dx.doi.org/10.14227/DT320125PGC13

Consistency Evaluation of Dissolution of Granisetron Hydrochloride Tablets in China

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ABSTRACT

Introduction: A method for checking the dissolution of granisetron hydrochloride tablets was established to evaluate its consistency with the in vitro dissolution of the original preparation. **Methods:** Two fully automated dissolution testers (Agilent and Sotax) were used at 50 rpm with 900 mL of three different pH dissolution media at 37 ± 0.5 °C (pH 1.2 hydrochloric acid, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer). The generic and original preparations of granisetron hydrochloride tablets were analyzed by high performance liquid chromatography. Dissolution rates were determined, and dissolution curve similarity was analyzed for in vitro consistency evaluation. **Results:** The dissolution method had strong specificity, a linear relationship, no adsorption of the filter membrane, and good precision, accuracy, solution stability, and robustness, all of which satisfied the required specifications for dissolution determination. The generic and original preparations released more than 85% of drug within 15 minutes in all three dissolution media, which is consistent with the dissolution curve of the original drug. **Conclusion**: The method can be used for in vitro dissolution evaluation and comparison of granisetron hydrochloride tablets.

Keywords: Granisetron hydrochloride tablets, original preparation, generic preparation, dissolution curve, consistency evaluation

INTRODUCTION

Granisetron hydrochloride is a highly selective 5-HT3 receptor blocker approved by the US Food and Drug Administration for the treatment of nausea and vomiting caused by chemotherapy and radiotherapy, as well as for the prevention of post-operative nausea and vomiting (in some countries) (*1*, *2*). Radiotherapy, chemotherapy, and surgery can cause intestinal chromaffin cells to release 5-HT, which can activate 5-HT3 receptors in the central or vagus nerve endings and trigger a vomiting reflex. Granisetron hydrochloride tablets inhibit the occurrence of nausea and vomiting by antagonizing 5-HT3 receptors in the central chemoreceptor area and peripheral vagus nerve endings (*3*).

The degree of drug dissolution or release after oral solid dosage administration is the main factor affecting drug absorption, and the dissolution curve can be plotted from the dissolution of the drug at each time point. Therefore, the dissolution curve is of great significance for consistency evaluations of quality and efficacy of oral solid dosage forms (*4*, *5*). The 2020 *Chinese Pharmacopoeia* does not specify requirements for the dissolution of granisetron hydrochloride tablets (*6*). In contrast, the United States Pharmacopeia (USP) quality standards do have such requirements, and the USP dissolution method has been included in the Japanese Orange Book (*7, 8*). The USP and Japanese Orange Book dissolution methods are basically the same, except for slight differences in the dissolution medium and injection volume. According to these existing standards, the detection method, wavelength, dissolution medium, rotation speed, and sampling time points for dissolution evaluation of granisetron hydrochloride tablets were selected.

In this study, the in vitro dissolution rates of generic and original granisetron hydrochloride tablets were measured in different pH dissolution media using a high-performance liquid chromatography (HPLC) method. The method will serve as a reference for consistency evaluation of granisetron hydrochloride tablets in vitro dissolution rates (*4*, *9*–*11*).

METHODS

Chemicals and Reagents

Granisetron hydrochloride tablets were obtained from Fuan Pharmaceutical Group Ningbo Team Pharmaceutical, Co., Ltd (batch nos. 211001, 211002, 211003, expiration October 2024) and Atnahs Pharma Netherlands B.V (batch no. M1052B07, expiration March 2024). The reference substance of granisetron hydrochloride tablets was obtained from China Institute for Food and Drug Control (batch no. 100558-201403, purity 99.2%).

Additional chemicals included HPLC-grade acetonitrile, methanol, and tetrahydrofuran from TEDIA. Phosphoric acid, sodium chloride, sodium dihydrogen phosphate, potassium dihydrogen phosphate, and sodium hydroxide were obtained from National Pharmaceutical Group Chemical Reagent Co., Ltd. Water was purified through a 0.22-µm filter membrane.

Solution Preparation

The dissolution media were 900 mL each of pH 1.2 hydrochloric acid (HCl), pH 4.5 acetate buffer, and pH 6.8 phosphate buffer, prepared in accordance with *Chinese Pharmacopoeia* (*6*).

The working standard solution was prepared in a 100-mL volumetric flask with 11 mg of granisetron hydrochloride reference standard (Mettler Toledo electronic balance, XS205DU) and pH 6.8 phosphate buffer, diluted up to the mark on the flask. Samples (1-mL) were placed in separate 100-mL volumetric flasks then further diluted with buffer to the mark and shook well.

To prepare the sample solutions, 11 mg of granisetron hydrochloride reference standard was put in a 100-mL volumetric flask, 1.1 g of blank excipients was added to the same flask, then dissolution medium was added to the mark. The sample solutions were placed in an ultrasonic bath (Ningbo Scientz, SB25-1 2DT) for 20 minutes, then allowed to cool. Samples (1 mL) were collected and put in a separate 100-mL volumetric flask, then diluted with dissolution medium to the mark and shook well.

Sodium chloride (100 mg) was used to prepare the blank excipient solution.

pH levels were measured with a Five Easy plusFE28 pH meter (Mettler Toledo).

Investigation of Chromatographic Conditions

Except for a difference in injection volume, the chromatographic conditions for dissolution detection used in the USP and Japanese Orange Book are basically the same. Therefore, according to USP, octadecylsilane bonded silica gel was used as the filler (4.6 × 150 mm, 5 µm), mobile phase was 0.1 mol/L phosphate solution (pH 2.0): methanol: tetrahydrofuran (v:v:v 75:24:1.1), detection wavelength 300 nm, flow rate 1.2 mL/min, column temperature 30 °C, and injection volume 100 µL.

Samples (10 mg) of the prescribed proportion of blank excipients and an appropriate amount of granisetron hydrochloride were dissolved in each dissolution medium and diluted to approximately 2 µg of granisetron per 1 mL (*12*). The results showed that the blank dissolution medium and blank excipients

did not interfere with the detection. The peak shape of the main peak was good and the number of theoretical plates was high, but the retention time of the main peak was late. Therefore, to detect more efficiently, the column was replaced with a C18 (4.6 × 100 mm, 3.5 μm), the mobile phase was adjusted to 70:29:1.1 (v:v:v), and the flow rate changed to 1.0 mL/min. The results showed that the analysis time was significantly shortened after replacing the short column with a small particle size and increasing the proportion of organic phase (blank media and excipients did not interfere with the detection, main peak shape was good, number of theoretical plates was high). Therefore, the final dissolution determination column was determined to be octadecylsilane bonded silica gel (4.6 × 100 mm, 3.5 μm or equivalent efficiency column) with a mobile phase of 0.1 mol/L phosphate solution (pH 2.0): methanol: tetrahydrofuran 70:29:1.1 (v:v:v), detection wavelength 300 nm, flow rate 1.0 mL/min, column temperature of 30 °C, injection volume of 100 μL

Chromatographic Analysis

For all samples, HPLC analysis was performed using an Agilent 1260 separation module equipped with ultraviolet detector, degasser, quaternary pump, and autosampler system.

The chromatographic conditions were as follows: C18 column: 4.6 × 100 mm, 3.5 μm; column temperature: 30 °C; mobile phase: 0.1 mol/L phosphate solution; adjust pH to 2.0 with methanol: tetrahydrofuran (v:v:v 70:29:1.1); flow rate: 1.0 mL/min; injection volume: 100 μL; wavelength: 300 nm.

Method Validation

Verification of the dissolution method, including adsorption of filter membrane, specificity, linearity, range, accuracy, precision, durability, and solution stability, was conducted in accordance with the principles set out by the International Council on Harmonization (*13*).

Adsorption of Filter Membrane

To assess adsorption of the filter membrane, the change of peak area should be less than 2.0%. One granisetron hydrochloride tablet was placed in 900 mL of each dissolution medium. For each solution, three samples with different volumes (2, 5, and 10-mL) were filtered with a 0.45-μm aqueous (polyethersulfone) first-stage filter head. The same steps were repeated with a secondary filter head (25 mm × 0.45 μm water system). A sample (100 μL) of each solution was analyzed by HPLC.

Specificity

To assess specificity, the blank solvent and excipients must be free from any interference; the number of theoretical plates of the main peak should not be less than 2000; the trailing factor should not be more than 1.5; and the purity angle of the main peak should not be less than the purity threshold. One granisetron hydrochloride tablet was put into each dissolution medium. After 15 minutes, a sample (100 μL) of each solution (including blank excipient solution and blank dissolution medium) was collected and filtered, then analyzed to determine specificity.

Linearity

The linear correlation coefficient of each medium should be greater than 0.999. To assess for linearity, a stock solution was prepared with 11 mg of granisetron hydrochloride reference standard placed in a 100-mL volumetric flask, then pH 6.8 phosphate buffer was added to dissolve and dilute the solution to the mark. Samples of 1, 2, 4, 5, 6, and 5 mL of stock solution were placed into a 100, 50, 50, 50, 50, and 25-mL volumetric flask, respectively, then diluted with each dissolution medium to the mark.

Accuracy

Accuracy of the method was investigated with the sample solution in pH 1.2 hydrochloric acid solution, pH 4.5 acetate buffer, and pH6.8 phosphate buffer. The recovery rate of each medium should be between 95% and 102%, and the relative standard deviation (RSD) should be less than 5.0% (*14*).

Precision

Precision of the method was determined using six samples of the standard and sample solutions (relative SD should not exceed 2.0%). Intermediate precision tests were performed in the same laboratory by different operators on different days using different instruments.

Robustness

Robustness of the method was assessed by modifying the dissolution parameters, including the rotational speed (± 5 rpm), temperature (± 2 °C), degassing, and rinsing volume (± 1 mL). Compared with the normal conditions, the difference in mean dissolution should be less than ± 10%, and the difference between the 15-min time point and subsequent time points should be less than ± 5%.

Stability

For stability assessment, the standard and sample solutions were re-tested after room temperature storage for up to 24 hours to document any alterations in the primary peak region. Change in peak area should not exceed 2.0% when compared to the 0-hour measurement.

Dissolution Evaluation

For dissolution tests, two fully automatic intelligent dissolution meters were used (Agilent 708-805DS a nd SOTAX AT7smart) (paddle apparatus) at 50 rpm. Twelve tablets from each product (three generic and one original) were used placed into 900 mL of dissolution medium at 37 ± 0.5 °C. Samples (x mL) were taken at 5, 10, 15, 30, and 45 min and filtered for HPLC analysis. The cumulative dissolution for each product was calculated.

RESULT AND DISCUSSION

Method Validation Results

Adsorption of Filter Membrane

As shown in Table 1, the peak area change was less than 2.0%, i.e., the primary and secondary filter heads had no adsorption of the drug in granisetron hydrochloride tablets.

Specificity

Blank solvents and excipients did not interfere with determination of samples, the number of theoretical plates of the main peak was more than 2000, the trailing factor was not more than 1.5, and the purity angle of the main peak was more than the purity threshold. Therefore, the dissolution specificity of granisetron hydrochloride tablets was good under this condition.

Table 1. Adsorption of Filter Membrane Test Results

Dissolution Medium	First-Stage Filter Head				Second-Stage Filter Head		
	Filter Head	Filtration Volume (mL)	Peak Area	Peak Area Change (%)	Filtration Volume (mL)	Peak Area	Peak Area Change (%)
pH 1.2 hydrochloric acid	SOTAX water system	2	241,277	Reference	2	241,233	Reference
		5	240,500	–0.32			
		10	242,213	0.39	5	241,194	–0.02
	Agilent water system	2	240,793	Reference			
		5	240,560	–0.10	10	241,108	–0.05
		10	241,697	0.38			
pH 4.5 acetate buffer	SOTAX water system	2	239,639	Reference	2	242,095	Reference
		5	236,506	–1.31			
		10	238,311	–0.55	5	242,737	0.27
	Agilent water system	2	240,790	Reference			
		5	239,096	–0.70	10	241,597	–0.21
		10	239,393	–0.58			
pH 6.8 phosphate buffer	SOTAX water system	2	238,938	Reference	2	240,180	Reference
		5	239,635	0.29			
		10	241,463	1.06	5	241,131	0.48
	Agilent water system	2	243,015	Reference			
		5	245,960	1.21	10	242,008	0.76
		10	245,666	1.09			

Linearity

Figure 1 shows that within the concentration range of 0.11270–2.25400 µg/mL (10.24–204.91%), the linear correlation coefficients were 0.9998, 0.9995, and 1.000 in pH 1.2 HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer, respectively, which met the requirements for a good linear relationship.

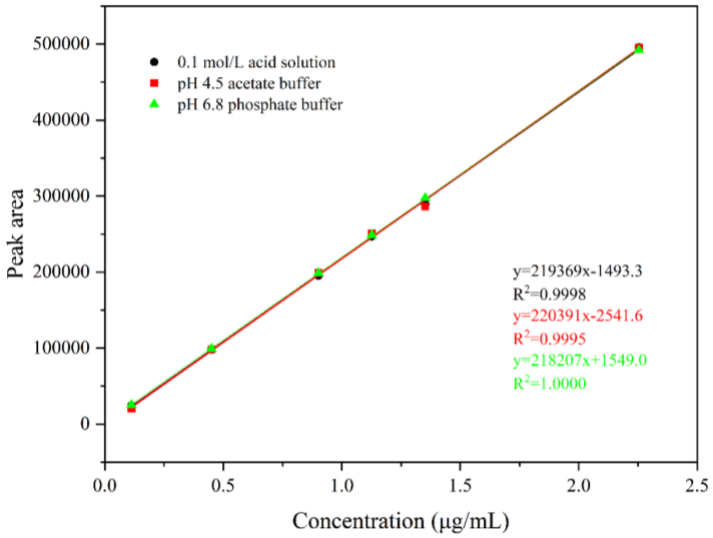

Figure 1. Linear results of the dissolution.

Accuracy and Precision

The recovery rate was 98.8% in pH 1.2 HCl, 97.2% in pH 4.5 buffer, and 99.0% in pH 6.8 buffer, and RSD was less than 5.0% for all. The mean (RSD) recovery rates were 99.4% (0.7%), 98.0% (1.2%), and 99.2% (0.6%) in pH 1.2 HCL, pH 4.5 buffer, and pH 6.8 buffer, respectively. That is, the dissolution determination method had high accuracy and precision.

Robustness

With modified parameters, the mean dissolution difference was less than ± 10% compared with normal conditions, and the difference between the 15 min time point and subsequent time points was less than ± 5%. That is, the dissolution method of this product under standard conditions and with different dissolution instruments had good durability.

Solution Stability

Table 2 shows that the peak area difference of the sample solution after 24 hours of storage was less than 2.0% in pH 1.2 HCl, pH 4.5 buffer, and pH 6.8 buffer compared with 0 hours, indicating that the sample solution was stable for 24 hours.

Table 2. Solution Stability Results

Dissolution Medium	Storage Time (h)	Sample Solution		Standard Solution	
		Peak Area	Peak Area Change (%)	Peak Area	Peak Area Change (%)
pH 1.2 hydrochloric acid	0	222,430	Reference	230,878	Reference
	2	222,779	0.2	230,466	–1.0
	4	219,580	–1.3	233,289	0.2
	8	218,224	–1.9	230,004	–1.2
	12	222,280	–0.1	230,670	–0.9
	24	219,502	–1.3	229,848	–1.3
pH 4.5 acetate buffer	0	221,378	Reference	232,327	Reference
	2	219,599	–0.8	233,298	0.4
	4	219,087	–1.0	232,992	0.3
	8	220,944	–0.2	231,760	–0.2
	12	220,423	–0.4	233,693	0.6
	24	219,507	–0.8	232,302	0.0
pH 6.8 phosphate buffer	0	228,790	Reference	232,117	Reference
	2	228,915	0.1	232,508	0.2
	4	229,736	0.4	233,303	0.5
	8	229,571	0.3	232,147	0.0
	12	229,198	0.2	233,542	0.6
	24	228,276	–0.2	231,877	–0.1

Dissolution Evaluation

In all three media, cumulative dissolution of the generic and original granisetron hydrochloride tablets was greater than 85% at 15 min, and the dissolution plateau was generally reached at 15 min. As shown in Table 3 and Figure 2, there were no significant differences in the dissolution curves between different samples of the same batch and between samples of different batches, and the intra-batch and inter-batch uniformity was good (*15*). Therefore, in vitro dissolution of the generic tablet formulations was similar to that of the original formulation.

The paddle apparatus is a conventional dissolution method used for granisetron hydrochloride tablets in the USP and Japanese Orange Book, except for a slight difference in the dissolution medium and rotation speed (50 rpm is the minimum speed recommended, so there is no need to develop dissolution conditions for less than 85% drug release in 15 minutes by reducing the speed). The USP dissolution medium is 500 mL of phosphate-buffered saline solution at pH 6.5, whereas the Japanese Orange Book is 900 mL of phosphate-buffered saline at pH 6.8. Both methods were reproduced, and the comparison showed that dissolution in 15 minutes was greater than 85%, and dissolution results after 15 minutes were basically the same. Because the mean RSD for each sampling point in 900 mL was smaller than that in 500 mL, the dissolution medium was 900 mL of phosphate buffer at pH 6.8 (prepared in accordance with China's guiding principles), and the sampling time point was 15 minutes. In the process of consistency evaluation of granisetron hydrochloride tablets, in vitro similarity studies were carried out with reference preparations by this method, and bioequivalence studies have been passed. Thus, this dissolution method can distinguish the similarity between generic and original preparations.

Table 3. Dissolution Test Results of Generic and Original Preparation in Three Dissolution Media

Dissolution Medium	Product	Batch No.	Mean Cumulative Dissolution (%) ± RSD (%)				
			5 min	10 min	15 min	30 min	45 min
pH 1.2 hydrochloric acid	Generic	211001	74.1 ± 16.6	95.1 ± 2.5	97.0 ± 0.68	97.1 ± 0.72	97.3 ± 0.56
	Generic	211002	75.1 ± 17.6	96.4 ± 4.9	98.8 ± 2.0	100.4 ± 1.4	100.5 ± 1.4
	Generic	211003	79.8 ± 13.4	97.9 ± 1.3	99.3 ± 1.1	99.4 ± 1.2	99.5 ± 1.1
	Original	M1052B07	74.5 ± 22.8	96.7 ± 5.1	99.3 ± 2.0	100.7 ± 1.4	101.0 ± 1.6
pH 4.5 acetate buffer	Generic	211001	75.5 ± 17.2	96.2 ± 4.1	98.1 ± 2.0	98.4 ± 1.7	98.4 ± 1.7
	Generic	211002	67.6 ± 25.3	94.7 ± 5.5	99.2 ± 1.1	100.4 ± 1.4	100.5 ± 1.4
	Generic	211003	71.4 ± 22.2	94.8 ± 5.8	98.1 ± 1.4	99.0 ± 1.1	99.0 ± 1.1
	Original	M1052B07	80.5 ± 16.2	98.3 ± 2.2	99.1 ± 1.7	99.9 ± 1.9	99.8 ± 1.4
pH 6.8 phosphate buffer	Generic	211001	70.9 ± 18.6	96.5 ± 2.8	98.8 ± 1.5	99.1 ± 1.4	99.1 ± 1.5
	Generic	211002	71.4 ± 22.1	97.8 ± 3.7	100.4 ± 1.2	100.9 ± 1.0	101.1 ± 1.0
	Generic	211003	68.2 ± 16.2	95.7 ± 2.8	98.6 ± 1.4	99.0 ± 1.4	99.1 ± 1.5
	Original	M1052B07	77.9 ± 16.2	98.2 ± 1.9	100.1 ± 1.5	100.6 ± 1.7	100.6 ± 1.6

RSD: relative standard deviation.

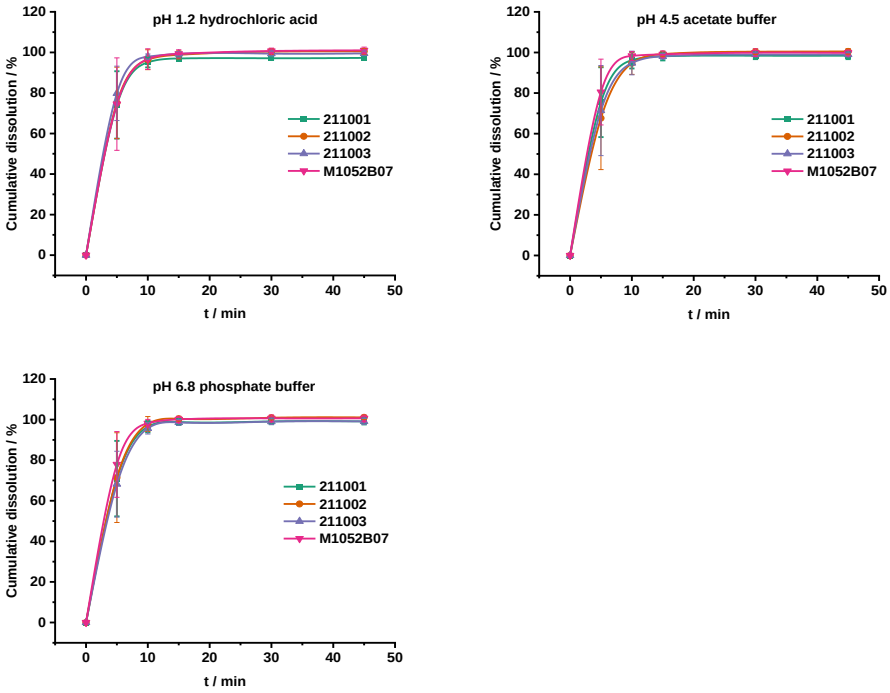

Figure 2. Dissolution curves of granisetron hydrochloride tablets in three dissolution media.

Investigation of Solubility

The solubility of granisetron hydrochloride in water, pH 1.2 HCl, pH 4.0 acetate buffer, and pH 6.8 phosphate buffer at 37 °C was investigated and compared with solubility values published in the Japanese Orange Book (*8*). As shown in Figure 3, solubility of granisetron hydrochloride was greater than 300 mg/mL, which is consistent with Japanese Orange Book. That is, the solubility of granisetron hydrochloride at pH 1.2, 4.0, and 6.8 was good, and there was no pH dependence.

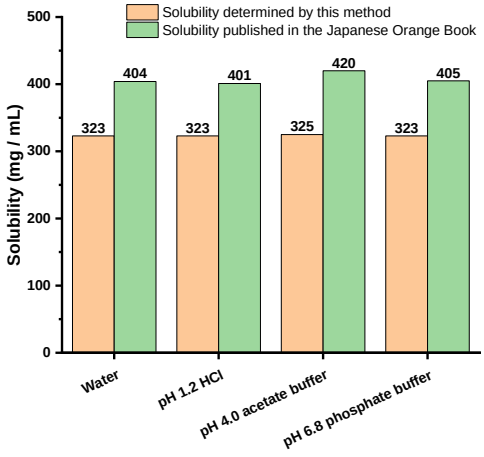

Figure 3. Comparison of solubility results of this study with that of Japanese Orange Book (8). HCL: hydrochloric acid.

CONCLUSION

A consistency evaluation of generic and original granisetron hydrochloride tablets was performed to compare the rate of drug release via HPLC. The dissolution method was feasible, and the results indicated that in vitro dissolution behavior was similar in all three dissolution media (at pH 1.2, 4.5, and 6.8). Thus, the quality of the generic tablets is comparable to the original tablets.

DISCLOSURES

The authors received no financial support for this work and have no conflicting interests.

REFERENCES

1. Aboyoussef, A. M.; Mohammad, M. K.; Abo-Saif, A. A.; Messiha, B. A. S. Granisetron induced sepsis. *J. Pharmacol. Sci.* **2021**, *147* (4), 358–366. DOI: 10.1016/j.jphs.2021.08.005.
2. Erdogdu, F. N.; Saltali, A. O.; Sari, M.; Onal, O.; Celik, J. B.; Apiliogullari, S. The use of granisetron on bupivacaine induced sciatic nerve block in rats. *Somatosens Mot Res*. **2024**, *41* (1), 42–47. DOI: 10.1080/08990220.2023.2165059.
3. Alshawadfy, A.; Ibrahim, E. A.; Helmy, A.; Elsadany, M. A.; Alyeddin, W. F. Attenuation of spinal anesthesia induced hypotension with granisetron in type I diabetic parturients: A randomized controlled clinical trial. *Egypt. J. Anaesth.* **2022**, *38* (1), 431–438. DOI: 10.1080/11101849.2022.2108063.
4. Tang, J. F.; Xin, H. L. Consistency evaluation of dissolution of generic and original preparation of calcium dobesilate tablets. [Article in Chinese] *Drugs & Clinic*. **2022**, *37* (7), 1487–1491. DOI: 10.7501/j.issn.1674-5515.2022.07.009.
5. Sun, T.; Jiang, J.; Zhang, J.; Zhang, X.; Xu, Y.; Wang, L.; Jiang, N. Consistency evaluation of in vitro quality of nitroglycerin tablet reference preparation and imitative preparation. *China Pharmacy.* **2020**, *12*, 586–590.
6. 0931 Dissolution and drug release test. In *Pharmacopoeia of the Peoples Republic of China*: Vol IV. China Food and Drug Administration, China Medical Science Press, 2020.
7. USP Monographs, Granisetron Hydrochloride Tablets. In *USP–NF*. United States Pharmacopoeia, 2024. DOI: 10.31003/USPNF_M35870_04_01.
8. Granisetron hydrochloride tablets. Japanese Orange Book Database. www.drugfuture.com/jporangebook/disslist.aspx?orangebookid=232 (accessed Feb 13, 2025).
9. Zhang, L.; Gao, Y.; Li, H.; Zhang, Z. Evaluation of dissolution consistency of pivastatin calcium tablets. [Article in Chinese] *Drug Eval. Res.* **2021**, *44* (4), 751–755. DOI:10.7501/j.issn.1674-6376.2021.04.011.
10. Shao, P.; Jing, Y.; Chen, S.; AI, J.; Chen, Y. Study on consistency evaluation of the dissolution of generic and original preparations of clozapine tablet. *Chin. J. Mod. Appl. Pharm.* **2018**, 35 (2), 177–181. DOI: 10.13748/j.cnki.issn1007-7693.2018.02.006.
11. You, J., Sheng, K.; Huang, P. In vitro consistency evaluation between generic and original TS-1 preparations. *Chin. J. Mod. Appl. Pharm.* **2021**, 38 (5), 604–608. DOI: 10.13748/j.cnki.issn1007-

7693.2021.05.017.

12. Guidance for dissolution curve determination and comparison of oral dosage [EB/OL]. Chinese National Medical Products Administration, 2016. https://www.nmpa.gov.cn/zhuanti/ypqxgg/ggzhcfg/20160318210001633.html.
13. Wu, J.; Zhang, H.; Zhao, H.; Qin, B.; Lou, T.; Yu, Y.; Huang, L.; Cheng, J.; Zhao, H. Validation of an ion-pair reverse phase high-performance liquid chromatography method for the detection of major components and related substances in diquafosol sodium eye drops. *ACS Omega* **2024**, *9* (9), 10160–10168. DOI: 10.1021/acsomega.3c06658.
14. Zhang, L.; Shang, Q.; Chen, C.; Tang, W.; Xu, Y.; Liu, W. Synchronous fluorometric method for continuous assay of monophenolase activity. *Spectrochim. Acta A Mol. Biomol. Spectrosc.* **2021**, *252*, 119486. DOI: 10.1016/j.saa.2021.119486.
15. Huang, M.; Wang, X.; Cao, Y.; Huang, S.; Cao, M. Consistency evaluation of the dissolution of generic and original preparations of cobamamide capsules. *Chin. J. Mod. Appl. Pharm.* **2022**, 39 (2), 187–191. DOI: 10.13748/j.cnki.issn1007-7693.2022.02.008.