by the same method and calculated by peak area according to the standard external method.

2.8 Preparation of prescription processes samples

According to the prescription process of this experiment, samples were prepared in the laboratory to verify the operability of the process and ensure the control of quality. Thus, three batches of samples (S200101, S200102, S200103) were prepared, and the quality was analyzed.

2.9 Comparison of sample release

The samples prepared above (batch Number: S200101) and the duloxetine hydrochloride enteric-coated tablets (batch number: 200701) sold by Shanghai Zhongxi Pharm were tested according to the release determination method (second method of XD in Appendix II of Chinese Pharmacopoeia 2015 edition) [11]. First, 750 mL of hydrochloric acid solution (9 → 1000) was used as the release medium, and the rotation speed was 100 revolutions per minute. After 2 h, no discoloration, cracks, or disintegration occurred in the six tablets. Then 250 mL of 0.2 mol/L sodium phosphate solution preheated to 37 °C was added to the dissolution cup and mixed. At 5, 10, 15, 20, 30, and 45 min, an appropriate amount of the solution was taken out and centrifuged, and the supernatant was taken as the test solution. In addition, an appropriate amount of duloxetine hydrochloride reference substance was accurately weighed and dissolved in a 30% ethanol solution. Finally, the above phosphate buffer solution (hydrochloric acid solution (9 → 1000)-0.2 mol/L sodium phosphate solution (3:1), 2 mol/L hydrochloric acid solution or 2 mol/L sodium hydroxide solution to adjust pH to 6.8) was quantitatively diluted to make a solution containing about 22.4 µg of duloxetine hydrochloride in each mL as a reference solution. Then, 10 µL of each of the above two solutions were used to calculate the release amount of each tablet according to the method under content determination.

2.9.1 Data analysis

Data were shown as the mean ± standard deviation of the means and analyzed using GraphPad v5.0 software (GraphPad Software, Inc., La Jolla, CA, USA). $P < 0.05$ was considered indicative of a statistically significant difference.

3 Results

3.1 Determination of angle of repose of prescription

In the preparation of tablets, the fluidity of powder had a great influence on the weight difference in the forming process. To ensure good fluidity, the repose angle of particles should be less than or close to 30°. At this time, the fluidity of particles was good, and when the repose angle was greater than 40°, the fluidity of particles was poor. The results of trial production are shown in Table 3.

In the process of tableting, hardness was controlled within the range of 6–8 kg. The repose angle and disintegration time of prescription 3 were slightly superior, related to the additional polyvidone K30. On the other hand, the dosage of povidone K30 in prescription 1 and prescription 2 resulted in excessive viscosity of the

Table 3 Results of trial production of prescription samples

Prescription	Mobility	Angle of repose	Compressibility	Disintegration time
Prescription 1	good	38.9°	good	9 min
Prescription 2	good	37.6°	good	9 min
Prescription 3	good	35.6°	good	6 min

adhesive, which was not conducive to granulation. To obtain a suitable viscosity, 1/2 povidone K30 was dissolved in an ethanol solution, and the rest was mixed with excipients.

3.2 Determination of dissolution

Colloidal silica was added to the prescription to reduce the amount of magnesium stea rate affecting drug release. The isolation layer and enteric layer were coated on the above prescription and the dissolution was compared. The results are shown in Table 4. The experimental results showed that prescription 3 had advantages in particle fluidity, disintegration time, and dissolution. In the process of finding the coating solution configuration, coating prescription 4 had more water-soluble sucrose, and the viscosity of the prepared solution was larger. When coating, purified water had to be added to reduce the solid content to less than 10%, which extended the coating time. Prescription 6 was severely blocked when coating and the coating appearance was not clean. The coating process of prescription 5 was successful, and the appearance of coated tablets was clean. Three batches of enteric-coated tablets were dissolved and compared. The results are shown in Table 5. The experimental results showed that the coating process of prescription 5 was stable, and the dissolution residue in the cup was relatively good, which had obvious dissolution advantages. The dissolution rate conforms to the standard of Chinese Pharmacopoeia [11]. Thus, prescription 5 was selected as the isolation layer prescription.

3.3 Selection of prescription process

The final formulation selected by chip and isolation layer prescription is shown in Table 6. The process flow of duloxetine hydrochloride enteric-coated tablets was as follows: a. Duloxetine hydrochloride and lactose were mixed and powdered (duloxetine) has a lower density, and the mixed powder can be better dispersed). Sucrose and 1/2 of the prescribed povidone K30 were sieved through a 60-mesh sieve and mixed evenly. b. The remaining half of povidone K30 was dissolved in 45–55% ethanol as an adhesive. c. The solution of the second step was added into the raw and auxiliary materials evenly mixed in the first step and stirred for granulation. d. The soft material was dried in the oven at 40–45 °C, removed, and cooled to room temperature. The crosslinked povidone, silica gel, and magnesium stearate were added. After 20-mesh screening, the whole particle was mixed and pressed. e. Encapsulation isolation layer: approximately half of the prescription amount of distilled water was heated to 70 °C, and HPMC was added while stirring. The amount of talc powder in the prescription was added into the other half of the water, homogenized for 5–10 min, dispersed evenly, and added into the HPMC solution in the stirring. Next, the sucrose and titanium dioxide were added, mixed evenly, and passed through a 60-mesh sieve to obtain the isolation layer coating solution. Under slow stirring, the high-efficiency coating pot was used for coating operation. The basic process parameters were sheet bed temperature of 30–40 °C and inlet air temperature of 50–70 °C. f. Intestinal dissolving coating: water dispersion of acrylic resin was weighed according to prescription quantity, and 1/2 prescription quantity of water was added while stirring well. The triethyl citrate and talc were added to the remaining water and homogenized for 5–10 min. The latter was slowly poured into the former and stirred for 30 min, and the enteric coating solution was obtained through a 60-mesh sieve. The basic process parameters for the bed temperature were 25–35 °C, and the inlet air temperature

Table 4 Dissolution test results of prescription samples

Prescription	Dissolution %						
	1	2	3	4	5	6	Average
Prescription 1	86.9	89.4	86.6	88.9	90.1	89.7	88.6
Prescription 2	88.7	88.9	92.5	87.6	91.3	97.6	89.4
Prescription 3	92.4	95.6	91.6	89.5	91.5	90.2	91.8

Table 5 Dissolution test results of prescription samples with different isolation layers

Dissolution %								
Prescription	Dissolution phenomenon	1	2	3	4	5	6	Average value
Prescription 4	All dissolved in 20 min, a little powdery white precipitation in 45 min	92.9	94.8	91.8	92.1	94.7	93.9	93.3
Prescription 5	All dissolved at 18 min, no precipitation at 45 min	96.5	97.6	93.9	92.9	98.1	94.6	95.6
Prescription 6	All dissolved at 17 min, small white film	90.3	89.2	86.9	90.1	87.5	88.2	88.7

was 35–55 °C. g. Curing treatment: After coating, the coating pieces were put in the oven at 38–42 °C for about 2 h to cure the resin.

3.4 Sample quality test results

The weight difference, content, release degree, and related substances of the three batches of samples were in line with the provisions of the Pharmacopoeia. The test results are shown in Table 7.

3.5 Comparison of sample release

It can be seen in Table 8 that the release degree of the two batches of samples was similar, indicating a similar release behavior of the two batches of samples. The acid was released for 2 h and taken out for weighing to calculate the weight gain. The results are shown in Table 9. The dissolution phenomenon showed that when the dissolution time was 45 min, there was obvious white enteric-coated film deposition at the bottom of the dissolution cup in 200701, while S200101 had almost no deposition.

4 Discussion

As Duloxetine Hydrochloride is unstable in acidic environment, the marketed drug is made into enteric coated pellets by fluidized bed coating technology to avoid drug degradation in the stomach and release the drug when the pellets are transported to the small intestine. Pellets are typical multi unit drug delivery systems. Their

Table 6 Formulation: (calculated as 1000 tablets)

Raw and auxiliary materials	Unit: g	Function
Duloxetine hydrochloride	22.4	Main drug
Povidone K30	3.75	Adhesive
Sucrose	138.0	Filler
Lactose	80.0	Filler
Crosslinked povidone	2.5	Disintegrating agent
Magnesium stearate	About 1.5	Lubricant
Colloidal silica	0.5	Lubricant
Ethanol	4–55% appropriate amount of ethanol	Solvent
Hydroxypropyl methylcellulose	6.5	Film-forming material
Sucrose	8.7	Filler
Talc	3.5	Anti-sticking agent
Titanium dioxide	1.3	Shading agent
Purified water	Proper amount (solid content about 15–20%)	Solvent
Acrylic resin (L30D-55)	About 52.2	Enteric-coated material
Triethyl citrate	About 1.6	Plasticizer
talc	About 2.6	Anti-sticking agent
Purified water	Proper amount (solid content about 20%)	Solvent

Table 7 Yield of three batches of samples and results of main inspection items (Specification: 22.4 mg/tablet)

Batch number	Feeding quantity	Weight difference	Content (%)	Dissolution rate	Related substances (%)
S200101	2000 pieces	Qualified	100.15	Qualified	0.14
S200102	2000 pieces	Qualified	99.8	Qualified	0.13
S200103	2000 pieces	Qualified	96.28	Qualified	0.19

Table 8 Release comparison test

Time min/Batch number	Dissolution rate%					
	5	10	15	20	30	45
S200101	0.35	26.09	76.56	88.17	94.25	94.50
200,701	0.42	29.68	69.96	84.76	90.51	93.29

Table 9 Comparison of weight gain of prescription tablets

Batch number	Weight gain %						
	1	2	3	4	5	6	Average
S200101	4.6	2.3	3.9	3.2	4.1	4.2	3.7
200,701	3.8	3.4	4.5	2.1	3.6	3.7	3.5

advantages lie in that they are transported and released in the form of multiple particles in the gastrointestinal tract, which can effectively reduce the individual differences in drug release and absorption. Gao Hao et al. [12] had compared the effects of two enteric coating materials, hydroxy progylme thyl celluloseace tatesuccinate (HPMCAS) and methacrylate resin (Eudragit® L30D-55), on the release stability of duloxetine enteric coated pellets. The results showed that the pellets prepared by HPMCAS had better stability. Chen Ying et al. [13] prepared duloxetine hydrochloride enteric coated pellets with Eudragit® L30D-55 as coating material, and studied the release in vitro. It was found that, by optimizing the formulation, a generic preparation with similar release behavior to the reference preparation could be obtained. Due to the low solubility of duloxetine in water, reducing the particle size of raw materials through wet grinding technology could significantly increase the in vitro release rate of enteric coated preparations [14]. It had also been reported that duloxetine was made into enteric coated adhesive microspheres [15], oral film [16] or patch [17], so as to avoid the first metabolism of drugs in the liver and increased the bioavailability.

The goal of these experiments was to design a new prescription process that improves product quality. In this study, duloxetine hydrochloride was mixed with excipatory materials, adhesive was added, and the mix was stirred until granulation occurred. Experiments confirmed that duloxetine hydrochloride might cross-react with acrylic resin, an enteric-coated material, affecting the release of duloxetine hydrochloride enteric-coated tablets and reducing stability. Therefore, we needed to improve the isolation layer prescription. By screening the process conditions, we found a better prescription process. The duloxetine enteric-coated tablets prepared by the selected prescription process had obvious advantages compared with duloxetine enteric-coated tablets purchased in the market.

5 Conclusion

In this study, the formulation of duloxetine hydrochloride enteric-coated tablets was improved. The experiment showed that the most suitable adhesive for the preparation of Doloxetine hydrochloride enteric-coated tablets was 1/2 the dosage of povirone K30 dissolved in ethanol, and the dissolution of the drug could be improved when 1.3 g colloidal silica was added to the prescription. The dosage of magnesium stearate was 1.48 g. The sucrose and talcum powder ratio was 138/8.7, which could effectively configure the coating solution with a solid content of 15–20% so that the coating process could be carried out smoothly.

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Authors' contribution JG and CZ: designed the study; ZY: collected the data; YQ: analyzed the data and reviewed the article; MY and YQ: submitted the article.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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