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Comparative *In vitro* Evaluation of some Commercial Brands of Ramipril Tablets Marketed in India

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ABSTRACT

The availability of several brands of Ramipril tablets in Indian pharmacies now poses a generic replacement concern for doctors. The goal of this study was to evaluate and compare different brands of Ramipril manufactured by various Indian pharmaceutical businesses under various trade names in order to reduce health risks and ensure the safety of local residents. General quality assessments of these tablets, such as diameter, thickness, hardness, weight variation, friability, disintegration, and dissolution tests, were also carried out according to recognised protocols, with test results falling within the acceptable range. Active components were measured using an approved UV spectrophotometric technique. This type of research is useful for determining the idealness of commercial products.

Key words: Ramipril, In-vitro evaluation, dissolution study, disintegration test

1. INTRODUCTION

India, a developing country in Southeast Asia, is the world's second most populous country, with 1.4 billion people, and the pharmaceutical industry is one of the country's most developed sectors. This sector meets 97 percent of the local market's overall medicinal needs, therefore post-market drug monitoring is critical for determining the quality, therapeutic efficacy, and safety of medicines. As a result, data gathered from such monitoring could be useful for product development and regulatory upgrades. Physical properties of commercially available ramipril tablets were investigated in this study.[1]

Hypertension is one of the most common chronic diseases today, and while it cannot be cured, it may be managed. For the pharmacological management or control of hypertension, several medication therapies, single doses or combinations of diuretics, betablockers, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, and angiotensin II receptor (AT1) antagonist (ARA) are used. Ramipril is an anti-hypertensive medicine that works by inhibiting the actions of the angiotensin converting enzyme (ACE), which reduces the formation of angiotensin II and the breakdown of bradykinin. As blood is pumped through dilated arterioles, a decrease in the enzyme angiotensin II causes relaxation of arteriole smooth muscle, lowering total peripheral resistance and lowering blood pressure (BP). Carboxylesterase converts the precursor or prodrug ramipril to the active metabolite ramiprilat. The kidneys are responsible for the majority of its excretion. It has a half-life of 3-16 hours, which is lengthened by heart, liver, and renal failure.

The drug is used to treat high blood pressure alone or in conjunction with other drugs. The medicine is also used to lower the risk of stroke and heart attack in people who are at high risk for these disorders, as well as to increase survival in those who have heart failure after a heart attack. It is taken once a day at a dose of 80 mg or 160 mg.

In a process catalysed by angiotensin converting enzyme, angiotensin II is produced from angiotensin I. Angiotensin II is the major pressor of the rennin-angiotensin system, affecting vasoconstriction, aldosterone synthesis and release, cardiac stimulation, and sodium reabsorption in the kidneys. Ramipril reduces angiotensin II's vasoconstriction and aldosterone secretion actions by preventing angiotensin II's binding to the angiotensin II type 1(AT1) receptor, causing blood vessels to relax and widen, lowering blood pressure and improving blood flow. Only 25% of Ramipril is absorbed after oral dosing. Ramipril's limited bioavailability is due to its weak water solubility. Ramipril is easily soluble in alkaline solution as the equivalent salt, despite its lower water solubility.[2-11] Ramipril is a Class II drug with poor solubility and high permeability, according to the Bio-pharmaceutics Classification System [BCS].

Because of their tremendous importance in forecasting bioavailability and product quality, India is a market that places a strong emphasis on disintegration and dissolution studies. Other general quality criteria of these tablets were assessed using known protocols, including diameter, thickness, hardness, friability, weight fluctuation, disintegration time, UV spectrophotometric method. [12-15]

2. MATERIALS AND METHODS

2.1 Materials

2.1.1 Ramipril Drug

Standard was a generous donation from Popular Pharmaceuticals Ltd. in India.

2.1.2 Dosage method

Three different brands of ramipril tablets (5 mg) were obtained from a local drug store in Salem. The samples' manufacturing licence numbers, batch numbers, production, and expiry dates were all double-checked. They were coded A, B, and C at random and stored properly.

2.1.3 Solvents and reagents

The potassium dichromate and hydrochloric acid employed in this study were analytical-reagent grade, and the study also included distilled water and phosphate buffer.

2.1.4 Instruments

Frability test instrument, single pan balance, UV/visible spectrophotometer, Ultarsonic bath sonicator venire caliperse, tablet hardness tester, tablet disintegration test machine, tablet dissolving tester (thickness tester).

2.2 Methodologies

2.2.1 Diameter and thickness measurement tests

The diameter and thickness of 20 tablets from four different brands were measured with an electronic digital calliper (MEGA Digital Clipper) to estimate the average diameter and thickness.

2.2.2 Test for hardness

Tablets must have a certain level of strength, hardness, and resistance to friability, as well as the ability to endure mechanical shocks during packaging and shipment. Pfizer and Monsanto use a tester to determine the hardness of the pills. To conduct this test, ten tablets from each brand were randomly picked and placed between two plungers, with force applied to the plungers and the pressure at which each tablet was crushed recorded. As a result, tablet crushing strength is frequently referred to as hardness.

2.2.3 Friability test

Pre-weighed tablets (20) were placed in Roche friabilator and were subjected to 100 revolutions at 25rpm for 4 minutes at a height of 6 inches. The tablets were de-dusted and reweighed.

$$\% F = \frac{\text{initial } weight - final\ weight}{\text{initial weight}} \times 100$$

2.2.4 Weight variation

20 tablets were selected randomly from a batch and were individually weighed and then the average weight was calculated. The individual weight was then compared with the average value to find the deviation in weight.

$$\text{Average weight of tablet} = \frac{\text{total weight of 20 tablets}}{20}$$

$$\text{Deviation (\%)} = \frac{\text{weight of each tablet} - \text{average weight of tablet}}{\text{average weight of tablet}} \times 100$$

2.2.5 Disintegration test in vitro

The Tablet Disintegration Tester (Veego, India) vessel was first filled with 900 ml distilled water and the temperature was set to 37°2°C. The assembly should be raised and lowered 30 times per minute in the 0.1 N HCl maintained at 37°2°C. Six tablets from each brand were taken and placed in the disintegration chamber's

basket, along with the disc. The machine was started, and the disintegration time (DT) was measured and recorded as the time when no particle remained on the system's basket.

2.2.6 Dissolution studies in vitro

The dissolution research of four brands of Ramipril was conducted using a dissolution tester (Electrolab, India) with a USP apparatus type II (paddle) spinning at 75 RPM. The dissolution medium consisted of 900 cc of 0.1 N HCl and phosphate buffer (pH 5.8) kept at 370.5°C. 5 ml of dissolution sample was pulled out at 0, 10, 20, 30, 40, 50, and 60 minutes in all tests and replaced with an equal volume of fresh medium at every 5-minute interval. The samples were filtered before being measured at 210 nm with a UV-VIS spectrophotometer. A standard curve of pure API was used to determine sample concentration, and sample concentration was determined using the Y= mX + C equation.

2.2.7 Assay

Each brand's tablets were weighed and then coarsely pulverised. The powder equivalent to 5 mg of Ramipril was dissolved in phosphate buffer (pH 5.8) and sonicated to dissolve the powdered material in flasks. The solution was then filtered, and the filtrate was diluted appropriately. A UV-VIS spectrophotometer was used to measure absorbance values at the maximum wavelength (max) of these concentrations. By scanning samples from 200 to 400 nm, the maximum wavelength (max) was discovered to be 206 nm.[16-17]

3. RESULTS AND DISCUSSION

3.1 Thickness Measurement Test

A venire caliperse was used to measure the thickness of 20 tablets randomly selected from each formulation trial batch. The results were shown in table no. 1

Table No 1

BRAND NAME	AVERAGE THICKNESS(mm)
Ramistar	3.97±0.03
Ramilace	3.31±0.23
Cardace	3.60±0.61
Ziram	3.38±0.12

3.2 Hardness Test

Handling in the manufacturing, wrapping, and transportation processes requires a suitable hardness. Pfizer and Monsanto use a tester to determine the hardness of the pills. Tablets must be sufficiently hard to develop into high-quality items. The results were shown in table no2

Table no 2

BRAND NAME	AVERAGE HARDNESS	STANDARD DEVIATION
Ramistar	2	0.0083666
Ramilace	4	0.0130384
Cardace	3	0.0089442
Ziram	4	0.0140364

3.4 Weight Fluctuation Test

The average weight was computed after 20 tablets were randomly picked from a batch and individually weighed. The variance in weight was calculated by comparing the individual weight to the average value. The results were shown in table no. 3

Table No 3

BRAND NAME	AVERAGE WEIGHT/MG
Ramistar	502.6±0.13
Ramilace	497.1±0.16
Cardace	505.7±0.17
Ziram	503.0±0.35

3.5 Disintegration Test

The disintegration time was calculated using a Tablet Disintegration Tester with 900ml of 0.1N HCl as the disintegrating medium and phosphate buffer at 37°C 2°C. The results were shown in table no 4.

Table No 4

Brand Name	Disintegration time/minutes
Ramistar	5 min 20 sec
Ramilace	30 sec
Cardace	3 min 40 sec
Ziram	30 sec

3.6 Conduct a Dissolution Test

The capsules were filled with the pure medication, produced PM, and SD, and the in vitro dissolving test was performed. Throughout the in vitro study, the disso apparatus (as per USP XXIII specifications) and application of a paddle stirrer were used to maintain a PH of 1.2 at a temperature of 37 0.5oC (using 0.1 N Hydrochloric acid). Sink conditions were maintained while a sample of 5 ml of dissolution media was taken every 5 minutes till 45 minutes. Filters with a pore size of 0.45 m were used to filter these aliquots. The absorbance of these filtered samples at 258nm after suitable dilution with 0.1N HCl was measured to determine drug release by individual formulation. The amount of Ramipril released (percentage) was calculated, and a figure 1 was shown against time. The results were shown in table no. 5.

Table No 5

Time (min)	Cumulative %drug release			
	RA	RB	RC	RD
0	0	0		
10	0.630	0.611	0.612	0.633
20	0.608	0.569	0.601	0.591
30	0.618	0.569	0.584	0.596
40	0.560	0.519	0.535	0.544
50	0.527	0.532	0.549	0.539
60	0.517	0.514	0.491	0.572

3.7 Assay

Analysis of drug potency in tablets confirms the existence of the drug in dosage form, as well as its stability. Table 6 shows that the active content of all the brands ranged from 100.4 percent (brand-C) to 99.6 percent (brand-D) (brand-B). The results show that the content of active moiety in two brands, A and D, was 99.2 percent and 98.8 percent, respectively, and was within the USP specification of 100-10 percent, with the exception of one brand (D), which was out of specification.

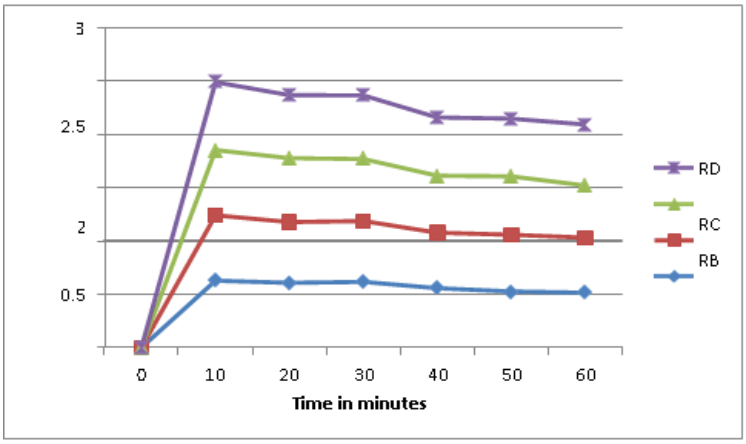

Figure 1

Table No 6

S. No	Drug Name (Brand)	Concen -tration (µg/ml)	Absor- bance 206nm	Label Claim (mg)	Amout Deter mined	% assay
1	Ramistar	8 µg/ml	0.4060	2.5mg	2.48	99.2 %
2	Ramilace	8 µg/ml	0.3740	2.5mg	2.49	99.6 %
3	Cardace	8 µg/ml	0.4074	2.5mg	2.51	100.4 %
4	Ziram	8 µg/ml	0.4128	2.5mg	2.47	98.8 %

3.8 UV Spectrophotometric Absorbance

3.8.1 ramistar absorbance spectrum and calibration curve:

The stock solution for testing the absorbance at max 206 nm is prepared with 0.1 N hydrochloric acid as the medium. The standard curve was generated using concentrations in multiples of 2 g/ml (Range 2, 4, 6, 8,10 g/ml) and UV- Spectrophotometer absorbance. The results were shown in table no 7. whereas figure 2 shows the spectrum and calibration graph.

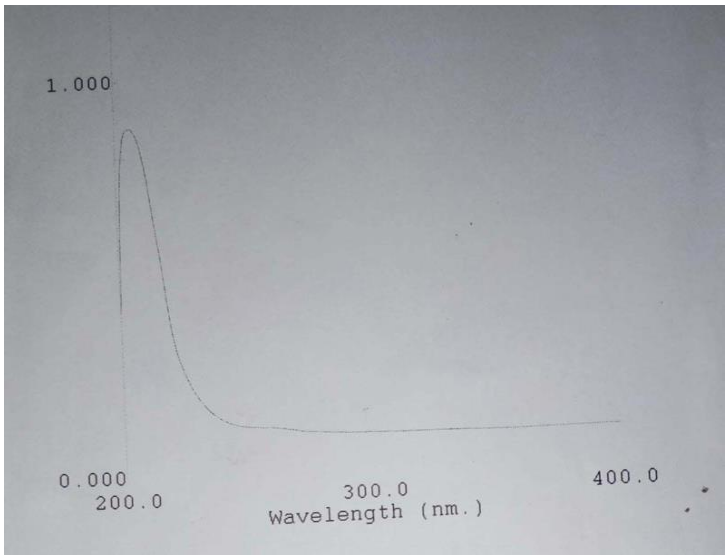

Figure No 2. (a) UV-Spectrum for Ramistar

Table No 7: Calibration data

S.No	Conc. (µg/ml)	Absorbance
1	2	0.374
2	4	0.385
3	6	0.390
4	8	0.406
5	10	0.417
6	**Slope**	0.0107x + 0.3623
7	**Corelation Coefficet**	0.9792

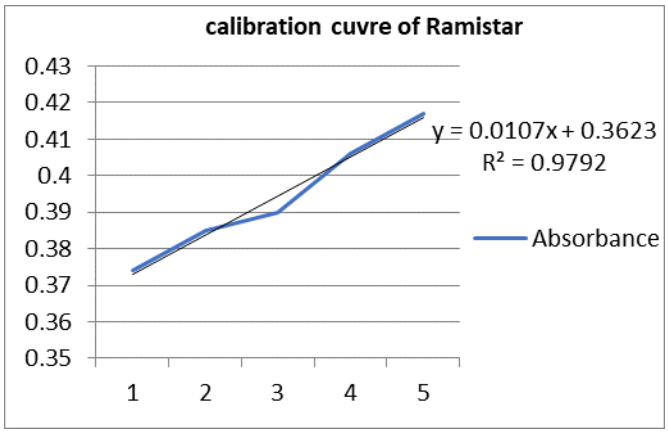

Figure No 2 : (b) Calibration Curve of Ramistar

3.8.2 Ramilace Absorbance Spectrum and Calibration Curve

The stock solution for testing the absorbance at max 206 nm is prepared with 0.1 N hydrochloric acid as the medium. The standard curve was generated using concentrations in multiples of 2 g/ml (Range 2, 4, 6, 8, 10 g/ml) and UV- Spectrophotometer absorbance. The results were shown in table no 8. Whereas Figure 3 shows the spectrum and calibration graph.

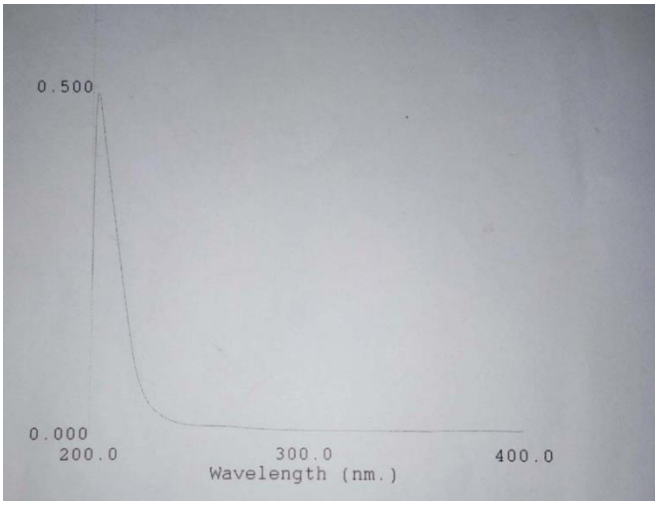

Figure No: 3 (a) UV-Spectrum for Ramilace

Table No 8: Calibration Data

S.No	Conc. (µg/ml)	Absorbance
1	2	0.345
2	4	0.355
3	6	0.364
4	8	0.373
5	10	0.382
6	**Slope**	0.0046x + 0.3362
7	**Co relation Co efficient**	0.9995

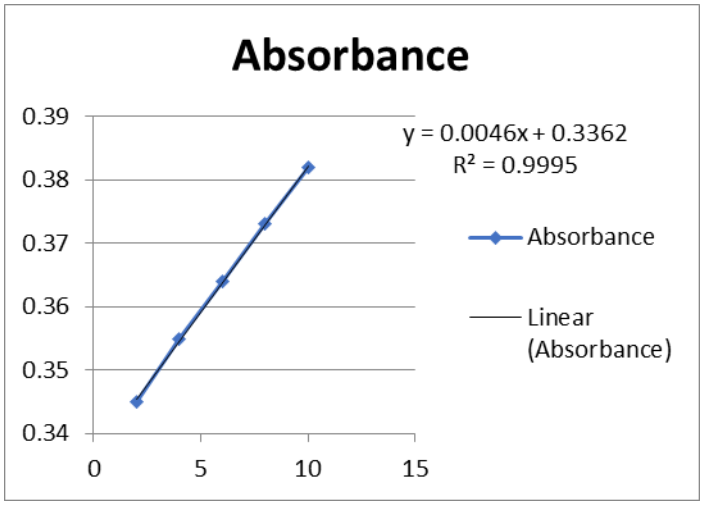

Figure No:3 (b) Calibration Curve of Ramilace

3.8.3 Cardace absorbance spectrum and calibration curve

The stock solution for testing the absorbance at max 206 nm is prepared with 0.1 N hydrochloric acid as the medium. The standard curve was generated using concentrations in multiples of 2 g/ml (Range 2, 4,6,8,10 g/ml) and UV- Spectrophotometer absorbance. The results were shown in table no 9 whereas Figure 4 shows the spectrum and calibration graph.

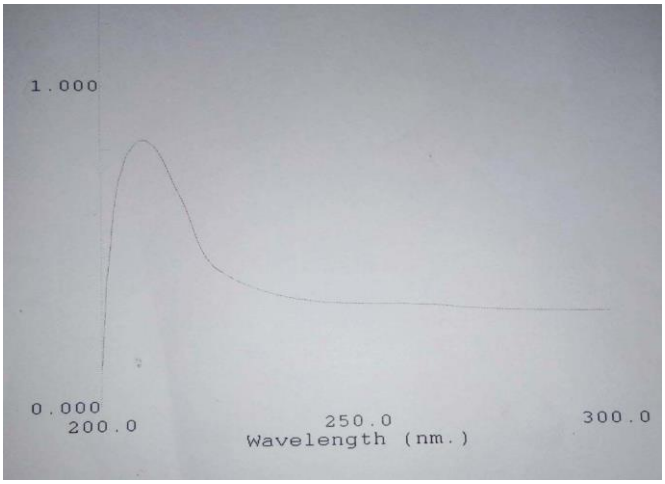

Figure No :4(a) UV-Spectrum for Cardace

3.8.4 ziram's absorbance spectrum and calibration curve

The stock solution for testing the absorbance at max 206 nm is prepared with 0.1 N hydrochloric acid as the medium. The standard curve was generated using concentrations in multiples of 2 g/ml (Range 2, 4,6,8,10 g/ml) and UV- Spectrophotometer absorbance. The results were shown in table no10. whereas Figure 5 shows the spectrum and calibration graph.

Table No 9: calibration data

S.No	Conc. (µg/ml)	Absorbance
1	2	0.3722
2	4	0.3858
3	6	0.399
4	8	0.412
5	10	0.4552
6	**Slope**	0.0096x + 0.3472
7	**Co relation Co efficient**	0.9123

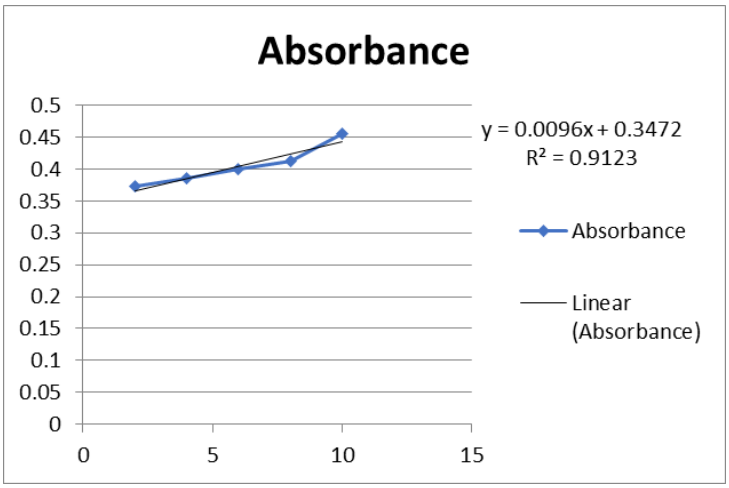

Figure No : 4 (b) Calibration curve of Cardace

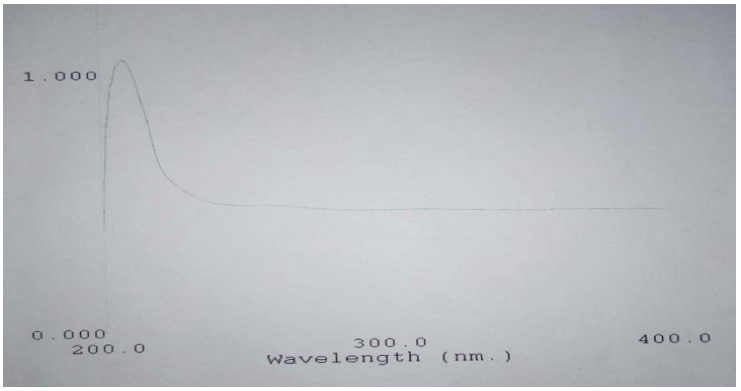

Figure No: 5 (a) UV-Spectrum for Ziram

Table No 10: Calibration Data

S.NO	Conc. (µg/ml)	Absorbance
1	2	0.3784
2	4	0.3882
3	6	0.3983
4	8	0.4085
5	10	0.4183
6	**Slope**	0.005x + 0.3683
7	**Corelation Coefficient**	0.9999

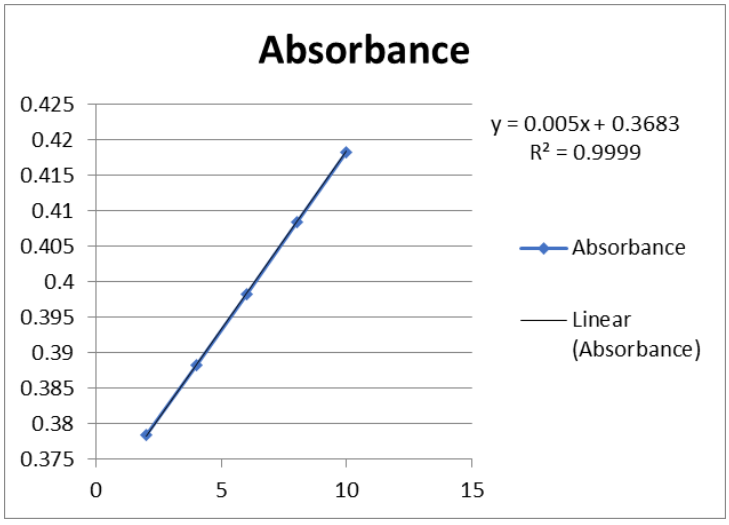

Figure No :5 (b) Calibration Curve of Ziram

4. CONCLUSION

The Ramipril tablets utilised in this study were all within their expiration dates. All tablets had a three-year shelf life from the date of manufacture on the label. To assess quality parameters, all tablets were put through a series of tests. The physical looks of all pills from different brands show no irregularities. The correct quality status of ramipril pills was determined. The marketed sample of Ramipril tablets was analysed for this purpose using accepted procedures and apparatus. All of the study's parameters were found to be within the Pharmacopoeial limit. As a result of these findings, we can conclude that Ramipril products sold in Salem meet the quality criteria required for therapeutic efficacy. All of the brands have demonstrated that their products meet the specified specifications in terms of quality. According to the findings of this investigation, samples produced by lower-ranked companies are also of high quality and meet official requirements. This research will assist the Drug Control Authority in determining the quality of Ramipril tablets sold in Salem.

5. ACKNOWLEDGMENT

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