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Original article

A comprehensive quality control and cost comparison study of branded and generic angiotensin receptor blockers

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ABSTRACT

This study was designed to assess both the quality and cost aspects of various branded and generic formulations of angiotensin receptor blockers, specifically Irbesartan, Losartan Potassium, Olmesartan Medoxomil, Telmisartan, and Valsartan. The collected samples underwent distinct quality evaluations using the methods outlined in different global Pharmacopoeias (British Pharmacopoeia/European Pharmacopoeia, Indian Pharmacopoeia and United States Pharmacopoeia). These drugs were characterized using Fourier-Transform Infrared Spectroscopy and Nuclear Magnetic Resonance techniques, while their quality and concentration were analysed using High Performance Liquid Chromatography. The release profile of the drugs was examined through dissolution testing. Additionally, a cost comparison analysis was carried out by determining the prevailing market prices of the drugs. The evaluated branded and generic angiotensin receptor blockers were found to meet the established standards for impurities, active drug content, and dissolution as set by these Pharmacopoeias, indicating their optimal quality. Notably, the generic drugs exhibited significantly lower costs compared to their branded counterparts. This study confirms that the quality of generic angiotensin receptor blockers is equivalent to that of their branded counterparts. Consequently, these findings support the practicality of utilizing generic drugs as a more economically sustainable and cost-effective approach to managing diseases, especially those of chronic nature.

1. Introduction

Hypertension represents a significant variable contributing to global morbidity and mortality, correlating with an elevated risk of cardiovascular diseases. Primarily characterized by continuous increased blood pressure in systemic arteries, hypertension is defined by the ratio of systolic blood pressure (the pressure exerted by blood on arterial walls during heart contraction) to diastolic blood pressure (the pressure during heart relaxation) (Oparil et al., 2018). Clinically, hypertension is diagnosed when systolic blood pressure is $\geq$ 140 mmHg and/or diastolic blood pressure is $\geq$ 90 mmHg after repeated examinations (Unger Thomas et al., 2020, Heidari et al., 2022). Often referred to as a silent killer, many individuals with hypertension remain unaware due to the absence of noticeable signs or symptoms. Hypertension poses a severe threat to heart health, as elevated blood pressure can lead to vessel hardening, diminishing blood flow and oxygen supply to the heart. This can result in chest pain or angina, heart attacks, irregular heartbeats, and even sudden death. Moreover, hypertension can obstruct arteries supplying blood and oxygen to the brain, increasing the risk of strokes. Additionally, the condition can lead to kidney damage, potentially culminating in kidney failure (Fuchs, Whelton, 2020, World Health Organization, 2023).

Major modifiable risk factors for hypertension include unhealthy diets (characterized by increased salt intake, high saturated and *trans*-fat content, and low consumption of vegetables and fruits), physical inactivity, tobacco and alcohol consumption, and obesity. Non-modifiable

Abbreviations: **ACN**, Acetonitrile; **ARBs**, Angiotensin Receptor Blockers; **BP**, British Pharmacopoeia; **CP**, Chromatographic Purity; **EP**, European Pharmacopoeia; **HPLC**, High-Performance/Pressure Liquid Chromatography; **IP**, Indian Pharmacopoeia; **USP**, United States Pharmacopoeia.

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risk factors such as genetics, age over 65 years, and concomitant diseases like diabetes or renal disorders also contribute to hypertension symptoms (World Health Organization, 2023). Additional potential risk factors comprise cigarette smoking, exposure to air pollutants, psychological stress, sleep disorders, and noise pollution (Mills et al., 2020, World Health Organization, 2021).

As per the guidelines published in International Society of Hypertension a majority of hypertensive patients have additional cardiovascular risk factors and the most common additional risk factors are diabetes (15–20 %), lipid disorders and triglycerides (30 %), overweight obesity (40 %), hyperuricemia (25 %) and metabolic syndrome (40 %). Also, the presence of additional cardiovascular risk factors proportionally increases the risk of coronary, cerebrovascular and kidney diseases in the hypertensive patients.

The prevalence of hypertension varies across the countries/regions and is directly linked to the per capita income of the individual country. The WHO African region has the highest prevalence (27 %) while the America has the lowest prevalence of hypertension. The number of affected adults with hypertension is increased from 594 million in 1975 to 1.13 billion in 2013, and the major proportion of this increased number is seen in low-and middle-income countries. As per the WHO an estimated 1.28 billion adults with an age group of 30–79 years worldwide have hypertension, and most of them (two-thirds) are living in low- and middle-income countries. Approximate 46 % of adults with hypertension are unaware that they are living with this condition (Mills Catherine et al., 2020, World Health Organization, 2023, Rajput, 2022).

Treatment of hypertension includes lifestyle modifications and pharmacological therapy. As the healthy lifestyle choices can prevent or delay the onset of high blood pressure and can reduce the cardiovascular risks. Lifestyle modification is considered as the first line therapy of hypertensive treatment (Mills Catherine et al.,2020). Diuretics, angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs) and beta blockers (BBs) are generally the preferred categories of pharmacological treatment of hypertension (Whelton, Carey, Aronow, et al., 2018).

In the pathophysiology of hypertension; inappropriate activity of renin-angiotensin-aldosterone system (RAAS) plays a key role and the blockade of RAAS has been proven as a successful strategy to manage the hypertension (Robert D. Hill, Prabhakar Vaidya, 2023). Since, ARBs directly involve in the blockade of RAAS, thereby, these are considered as one of the highly effective pharmacological categories of antihypertensives. A numbers of major clinical trials study evidenced that ARBs provide significant outcome benefits in the hypertensive patients. Therefore, in the pharmacological treatment of hypertension ARBs can be used as a first line therapy or added at later stages of the treatment (Addison A. Taylor et al, Ferrario CM et al.,2011) and thus, selected for the current study. Common examples of ARBs are Irbesartan, Losartan Potassium, Olmesartan Medoxomil, Telmisartan and Valsartan. The rationale behind selecting these medications in our study lies in their inclusion in different global Pharmacopoeias, which emphasizes their widespread usage and regulatory significance. By comparing medications found in diverse Pharmacopoeias, we aim to explore potential variations, assess the consistency of regulatory standards, and contribute to a more comprehensive understanding of the global pharmaceutical landscape. This approach allows us to analyse the impact of varying regulatory frameworks on the quality and efficacy of these medications, providing insights that can be valuable for harmonization efforts and ensuring the safety and efficacy of pharmaceutical products on a global scale (NHS.UK, 2022).

Drug regulators worldwide have reliably prioritized the quality of pharmaceutical products. In pursuit of this objective, regulatory authorities across the globe have continually prescribed and updated stringent quality standards. The pharmaceutical market boasts a wide array of products, making it a challenging endeavour for drug regulators to ensure product quality. The pivotal role of independent testing in competent WHO prequalified and accredited laboratories cannot be overstated in this context. The present study was conceived and conducted with the aim of assessing the quality of some ARBs available in the Indian market. This evaluation was carried out independently in accordance with the standards outlined by the different global Pharmacopoeias [British Pharmacopoeia (BP)/European Pharmacopoeia (EP), Indian Pharmacopoeia (IP) and United States Pharmacopoeia (USP)] emphasizing the importance of stringent quality assessment.

1.1. Quality control of drugs

For a drug to achieve the minimum quality, standards are being prescribed in Pharmacopoeias globally. The standards in Pharmacopoeias are authoritative and legally enforceable. Pharmacopoeias contain procedure for analysis and specifications to determine the quality of pharmaceutical substances, excipients and dosage forms. Specifications/ standards in pharmacopoeias are mainly given in two parts i.e. General Chapters and Monographs. General chapters provide information about the tests, procedures used in the monographs which need to be followed by the stakeholders. A monograph in pharmacopoeia for official substance or preparation include the article's definition, description, identification, specific tests, assays, packaging, storage, labeling specifications, and impurities profile, one or more analytical procedures for each test, acceptance criteria and other requirements (Indian Pharmacopoeia, 2022, United States Pharmacopeia, 2023, Sharma, Arvind K. et al., 2022). Fig. 1 demonstrates a concise representation of key quality control tests outlined in the different global Pharmacopoeias.

1.2. Tests recommended for finished pharmaceutical products as per Pharmacopoeias (BP/EP, IP, USP)

1.2.1. Description

This test is general in nature and is not a standard test. It communicates the appearance of an article that complies with monograph standards.

1.2.2. Identification

Identification plays a crucial role in monographs, confirming the presence of labeled drug substances in products. It validates the drug's presence using techniques like HPLC, thin-layer chromatography, Infrared spectroscopy, mass spectrometry, and nuclear magnetic resonance. Accurate identification relies on comparing test results to a properly prepared reference standard.

1.2.3. Related substances

This test evaluates impurity levels in drug products, encompassing process-related byproducts, synthetic intermediates, inorganic, and organic compounds from both drug substances and manufacturing excipients. Monographs set limits for these impurities. During manufacturing and shelf life, degradation products may form due to various factors. Testing protocols must rigorously control toxic substances' presence.

1.2.4. Assay

Assay tests potency and content, confirming a drug product's label claim adherence, typically within $\pm$ 10 % acceptance range. It also monitors stability changes over time.

1.2.5. Dissolution

Dissolution is the process by which solid solute particles transition into a solution, determining the dissolution rate. The process of dissolution is crucial for drug absorption and release into the circulatory system (Anand O et al., 2011; Jambhekar SS, Breen PJ, 2013).

Within the scope of current article, branded tablets (Finished Products) of ARBs i.e. Irbesartan, Losartan Potassium, Olmesartan Medoxomil, Telmisartan and Valsartan which are currently part of BP/EP, IP

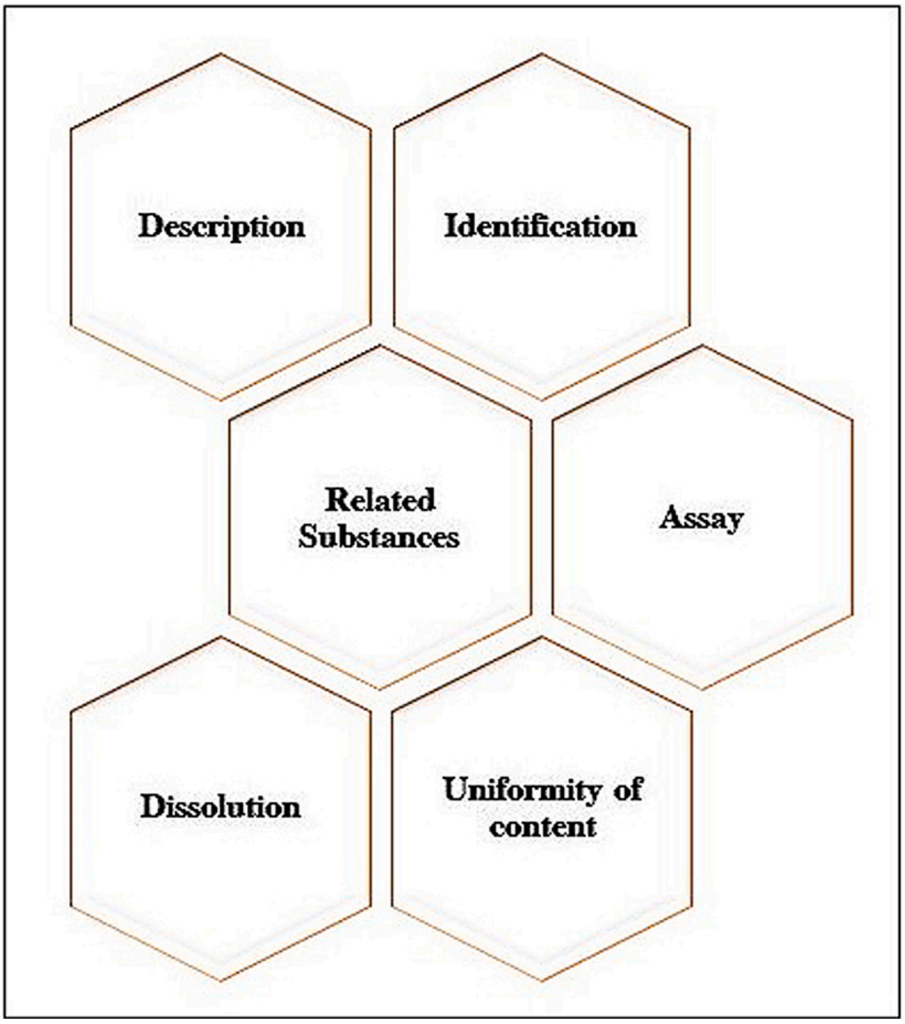

Fig. 1. Characteristic quality control tests as per Pharmacopoeias (BP/EP, IP, USP).

and USP; were meticulously scrutinized for their quality. This evaluation was carried out independently, adhering to the stipulations outlined in Pharmacopoeias (BP/EP, IP, USP). Additionally, a comprehensive analysis was conducted to compare the costs of the branded tablets with their corresponding generic counterparts.

2. Material and methods

For this study, a selection was made of ARBs that are available in the current editions of BP/EP, IP and USP. A comprehensive set of samples, branded tablets (finished products) from prominent pharmaceutical companies that are accessible in the market were gathered from three different local pharmacies. Four to five brands for each of selected active moiety were collected however, only a single brand was found available for Irbesartan in the market which is included in the study. Additionally, for each ARB, one generic drug sample (tablets) were acquired from the Pradhan Mantri Janaushadhi Kendra (PMJK), a prominent source for procuring a diverse range of generic drugs across India. The exact number of brands and tablets collected for the study are mentioned in Table 1. To maintain the confidentiality; branded tablets were coded with one initial alphabet of drug with number 1 to 5 and for Janaushadhi drugs; abbreviation J is used with the initial of particular ARB.

Table 1
Number of brands and tablets collected for the study.

S. No.	Drugs	Number of brands collected (including one generic sample)	Number of tablets collected for each selected brand	Total tablets collected for each selected drug
1	Irbesartan	2	30	2 * 30 = 60
2	Losartan Potassium	5	30	5 * 30 = 150
3	Olmesartan Medoxomil	6	30	6 * 30 = 180
4	Valsartan	5	30	5 * 30 = 150
5	Telmisartan	5	30	5 * 30 = 150

2.1. Reagents

Water: Water purified with a Milli-Q water purification system (Millipore) was used in all procedures. Acetonitrile: For HPLC and Spectroscopy, Manufactured by Finar Limited, CASR 75–05-8, Batch No. A04691001EV (Ahmedabad, India). Orthophosphoric Acid: For HPLC, Manufactured by Finar Limited, CASR 7664–38-2, Batch No.608300708GV (Ahmedabad, India). Methanol: For Chromatography, Gradient grade, Manufactured by Finar Limited, CASR 67–56-1, Batch No.61731127AW (Ahmedabad, India). Triethylamine: HPLC and Spectroscopy, Manufactured by Finar Limited, CASR 121–44-8, Batch No 541621026FQ, (Ahmedabad, India). Ammonium acetate: Emparta ACS, by Merck, CASR 1.93217.0521, Batch No. QD5650393(Mumbai India). Glacial Acetic Acid: For HPLC and Spectroscopy, Manufactured by Finar Limited, CASR 64–19-7, Batch No. 607611011FV (Ahmedabad,

India). Sodium hydroxide: Extrapure, Manufactured by Finar Limited, CASR 1310–73-2, Batch No. 843530210FT. Di-Potassium hydrogen *ortho*-phosphate: Extrapure, Manufactured by Finar Limited, CASR 7758–11-4 (Ahmedabad, India).

2.2. Apparatus

Balance for weighing model XP205 from Metler Toldeo, to measure the pH of solution pH meter from IGeneLabserve, Sonicator from Citizen scale Pvt ltd. India, the dissolution apparatus DS8000 from Lab India and HPLCs of Model 1260 infinity from Agilent and Ultimate 3000 of Dionex were used in this study.

FT-IR Spectrum One FT-IR Spectrometer (Perkin Elmer) and Spectrum version 5.0.1 software was used for IR spectroscopy. A frequency range of 4000 to 450 cm-1 was used for identification of selected samples. NMR 500 (Agilent Technologies) was employed for the characterization of reference substances of selected samples. Deuterated solvents from Merck (Billerica, USA) for NMR spectroscopy were used in this study. Vnmrj version 3.2 software was accessed to done this NMR study. For 1H NMR spectra the acquisition parameters are as follows: spectral width −2 to 14 ppm, scan 64, relaxation delay 1 s, pulse angle 30 degrees, block size 4, receiver gain 30 dB. For 13C NMR spectra the acquisition parameters are as follows: spectral width −14.3 to 234.3 ppm, scan 2000, relaxation delay 1 s, pulse angle 30 degrees, H1 decoupling Decoupled + NOE, block size 64, receiver gain 30 dB.

2.3. Sample preparation

For 1H NMR, 5 mg and for 13C NMR, 25 mg sample was taken in the 5 mm glass NMR tube and made completely dissolved in the suitable deuterated solvents (0.6 ml). Chromatographic conditions for selected samples were followed to determine the related substances and assay are mentioned in the Table 2. Dissolution methods were followed as per the Table 3. For related substances/ chromatographic purity (CP) and assay the preparation of mobile phase, reference solutions and test solution are done as Table 4 and Table 5 respectively.

3. Results

3.1. Identification

3.1.1. FT-IR spectral analysis

The IR spectra of Reference Substances of each of the selected ARBs are depicted in Fig. 2 which are traceable to the reference spectra provided in the current editions of BP/EP, IP and USP and the functional group assignment is represented in the Table 7.

3.1.2. NMR analysis

The chemical shift assignments for Irbesartan IPRS: 1H NMR (CH3OD, 500 MHZ): δ-0.87 (t, 3H), 1.33 (sextet, 2H), 1.51 (sextet, 2H), 1.81 (m, 2H), 1.96 (m, 6H), 2.40 (t, 2H), 4.76 (s, 2H), 7.14 (q, 4H), 7.55 (m, 2H), 7.67 (m, 2H). 13C NMR (CH3OD, 500 MHZ): δ-13.9, 23.1, 27.0, 28.4, 28.5, 38.3, 44.1, 77.2, 124.7, 127.9, 130.7, 131.6, 131.7, 132.4, 137.3, 140.4, 142.9, 157.0, 165.7, 187.4.

The chemical shift assignment for Losartan Potassium IPRS: 1H NMR (DMSO-d_6, 500 MHZ): δ-0.80 (t, 3H), 1.25 (q, 2H), 1.48 (t, 2H), 3.42(s, 2H), 4.31 (s, 2H), 5.21 (s, 2H), 5.36 (s, 1H), 6.90 (d, 2H), 7.09 (d, 2H), 7.28 (m, 1H), 7.34 (q, 2H), 7.54 (d, 1H). 13C NMR (DMSO-d_6, 500 MHZ): δ-13.6, 21.6, 25.8, 29.1, 46.4, 51.3, 125.2, 125. 6, 127.2, 129.4, 130.0, 130.4, 132.5, 134.6, 139.8, 141.1, 147.3, 160.0.

The chemical shift assignment for Olmesartan medoxomil IPRS: 1H NMR (DMSO-d_6, 500 MHZ): δ-0.92 (t, 3H), 1.57 (s, 6H), 1.65 (sextet, 2H), 2.13 (t, 3H), 2.65 (t, 2H), 3.39 (br, 1H), 5.11 (s, 2H), 5.26 (s, 1H), 5.47 (s, 2H), 6.92 (d, 2H), 7.09 (d, 2H), 7.66 (m, 4H). 13C NMR (DMSO-d_6, 500 MHZ): δ-9.1, 14.0, 21.0, 28.7, 30.1, 48.4, 54.5, 70.0, 116.6, 123.9, 129.6, 144.5, 157.9, 161.1.

The chemical shift assignments for Telmisartan IPRS: 1H NMR (CDCl3, 500 MHZ): δ-0.78(t, 1H), 1.17 (t, 3H), 2.01(sextet, 6H), 3.15 (t, 2H), 3.71 (s, 3H), 5.42 (s, 2H), 6.96 (s, 1H), 7.05 (s, 1H), 7.18 (d, 2H), 7.93 (sextet, 5H), 7.50 (m, 3H), 8.02 (d, 1H), 8.42 (d, 1H). 13C NMR (CDCl3, 500 MHZ): δ-14.3, 17.1, 22.6, 29.7, 30.2,31.9,34.1,49.0, 76.9, 77.1, 109.5, 111.19, 121.8, 123.5, 127.4, 128.8, 129.4, 130.4, 133.8, 134.6, 135.6, 141.8, 142.9, 143.8, 154.1, 156.6, 171.3.

The chemical shift assignment for Valsartan IPRS: 1H NMR (CH3OD, 500 MHZ): δ-0.84 (m, 3H), 1.0 (m, 3H), 2.41 (m, 3H), 0.78 (d, 1H), 0.82 (s, 1H). 0.95 (t, 1H), 1.24 (q, 1H), 1.37 (q, 1H), 1.57 (m, 2H), 4.58 (m, 1H), 4.66(m, 1H), 4.75 (m, 1H), 7.01 (m, 1H), 7.10 (d, 1H), 7.17 (d, 1H), 7.23 (d, 1H), 7.55 (q, 2H), 7.66 (m, 2H). 13C NMR (CH3OD, 500 MHZ): δ- 14.2, 19.33, 20.0, 20.5, 23.35, 28.4, 29.1, 34.4, 47.3, 50.5, 64.9, 67.8, 124.1,127.7, 128.8, 129.7, 130.3, 131.7, 132.4, 138.7, 139.5, 143.9, 156.6, 173.22, 177.0. The NMR spectra of reference substances of ARBs are attached as Fig. 3.

3.2. Related substances

In the chemical analysis conducted, no impurities were detected in Irbesartan tablet. The purities for branded tablets O1, O2, O3, O4, and O5 were measured at 99.65 %, 100 %, 99.45 %, 99.84 %, and 99.22 % respectively. The generic Olmesartan tablets displayed a purity level of 99.69 %. In the case of Losartan Potassium, all variants of branded tablets (L1, L2, L3, L4) exhibited a purity of 100 %, with L5 at 99.92 %. The generic Losartan Potassium tablets showcased an impressive purity of 99.99 %. Telmisartan branded tablets displayed purities of 99.74 %, 99.96 %, 99.85 %, and 99.94 % for T1, T2, T3, and T4 respectively, while the generic Telmisartan showed a purity of 99.99 %. Valsartan tablets maintained a purity of 100 % in its branded forms, whereas the generic Valsartan tablets had a purity of 99.74 %. The minimal purity standards as outlined in pharmacopoeias (BP/EP, IP, USP) for tablets were met, with Irbesartan at 99%, Olmesartan Medoxomil at 97.5%, and Losartan Potassium, Telmisartan, and Valsartan at 98 %.

The investigation also confirmed that both the branded and generic drugs samples adhered to the stipulated limits for related substances as per BP/EP, IP and USP. In the current study, Irbesartan tablets achieved the highest purity of 100 %, while Valsartan tablets exhibited the lowest at 99.94 % among the selected ARBs.

Table 2
Chromatographic conditions/method for Related Substances and Assay for selected samples by HPLC.

S. No.	Drugs	Column	Related Substances			Assay		
			Flow rate (ml/ min)	λmax (nm)	Injection Volume (µl)	Flow rate (ml/ min)	λmax (nm)	Injection Volume (µl)
1	Irbesartan	250X4.6 mm, C-18, 5µ	1	220	15	1	220	15
2	Losartan Potassium	250X4 mm, C-8, 5µ	1	237	20	1.5	235	10
3	Olmesartan Medoxomil	150X4.6 mm, C-18, 5µ (RS) 250X4.6 mm, C-18, 5µ (Assay)	1	215	10	1	215	20
4	Telmisartan	150X4.6 mm, C-18, 5µ	1	298	20	1.8	298	20
5	Valsartan	250X4.6 mm, C-18, 5µ	1	273	10	1	273	10

Table 3
Dissolution conditions/method of selected samples.

S. No.	Drugs	Dosage form	IP/USP Apparatus	Speed (rpm)	Medium	Volume (ml)	Sampling time (minutes)
1	Irbesartan	Tablet	II (Paddle)	50	0.1 M Hydrochloric acid	1000	20
2	Olmesartan Medoxomil	Tablet	II (Paddle)	50	0.1 M Hydrochloric acid	900	45
3	Losartan Potassium	Tablet	II (Paddle)	50	Water	900	45
4	Telmisartan	Tablet	II (Paddle)	75	Phosphate buffer, pH 7.5	900	30
5	Valsartan	Tablet	II (Paddle)	75	Phosphate buffer, pH 6.8	900	30

Table 4
Sample preparation method for Related Substances/ Chromatographic Purity by HPLC.

S. No.	Drugs	Reference Solution	Test Preparation
1	Irbesartan	75 mg Irbesartan RS dissolved in 50 ml methanol; 1 ml of this solution was further diluted to 10 ml with methanol.	40.47 mg of test was taken and diluted to 100 ml with methanol.
2	Losartan Potassium	Ref Sol. (a): 100 mg Losartan Potassium dissolved in 100 ml water solution of Losartan Potassium RS in water.Ref Sol. (b) : Dilute 1 ml of reference solution (a) to 100 ml with water	L1: 59.4 mg, L2: 87.6 mg, L3: 54.4 mg, L4:83.2 mg, LJ:71.2 mg was separately weighed and diluted with 100 ml water and filtered
3	Olmesartan Medoxomil	25 mg Olmesartan Medoxomil was dissolved in 100 ml solvent mixture; 1 ml of this solution was further diluted to 100 ml with solvent mixture	O1: 380.63 mg, O2: 454.37 mg, O3: 280 mg, O4: 807 mg, O5: 405 mg dissolved in 100 ml, OJ: 435 mg were separately weighed and dissolved in 100 ml
4	Telmisartan	50.45 mg Telmisartan reference standard was taken in 100 ml solvent mixture; 1 ml of this was further diluted to 100 ml with solvent mixture.	T1:647.2 mg, T2: 521.15 mg, T3: 424.27 mg, T4: 635.75 mg, TJ: 506.9 mg, was separately weighed and diluted with 100 ml solvent mixture and ultrasonicated and filter
5	Valsartan	Ref Sol. (a*):* 20.12 mg Valsartan reference standard dissolved in 20 ml Mobile phaseRef Sol. (b*):* 1.0 ml of reference solution (a)to 100.0 ml with the mobile phase	V1: 25.21 mg, V2: 25.14 mg, V3: 25.05 mg, V4: 25.11 mg, VJ: 25.08 mg were separately weighed and dissolved in 25 ml mobile phase and filtered.

Table 5
Sample preparation method for Assay by HPLC.

S. No.	Drug/sample name	Reference Solution	Test Solution
1	Irbesartan	15.34 mg of Irbesartan reference standard was dissolved in 100 ml with methanol	40.47 mg of test was taken and diluted to 100 ml with methanol.
2	Losartan Potassium	25 mg Losartan Potassium Reference Standard dissolved in 20 ml mobile phase; 10 ml of this solution was diluted with 100 ml mobile phase	10 tablets of L1, L2, L3, L4 and LJ was dissolved in 200 ml mobile phase; 1 ml of this solution was further diluted with 20 ml of mobile phase.
3	Olmesartan Medoxomil	40 mg Olmesartan Medoxomil dissolved in 100 ml solvent mixture; 1 ml of this was further diluted with 10 ml solvent mixture	O1: 304 mg, O2:360 mg, O3:224 mg, O4:648 mg, O5:322.8 mg, OJ:352 mg was separately weighed, taken in 100 ml; 2 ml of this diluted with 20 ml solvent mixture for each
4	Telmisartan	40 mg Telmisartan reference standard was dissolved in 100 ml Solvent mixture; 1 ml of this was further diluted with 10 ml solvent mixture	T1:258.8 mg, T2:205.4 mg, T3: 179.8 mg, T4:251.2 mg, TJ:191.2 mg was separately dissolved in 100 ml solvent mixture; 5 ml of this solution-50 ml solvent mixture
5	Valsartan	50 mg Valsartan reference standard was dissolved in 100 ml mobile phase; 1 ml of this dissolved in 10 ml mobile phase	V1:80.62 mg, V2: 51.56 mg, V3:48.06 mg, V4:56.68 mg, VJ:85.62 mg was separately weighed, taken in 100 ml with mobile phase; 5 ml of this solution was diluted to 50 ml with mobile phase

3.3. Assay

The percentage of the specified label claim for Irbesartan tablets was determined to be 95.53 %, while for branded Olmesartan Medoxomil tablets, the values were O1: 97.81 %, O2: 102.41 %, O3: 99.35 %, O4: 100.5 %. The generic Olmesartan tablets displayed a label claim of 99.8 %. In the case of branded Losartan Potassium tablets, the label claim percentages were L1: 99.67 %, L2: 102.25 %, L3: 96.02 %, L4: 102.51 %, and L5: 100.27 %. The generic Losartan tablets exhibited a label claim of 102.71 %. Moving on to branded Telmisartan tablets, the label claims stood at T1: 95.15 %, T2: 96.09 %, T3: 112.75 %, and T4: 105.79 %, while the generic Telmisartan tablets demonstrated a content of 106.23 %. For Valsartan, the label claims were branded tablets V1: 100.9 %, V2: 100.79 %, V3: 98.15 %, and V4: 99.1 %. The generic version of Valsartan tablets had a label claim of 97.29 %. Notably, the highest label claim was observed in the generic version of Telmisartan tablets while the lowest was recorded for Irbesartan tablets.

The assay limits for all these selected ARBs as per different global pharmacopoeias (IP, BP/EP and USP) are presented in the Table 6.

Table 6
Limits of Assay and Dissolution as per different Global Pharmacopoeias for selected samples.

S. No.	Name of sample	Assay %			% Dissolution (NLT)		
		IP	BP/EP	USP	IP	BP/ EP	USP
1	Irbesartan	90–110	95–105	90–110	75	75	80
2	Losartan Potassium	90–110	95–105	95–105	75	80	75
3	Olmesartan Medoxomil	90–110	95–105	90–110	70	70	75
4	Telmisartan	90–110	95–105	90–110	75	70	75
5	Valsartan	90–110	95–105	95–105	70	80	80

3.4. Dissolution

The drug release percentages were as follows: Irbesartan tablets exhibited a release of 99.54 %, while for Olmesartan Medoxomil, the values for branded tablets were O1: 89.37 %, O2: 98.55 %, O3: 95.66 %, O4: 97.3 %, and O5: 97.68 %. The generic Olmesartan Medoxomil tablets displayed a drug release percentage of 97.2 %. Concerning

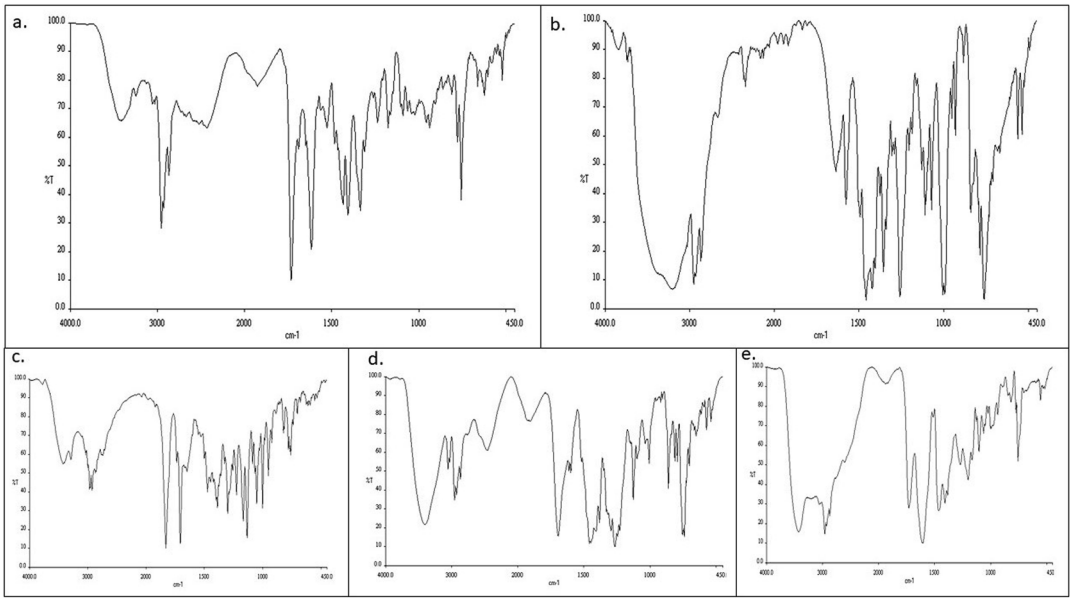

Fig. 2. IR spectra of reference ARBs (a. Irbesartan b. Losartan Potassium c. Olmesartan Medoxomil d. Telmisartan e. Valsartan).

Table 7
Functional group assignments of reference ARBs.

Drugs	Group Frequency (wave number cm^{-1})	Assignment
Irbesartan	1617.44	C = 0 Bending
	1733.07	C = 0 Stretching
	2959.43	C–H stretching of aliphatic ring
Losartan Potassium	1637.85	C = 0 Stretching
	1578.07	N–H bending
	2955.94	C–H stretching of aliphatic ring
Olmesartan Medoxomil	1589.30	N–H bending of pyrrolidine ring
	1707.59	C = 0 Stretching
	3166.03	C–H stretching vibration of aromatic ring
Telmisartan	1696.70	C = 0 Stretching
	1792.55	CHO bending
	1267.42	C–H bending
Valsartan	1680.45	C = 0 Bending
	1731.90	C = 0 Stretching
	2962.62	C–H stretching of aliphatic ring

Losartan Potassium, the release percentages for branded tablets were L1: 99.66 %, L2: 99.37 %, L3: 99.57 %, L4: 99.19 %, and L5: 99.25 %, with the generic version at 98.99 %. For Telmisartan, the values for branded tablets were T1: 99.04 %, T2: 103.95 %, T3: 101.9 %, T4: 102.3 %, and the generic Telmisartan demonstrated a drug release of 101.06 %. Valsartan's drug release percentages for different branded tablets were V1: 97.65 %, V2: 97.23 %, V3: 96.98 %, and V4: 95.25 %, with the generic version at 99.36 %. The highest drug release percentage was recorded for Telmisartan tablets at 101.65 %, while the lowest was observed for Olmesartan medoxomil tablets at 96.52 % among the selected ARBs samples.

The dissolution limits for selected ARBs as per different global pharmacopoeias (IP, BP/EP and USP) are presented in the Table 6.

3.5. Cost analysis

The cost analysis was performed by the authors wherein, the expensive medications stand as the primary impediment, serving as a significant roadblock to access vital treatments on a global scale, particularly in regions with limited economic resources. The adoption of generic pharmaceuticals emerges as a pivotal solution, offering immense benefits to patients and facilitating broader medication utilization across the world. A substantial disparity exists between the price points of generic medications and their branded alternatives. Generic drugs typically present a cost reduction ranging from 50 % to 90 % in comparison to their branded counterparts, making them a more affordable and accessible option for a wide-ranging population (Patterson JH, 2003).

In our study's findings, the average yearly expense bear by a single patient for branded Irbesartan tablets was approximately 137.376 USD. The expense for branded Losartan Potassium Tablets stood at 67.57 USD with the generic Losartan Potassium at 10.5 USD. Comparatively, the branded Olmesartan Medoxomil tablets incurred an average annual cost of around 120.79 USD while its generic alternative amounted to only about 14.88 USD. Regarding Telmisartan, the branded version's annual cost hovered around 96.07 USD, while its generic counterpart was priced at approximately 10.5 USD. The branded variant of Valsartan tablets, it amounted to about 194.32 USD conversely, the generic form of Valsartan carried a much lower cost, approximately 31.51 USD. Additionally, the analysis identified Valsartan as the most expensive among the selected samples, while Losartan emerged as the most economical choice in this cohort. The percentage cost variation analysis in between the branded tablets and the generics is represented in Fig. 4.

The investigation involved a comparative analysis of branded and generic drugs. Utilizing a *t-test*, the study determined that there are no discernible variations in terms of purity, label claim, and dissolution between the branded and generic ARBs. Nevertheless, a notable contrast emerged when considering the cost aspect, where a significant difference was observed between the expenses of branded ARBs and those obtained from generics ($p = 0.03011$). The specific statistical data is represented in Table 8, while a visual representation of the comparison is depicted in Fig. 5.

4. Discussion

Hypertension, a persistent medical condition, necessitates lifelong medication for affected individuals. As a result, the effective management of hypertension can impose significant financial strain on patients, potentially leading to dire consequences if the quality of the prescribed

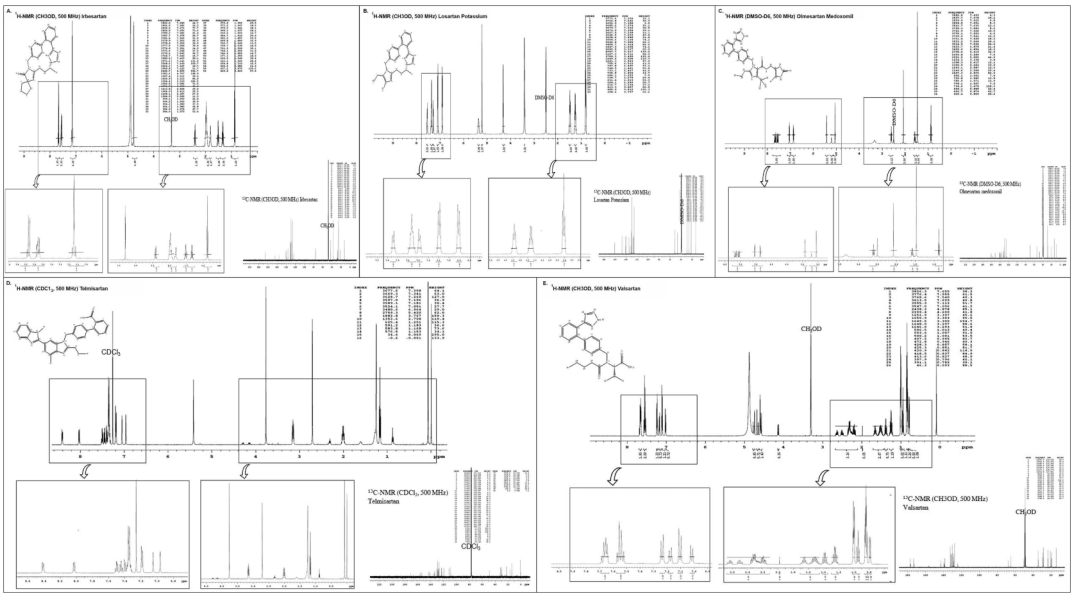

Fig. 3. ^{1}H and ^{13}C NMR spectra of reference ARBs (A. Irbesartan B. Losartan Potassium C. Olmesartan Medoxomil D. Telmisartan E. Valsartan).

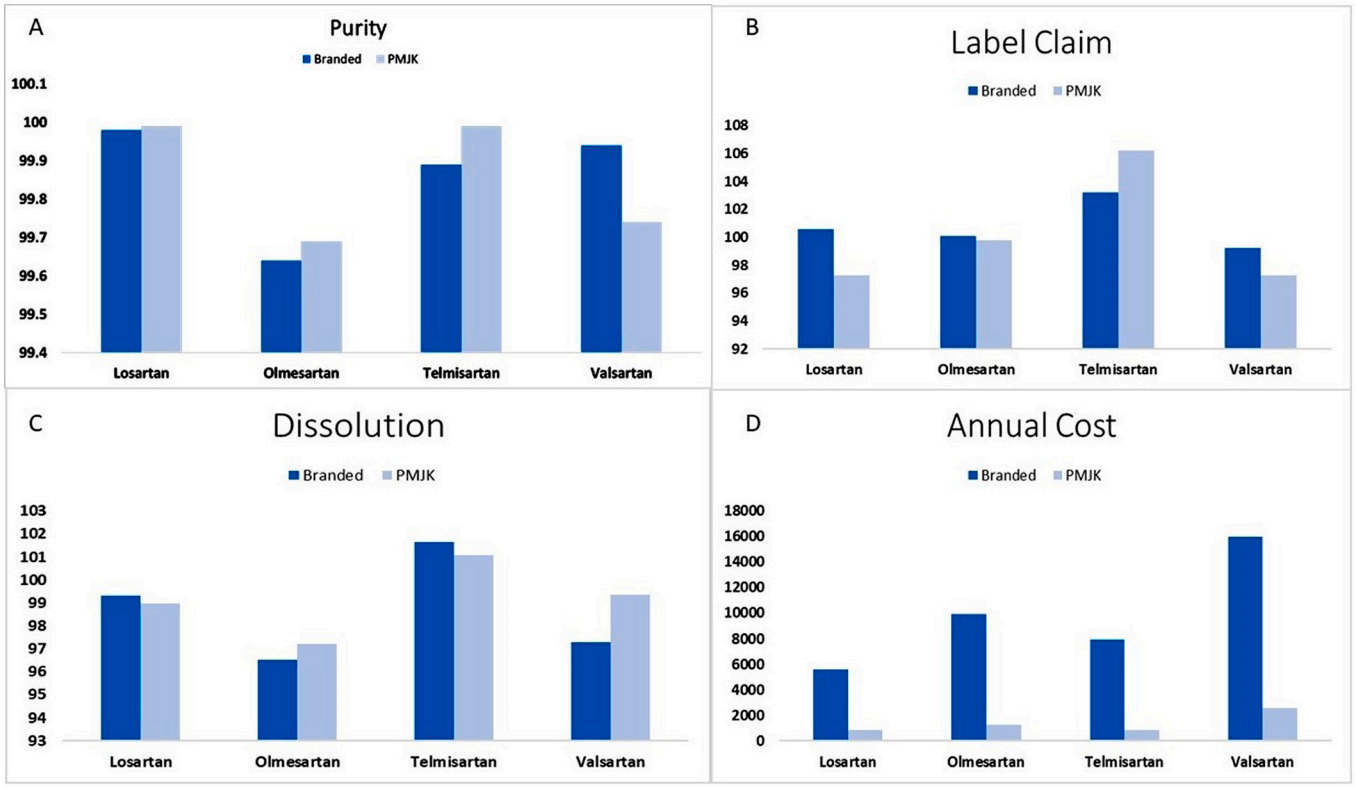

Fig. 4. Comparison of Branded ARBs and ARBs collected from PMJK (generics) [A. Purity B. label claim C. Dissolution D. Cost].

medications is compromised (Al-Makki et al., 2022). Maintaining the quality of medications consistently poses a challenge for all involved stakeholders, including drug regulatory authorities, manufacturers, and patients on a global scale (Pharmaceuticals & Medical Devices Bureau of India, 2023, Rahman MS et al., 2022; Kingori P et al., 2019; Newton PN et al.,2010). Manufacturers diligently strive to adhere to the standards set by regulatory authorities, aiming to ensure the optimal quality of their pharmaceutical products. However, the possibility of a drug product not meeting the required quality standard exists. Therefore, it becomes essential to conduct frequent and independent testing of drug products as a robust approach to ensuring their quality. With this principle in mind, the current study was conceived, involving the collection of samples from the class of drugs known as ARBs, which plays a pivotal role in managing hypertension. The gathered samples originated from reputable companies, supplemented by additional generic samples in counter to each brand. This comprehensive approach was adopted to ensure the quality of the generic counterparts in comparison to their branded counterparts. A prevailing perception suggests that branded medications tend to offer superior effectiveness and safety compared to their generic equivalents (Kovacs S et al., 2014).

Table 8
Statistical evaluation of samples.

S. No.	Particulars	Purity	Label claim	Dissolution	Cost
1	t	0.090366	0.27237	0.32611	3.7254
2	df	5.9872	3.9545	5.3246	3.2029
3	p value	0.9309	0.799	0.7568	0.03011
4	95 % CI	(-0.2609181, 0.2809181)	(-5.728764, 6.968764)	(-3.976783, 3.066783)	(1484.952, 15433.248)
5	Mean of branded ARBs	99.8625	100.7725	98.6975	9845
6	Mean of generics ARBs	99.8525	100.1525	99.1525	1386

A systematic review has revealed that both branded medications and their generic counterparts employed in the treatment of cardiovascular diseases exhibited nearly comparable clinical outcomes. Furthermore, the study concluded that there is no substantiated evidence of branded medicines being superior to their generic counterparts (Shafie AA, Hassali MA, 2008). Another study reveals that the utilization of generic medications does not indicate a compromise in either effectiveness or safety, and they exhibit comparable efficacy to branded or innovator drugs (Kesselheim AS, 2008; Manzoli L et al., 2015). However, it is also asserted that the utilization of generic drugs could potentially result in delayed treatment of an illness or even instances of therapeutic inefficacy (Gota V, Patial P, 2014). Therefore, it becomes essential to manage critical factors that impact the quality of generic drugs, namely purity, potency, and dissolution, in order to guarantee the highest possible quality of drug products.

This study has determined that all the samples, encompassing both branded and generic variations, align with the established criteria of pharmacopoeial standards for related substances, assay, and dissolution. Notably, the quality specifications encompassing related substances (indicative of purity), assay (reflecting label claim), and dissolution (representing drug release) consistently fell within the accepted ranges for both branded medications and their generic equivalents. Through this thorough analysis, it can confidently be affirmed that the collected samples from the market demonstrated high quality and suitability for use. Furthermore, the generic variants of these branded medications exhibited equivalent quality, ensuring equal potential benefits for patients when utilized. Alongside this parity in quality, these generic drugs present a significant advantage by being readily available at considerably lower costs compared to their branded counterparts.

The findings of this study indicate a substantial percentage cost variation between the most expensive collected brand and its corresponding generic version: Valsartan showed a percentage variation of 819 %, Telmisartan 1450 %, Losartan 1008 %, and Olmesartan showed a difference of 1065 %. Similarly, the percentage cost variation between the least expensive collected brand and its generic version was observed as follows: Valsartan 191 %, Telmisartan 383 %, Losartan Potassium 208 %, and Olmesartan Medoxomil with a variation of 282 % (Kumar GR, 2017). A substantial number of patients in low- and middle-income countries bear the expenses of medications directly, exemplified by India where over eighty percent of healthcare costs are covered by patients themselves (Kashyap et al., 2019). In certain developing nations, the use of generic drugs is not widespread, and even pharmacists lack the authority to substitute a branded drug with a generic alternative. This situation places a financial burden on patients. In contrast, countries like the USA permit such substitutions if endorsed by a physician,

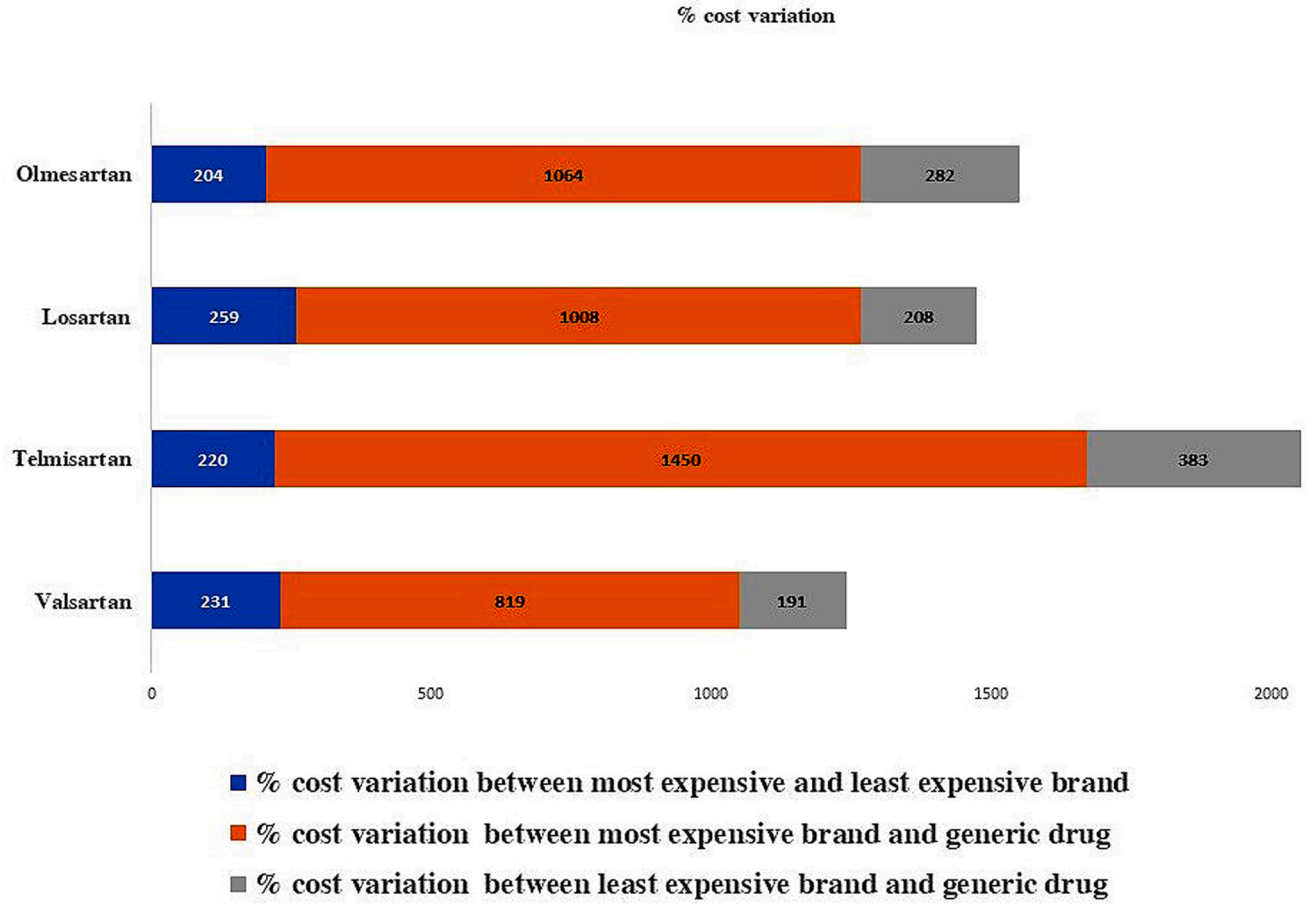

Fig. 5. % cost variation analysis between branded and generics (PMJK) ARBs.

and the practice of generic substitution has garnered strong support from health authorities in developed countries (Andrew C et al., 2004; DC S, 1999; Gupta R et al., 2019). The present study also has a few limitations. The main limitation of this study is the limited diversity for the gathered samples, as they exclusively represent a specific region. The findings could potentially yield more nuanced and valuable insights if samples from various regions had been included.

Presently, there is a global increase in the adoption of generic drugs, with governments worldwide promoting their use within their nations. India, for instance, has initiated the PMJK program as a means to facilitate easy access to generic medicines for its citizens. These stores offer medications at a lower cost while emphasizing high quality and safety (Meredith, P.A, 1996). As of March 31st, 2023, a total of 9303 PMJKs are operational across the country. These PMJKs have reportedly contributed to savings exceeding Rs. 20,000 crores for the nation's general population (Aivalli PK et al., 2018). A similar model could be implemented in other countries to enhance access to affordable medications for patients on a broader scale. Regular and independent quality checks will further reinforce the credibility of these drugs in the market.

5. Conclusion

This study confirms that the gathered samples (tablets) of various ARBs brands, namely Irbesartan, Valsartan, Losartan Potassium, Olmesartan Medoxomil, and Telmisartan, as well as their corresponding generic versions, align with the acceptable criteria for related substances, assay, and dissolution, in accordance with the current editions of BP/EP, IP and USP. Moreover, the study underscores commendable regulatory compliance among pharmaceutical stakeholders, as all samples (branded and generics) underwent independent collection and testing, yielding results that align with the expectations set forth by regulatory authority guidelines and pharmacopoeial standards.

The findings of this study hold the potential to bolster public confidence in generic drugs, given that these medications are more cost-effective and demonstrated comparable quality to their branded counterparts. Consequently, embracing generic drugs for disease treatment or management presents a financially prudent approach, particularly benefiting a substantial portion of the population, particularly in low- and middle-income countries, where many individuals still struggle to afford expensive branded medicines.

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CRediT authorship contribution statement

Arvind Kumar Sharma: Conceptualization, Formal analysis, Writing – original draft. **Shruti Rastogi:** Formal analysis. **Faraat Ali:** Writing – original draft. **Anuj Prakash Yadav:** Supervision, Formal analysis. **Ramesh K. Goyal:** Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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