IN-VITRO COMPARATIVE QUALITY EVALUATION OF DIFFERENT BRANDS OF RANOLAZINE TABLETS MARKETED IN ANDHRA PRADESH, INDIA

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Abstract. An extended-release tablet provides prolonged periods of drug in plasma levels thereby reduce dosing frequency, improve patient compliance and reduce the dose-related side effects. Ranolazine is indicated for the chronic treatment of angina in patients who have not achieved an adequate response with other anti-anginal agents. In this study, an attempt was made to investigate the in-vitro quality control testing of five different prominent pharmaceutical brands of Ranolazine hydrochloride tablets marketed in Andhra Pradesh, India. Five different brands of tablets used in the study, named brand A, brand B, brand C, brand D, and brand E were evaluated for weight variation, content uniformity, thickness, hardness, disintegration, dissolution, and assay. The study utilized standardized testing methods to ensure consistency and reliability across all assessments. Results revealed that all the brands of Ranolazine tablets complied with the official specification for hardness, friability, disintegration and assay. All the selected brands of Ranolazine tablets complied with the USP dissolution tolerance limits, the tablets demonstrated robust mechanical strength, minimal friability, and prompt disintegration of active pharmaceutical ingredients.
Keywords: *Ranolazine hydrochloride, drug quality, hardness, friability, disintegration, drug release*

Introduction

The healthcare status of the Indian people has become one of the most crucial concerns of the country. The quality control tests of medicines and pharmaceutical products have been performed to ensure that these medicines could meet acceptable standards of quality, efficacy, and safety (Immel, 2013). The Food and Drug Administration (FDA) constrains pharmaceutical manufacturers to employ a fixed manufacturing process, with specifications that are essential not only in quality confirming of products but because it could be capable of identifying variances batch to batch that may possibly have therapeutic consequences (Abbas et al., 2023). Extended-release drug delivery technology can provide smooth plasma levels of drug over longer periods of time, reduce dosing frequency and improve the patient compliance (Abbas et al., 2023). Ranolazine (*Figure 1*) is indicated for the treatment of chronic angina. Unlike other anti-anginal medications such as nitrates and beta blockers, ranolazine does not significantly alter either the heart rate or blood pressure. Hence, it is of particular use in individuals with angina that is nonresponsive to maximal tolerated doses of other anti-anginal medications (Thomson, 2007; Remington, 2006).

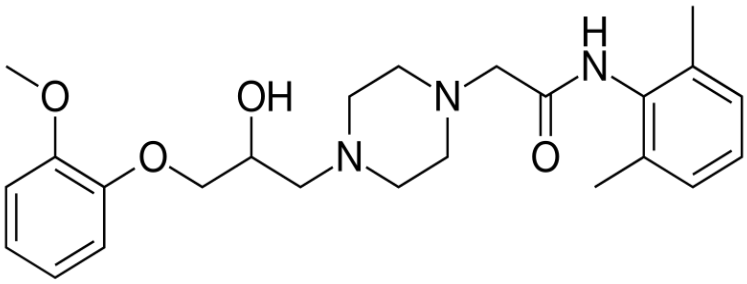

Figure 1. *Chemical structure of Ranolazine.*

The literature survey revealed that two UV methods (Doppa et al., 2019; Murthy et al., 2011) and some authors are formulated and conducted quality control tests of different extended-release matrix tablets of Ranolazine are reported till date (Gunda et al., 2022; Alexandar et al., 2017; Ugale and Mulgund, 2015; Kumari et al., 2012; Bidada et al., 2011; Priya et al., 2011). This study aimed to evaluate quality control considerations for commercial Ranolazine tablets in Andhra Pradesh. The different brands of Ranolazine 500 mg tablets were obtained from local pharmacy stores. Five brands of Ranolazine tablets were used in the study.

Materials and Methods

Reagents

The chemicals and reagents used to perform the experiments were the following: Standard Ranolazine (≥99%) was brought as a gift sample from Hetero Labs, Hyderabad, India. And is of IP reference standard. Analytical grade methanol, acetonitrile, and water was purchased from Thermo Fisher Scientific Pvt. Limited, Mumbai, India. The rest of the chemicals and reagents were procured from standard commercial supplier. Different brands of 500 mg Ranolazine hydrochloride tablets were bought from various pharmacy retail outlets in Andra Pradesh. All the brands used were within their shelf life at the time of study. The detailed descriptions of these products are presented in *Table 1*. The following equipment were used for the experiment: UV-Visible Spectrophotometer (Double beam Spectrophotometer, LAB INDIA, 3200), analytical balance (Essae, Vibra AJ-220E) Monsanto hardness tester (Sisco's), friability tester (Roche friabilator model EI 902 from EI), disintegration apparatus (Electolab ED-2L), dissolution apparatus (Electolab EDT-08Lx) type 2. The digital vernier callipers from Perfect Sales India and PH meter (Systronics-802) was used to provides accurate measurements.

Table 1*. List of selected brands of Ranolazine tablets.*

S.No.	Brand name	Composition	Manufactured by	Batch no.	Mfg. date	Expiry date
1	Rancard	Ranolazine 500 mg I.P.	Hetero Labs Ltd.	N2300321	Feb-2023	Jan-2025
2	Ranogard	Ranolazine 500 mg I.P.	Torrent pharmaceutical limited.	HTH0173	August-2022	July-2024
3	Ranozex	Ranolazine 500 mg I.P.	Sun Pharma	1384A	May-2023	April-2025
4	Ranalaz	Ranolazine 500 mg I.P.	Torrent pharmaceuticals.	2GD2K007	May-2023	April-2025
5	Ranx	Ranolazine 500 mg I.P.	Torrent Pharmaceuticals limited.	2GD2K014	July-2023	June-2025

Ranolazine UV-spectroscopy analysis

Preparation of standard stock solution

Primary stock solution of Ranolazine was prepared by dissolving accurately weighed 100 mg of drug and transferred in to a clean and dry 1000 mL volumetric flask and dissolved in a few mL methanol made the volume up to the mark using distilled water as a diluent to get 1000 µg/mL drug solution. The standard stock solution 1000 µg/mL was further diluted with distilled water to obtain the concentration of 100 µg/mL.

Selection of detection wavelength for estimation of Ranolazine

The prepared solution of Ranolazine (100 µg/mL) were scanned in the ultraviolet wavelength region (200-400 nm) to determine the wavelength of maximum absorption (λ). It was observed that the drug showed maximum absorbance at 272 nm.

Construction of standard calibration curve of Ranolazine

Appropriate aliquots (0.2,0.4,0.6,0.8,1.0,1.2,1.4,1.6,1.8 mL) of prepared standard stock solution were transferred into series of 10 mL volumetric flasks and diluted and made up to the mark with water to obtain final concentration of 20-180 µg/mL. The above solutions were scanned over the range of 200 nm to 400 nm against reagent blank and overlay spectra of Ranolazine was shown in the *Figure 2*. The absorbances of each solution were measured at 272 nm against water as a blank. The measured absorbances were plotted graph with concentration on x-axis and absorbances on y-axis s to get a calibration curve. The results of calibration curve were shown in *Figure 3*.

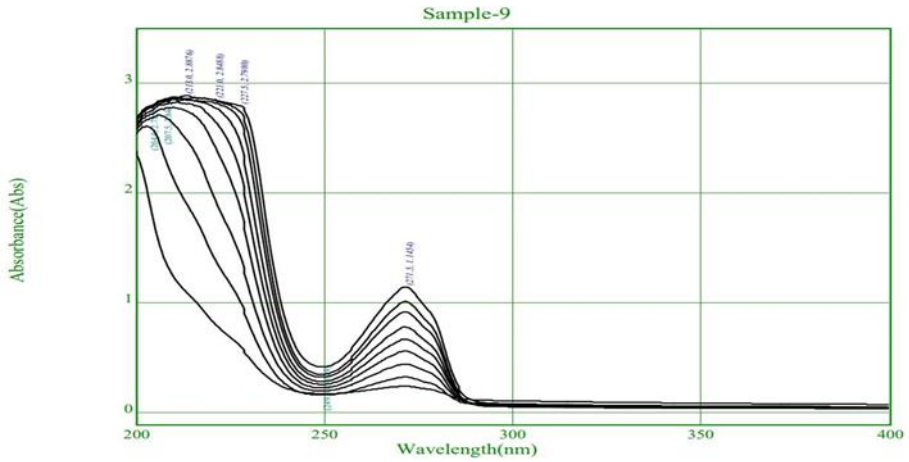

Figure 2. *Overlay spectra of Ranolazine.*

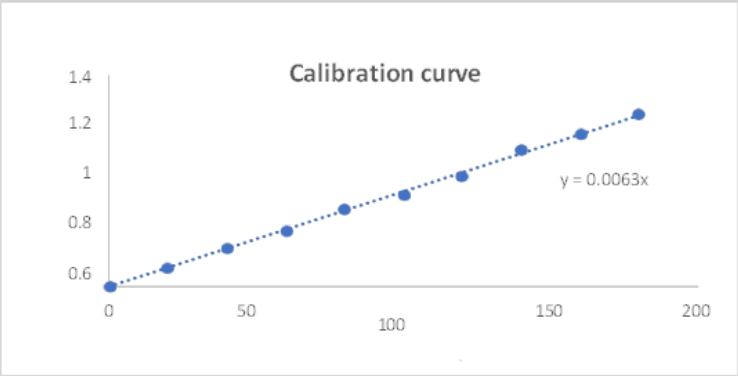

Figure 3. *Calibration curve of Ranolazine.*

Evaluation tests for the selected branded Ranolazine tablets

Different analytical and test methods are necessary for pharmaceutical formulations. For the evaluation of selected brands of Ranolazine tablets were conducted by official test methods includes weight variation test, dissolution test, content uniformity test, disintegration test and non-official tests includes friability, hardness and thickness test (Pujari et al., 2018; Raslan et al., 2018; Vambhurkar et al., 2018; Asaduzzaman et al., 2011).

Thickness measurement

The measurement of the diameter and the thickness was done for selected Ranolazine 20 tablets were taken from different brands, the diameter and thickness of the tablets were measured using micrometers to determine the average thickness and diameter. The mean, percentage deviation from the mean and Standard Deviation (SD) were calculated.

Weight variation test

The dosage uniformity of Ranolazine hydrochloride tablets was evaluated by weight variation, where twenty tablets from each of the five brands were selected by chance, weighed individually with an analytical balance. The average weights for each brand as well as the percentage deviation from the mean value were calculated (Abbas et al., 2023; Kassahun et al., 2019).

Hardness test

Tablet hardness testers function on the principle that it yields a definite extent of force to break down a tablet. The hardness of each tablet was determined by selecting six tablets randomly using a hardness tester. Each tablet was placed between two anvils and force was applied to the anvils, and the crushing strength that causes the tablet to break was recorded. Crushing strength of average of six tablets was recorded (Abbas et al., 2023; Kassahun et al., 2019).

Friability test

The friability test was completed using the Roche friabilator. Twenty tablets were selected randomly from each brand and weighed, then placed together in the friabilator device. All tablets were subjected to the combined effect of abrasion and shocks and it

was rotated at 25 revolutions per minute (rpm) for four minutes (100 times). Then, tablets were weighed and were compared with their initial weights and percentage friability was calculated (Abbas et al., 2023; Kassahun et al., 2019).

Disintegration test

The disintegration test apparatus (Electolab ED-2L) was used to determine the disintegration time of the selected tablets. Six tablets were placed in a disintegration tester filled with distilled water at 37±0. 5°C.The tablets were considered completely disintegrated when all the particles are passed through the wire mesh and time was recorded (Abbas et al., 2023; Kassahun et al., 2019).

Dissolution test

Dissolution is essential in determining the bioavailability of a drug. The dissolution test method was developed and validated for Ranolazine tablet dosage from quality control. In the present study, the in vitro dissolution study of Ranolazine tablets was done in simulated gastric fluid pH 1.2. The dissolution of Ranolazine hydrochloride was done using dissolution apparatus type II (paddle apparatus) with the rate of 50 rpm at 37±0.5°C on six tablets of each brand. The dissolution medium was 900 ml 0.1 N HCl (pH=1.2). 5 ml sample was withdrawn at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 h and an equivalent amount of fresh dissolution medium, maintained at equal temperature, was replaced. Filtered samples were then appropriately diluted (100-fold dilutions) and absorbance readings were taken with UV/Visible Spectrophotometer at wavelength of 272 nm. Solutions of Ranolazine working standard was also prepared using dissolution medium and absorbance was measured. 0.1 N HCl was used as a blank. The concentration of each sample was determined from calibration curve and the percent of drug release at each time was calculated (Abbas et al., 2023; Kassahun et al., 2019).

Drug content

The drug content of Ranolazine in the formulated tablets was measured by randomly picking 20 tablets from each brand were crushed separately and finely powdered by using a mortar and pestle. An accurately weighed portion of the powder was transferred, equivalent to about 100 mg Ranolazine, to a 100 ml volumetric flask. Methanol (30 ml) was added, shaken by mechanical means for 15 min, diluted with water to volume, and filtered, discarding the first few ml of the filtrate. The filtrate (10 ml) was diluted with water to 100 ml and 5 ml of the resulting solution was further diluted with water to 10 ml to obtain 50 µg/ml sample solution. The active pharmaceutical ingredient content of sample solutions was determined by measuring their absorbance against the reagent blank at 272 nm using an Ultraviolet-visible Spectrophotometer. The content of the drug in the tablet was found using the calibration curve (Abbas et al., 2023; Kassahun et al., 2019).

Results and Discussion

Thickness measurement

Results showed that the different brands were examined had the thickness within range of 5.67-5.87 mm (*Table 2*). All brands showed acceptable thickness as none of the

selected brands deviated by up to ±5.0 % from the mean value as stipulated by the reference.

***Table 2**. Thickness of selected brands of Ranolazine tablets.*

S.No.	Brand	Label claim (mg)	Thickness (mm) average of 20 tablets	Results
1	Ranozex	500	5.8792	Pass
2	Rancad	500	5.7801	Pass
3	Ranogard	500	5.6715	Pass
4	Ranolaz	500	5.7295	pass
5	Ranx	500	5.7105	pass

Weight variation test

All results for the weight variation test of the five marketed products from different companies are documented in *Table 3*. The weight variation test of the tablet is used to confirm that the prepared tablet has the accurate amount of active drug in which no more than two tablets are outside the percentage limit. The results indicate a weight uniformity in the selected tablets and all tablets within the usual range, and no one exceeds the allowed percent as per percentage specified in Indian Pharmacopoeia (IP) (Abbas et al., 2023; Kassahun et al., 2019).

***Table 3**. Weight variation of different brands of Ranolazine tablets.*

S.No.	Brand	Label claim (mg)	Average of 20 tablets (g)	% deviation	Results
1	Ranozex	500	0.7015	0.3355	Pass
2	Rancad	500	0.6794	0.1070	Pass
3	Ranogard	500	0.6745	0.7215	Pass
4	Ranolaz	500	0.7771	0.2104	pass
5	Ranx	500	0.7680	0.0101	pass

Hardness test

Sufficient tablet hardness is essential to ensure destruction resistance to endure mechanical shocks during production, packaging, and transportation. In addition, tablets should be able to tolerate reasonable mishandling by the consumer. The mean hardness values of Ranolazine tablets are Tabulated in *Table 4*. The results showed that the brands had mean hardness values within the range of 7.4 to 9.56 (kg/cm2) for Ranolazine tablets. For Ranolazine tablets studied, Rancad had the highest hardness value (9.56 kg/cm2) while Ranozex had the lowest value (7.4 kg/cm2). However, using different excipients or the same excipients in different ratios might be one of the reasons for the observed differences in hardness value among the samples; however, the deviation between tablet to tablet in the same brand was unexpected and needed more investigation (Abbas et al., 2023; Kassahun et al., 2019).

***Table 4**. Hardness studies of marketed Ranolazine tablets.*

S.No.	Brand	Label claim (mg)	Hardness (kg/cm^2)	Results
1	Ranozex	500	7.4	Pass
2	Rancad	500	9.56	Pass
3	Ranogard	500	8.6	Pass
4	Ranolaz	500	7.9	pass
5	Ranx	500	8.2	pass

Friability test

Tablets must resist corrosion when subjected to tensions from collision and tablet slip towards one another and other solid bodies, which can result in removing small pieces from the tablet surface. It is usually measured by a friability tester. In the

friability test, the friability values for Ranolazine tablet brands ranged from 0.007 to 0.617%. All five brands of Ranolazine have passed the friability test and met the IP specification, which specifies that any brand must not lose more than 1% of its initial weight presented in *Table 5* below. The result may further suggest the resistance of the tablets to external forces from manufacturing, distributing, and shipping. At the same time, high tablet strength should not interfere with the disintegration than the dissolution of the drug in the stomach (Abbas et al., 2023; Kassahun et al., 2019).

***Table 5**. Friability test of selected Ranolazine tablets.*

S.No.	Brand	Label claim (mg)	Friability (%)	Results
1	Ranozex	500	0.007	Pass
2	Rancad	500	0.007	Pass
3	Ranogard	500	0.044	Pass
4	Ranolaz	500	0.617	pass
5	Ranx	500	0.097	pass

Disintegration test

The mean disintegration times of the different brands of Ranolazine tablets are shown in *Table 6*. The results showed that all the brands passed the disintegration test according to USP in 2007, which specifies 120 min for enteric coated and delayed-release tablets. Tablet disintegration is prerequisite to dissolution and subsequent absorption of a drug from the dosage form. A drug incorporated in a tablet is released rapidly as the tablet disintegrates because the rate of disintegration affects the dissolution and subsequently the therapeutic efficacy of the medicine. Different formulation factors are known to affect results of disintegration test. The type and number/amount of excipients used in tablet formulation as well as the manufacturing process are all known to affect both the disintegration and dissolution parameters (Abbas et al., 2023; Kassahun et al., 2019).

***Table 6**. Disintegration test of Ranolazine tablets.*

S.No.	Brand	Label claim (mg)	Disintegration time (h)	Results
1	Ranozex	500	1 h:23 min	Pass
2	Rancad	500	1 h:30 min	Pass
3	Ranogard	500	1 h:35 min	Pass
4	Ranolaz	500	1 h:40 min	pass
5	Ranx	500	1 h:26 min	pass

Dissolution test

The dissolution profiles of the five brands of Ranolazine tablets are illustrated in *Figure 4*. According to USP, the amount of Ranolazine released within 12 should not be less than 60 % of the stated amount. From the dissolution test results shown in *Table 7*, all the brands of Ranolazine tablets studied released more than 60% within 12 h except Ranozex which has released only 55.32%. Hence, five of the products complied with USP dissolution tolerance limits but Ranozex failed to release the stated amount. Dissolution of drugs can be influenced by the physicochemical properties of the drug substance, the dosage form design, the manufacturing process, and the testing conditions (i.e., apparatus, agitation, medium, etc.) (Abbas et al., 2023; Kassahun et al., 2019).

***Table 7**. Time dependent drug release of selected brands of Ranolazine tablets.*

Time (h)	Ranozex (%)	Rancad (%)	Ranogard (%)	Ranolaz (%)	Ranx (%)
0	0	0	0	0	0

1	19.78	19.02	21.23	21.41	21.28
2	31.84	26.4	32.3	32.08	34.16
3	38.2	33.92	34.92	36.74	36.65
4	41.1	38.35	38.51	40.7	39.41
5	42.94	41.91	41.06	43.17	42.69
6	43.81	45.83	43.71	46.01	46.24
7	45.28	48.52	46.98	49.09	49.54
8	46.72	51.27	50.02	52.98	52.32
9	49.28	53.42	52.89	56.03	55.68
10	51.21	56.72	55.23	59.12	58.92
11	53.12	59.82	58.63	61.23	62.32
12	55.32	61.42	62.36	65.12	64.54

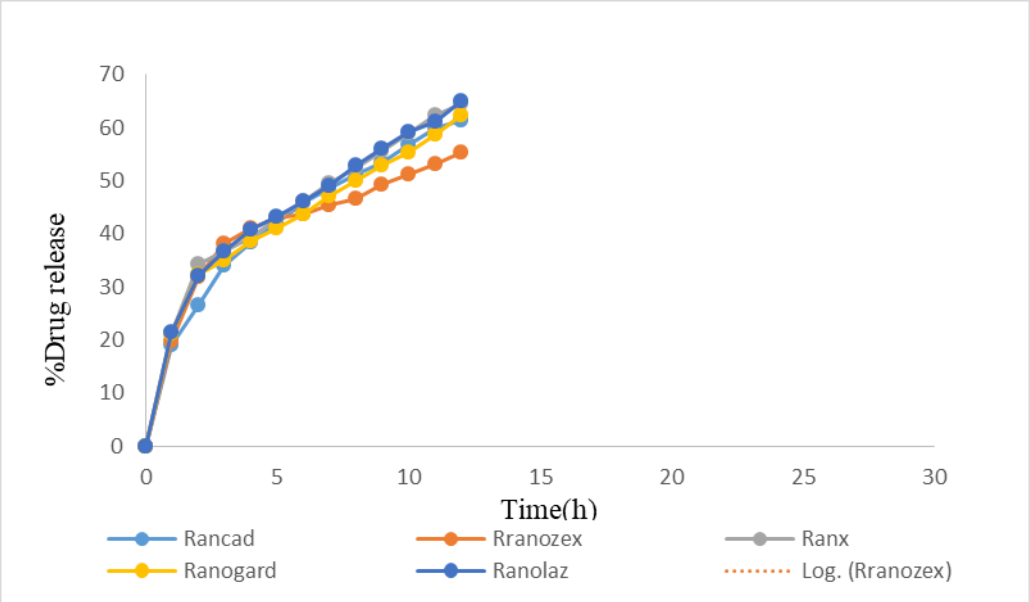

Figure 4. *Comparative In-Vitro dissolution profile of selected Ranolazine tablets.*

Drug content

Percentages of content uniformity tests for selected brands of Ranolazine tablets were shown in *Table 8*. The percentage range for all selected marketed tablets was found to be between 97.82% and 100.8%. In content uniformity testing for selected tablets, each individual content was within the limits range of the average content; therefore, all the selected tablets passed the uniformity of content test (Abbas et al., 2023; Kassahun et al., 2019).

Table 8*. Content uniformity of selected brands of Ranolazine tablets.*

	Ranozex (500mg) n=20		Rancad (500mg) n=20		Ranogard (500mg) n=20		Ranolaz (500mg) n=20		Ranx (500mg) n=20	
	A	B	A	B	A	B	A	B	A	B
Avg	500.99	100.4	499	99.8	504	100.8	489.1	97.82	499.3	99.86
SD	±2.260998		±4.323527		±5.313505		±7.0742		±4.223457	
RSD	0.452305		0.871187		1.062214		1.43034		0.462317	

Notes: A=Drug content (mg); B=Percentage of drug (%).

Conclusion

The results of this study showed that all brands of Ranolazine 500 mg (Ranozex, Rancad, Ranogard, Ranolaz, Ranx) oral tablets conformed to the official specification of standard pharmacopeia. All tablets disintegrated within a time limit of less than 120

minutes. An in vitro release study of the drug in 0.1 N HCl (pH 1.2) exceeded 65% after 12 h. According to the outcomes of this study, there were no deviations from pharmacopeial standards. This study provides valuable insights into the manufacturing processes of these pharmaceutical brands, instilling confidence in the reliability and effectiveness of their tablet formulations. Further research may explore additional parameters or variations in manufacturing conditions to enhance our understanding of tablet quality across different production scenarios.

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Conflict of interest

The authors confirm that there is no conflict of interest involve with any parties in this research study.

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