SAI PRIMUS LIFE BIOTECH PVT LTD	SAI PRIMUS LIFE BIOTECH PVT LTD Factory: R.S. No. 4/3, Plot No.33, Kurumbapet Industrial Estate, Villianur Commune, Puducherry-605009	Page 1 of 7 No.: FPS:R09
	FINISHED PRODUCT SPECIFICATION	Revision No: 02
Title:	RAMITHIAZIDE 5 mg/ 12.5 mg TABLETS (Ramipril and Hydrochlorothiazide Tablets)	Review Period: 3 Years
	Product Code:R09	Effective Date: 31/01/2024

01	**GENERAL**	**Pharmacopoeial Reference**	**IHS**
02	**Composition**	**Label Claim**	
	Each uncoated tablet contains:		
	Ramipril BP	5 mg	
	Hydrochlorothiazide BP	12.5 mg	
03	**Shelf life**	36 months	
04	**Quantity of sample taken for analysis**	Lubricated granules: 100 gm Bulk sample : 120'S (For complete analysis) Finished product: 12 X 10'S (For Physical parameter & Microbiological Limit Test only)	
05	**Control sample**	7[3 X 10'S]	
06	**Storage of Finished pack**	Store in cool and dry place. Protect from light and moisture.	

	Prepared by	Checked by	Approved by
Designation	Executive-QC	Sr. Executive-QC	Manager-QC
Signature			
Date	31/01/2024	31/01/2024	31/01/2024
Department: Quality Control		Date of Issue: 31/01/2024	

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	FINISHED PRODUCT SPECIFICATION	Revision No: 02
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	Product Code:R09	Effective Date: 31/01/2024

BULK GRANULES SPECIFICATION

S.No.	TEST	LIMIT	METHOD
01	DESCRIPTION	Pink coloured granular powder.	Follow section I of Method of analysis
02	ASSAY By HPLC		Follow section XII of Method of analysis
	Each 200 mg Granules Contains:		
	Ramipril BP-5mg	Not Less than 90.0 % and Not more than 110.0 %	
	Hydrochlorothiazide BP-12.5mg	Not Less than 90.0 % and Not more than 110.0 %	

	Prepared by	Checked by	Approved by
Designation	Executive-QC	Sr. Executive-QC	Manager-QC
Signature			
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	FINISHED PRODUCT SPECIFICATION	Revision No: 02
Title:	RAMITHIAZIDE 5 mg/ 12.5 mg TABLETS (Ramipril and Hydrochlorothiazide Tablets) Product Code:R09	Review Period: 3 Years Effective Date: 31/01/2024

BULK PRODUCT SPECIFICATION

S.No.	TEST	LIMIT	METHOD
01	DESCRIPTION	Pink coloured, flat, round, beveled edged uncoated tablet with break line on one side and plain on other side.	Follow section I of Method of analysis
02	AVERAGE WEIGHT	200.0 mg ± 5.0% (Limit:190.0 mg to 210.0 mg)	Follow section III of Method of analysis
03	UNIFORMITY OF WEIGHT	Not more than 2 of the individual weights deviate from the average weight by more than ± 7.5% and none deviate by more than ± 15.0%	Follow section IV of Method of analysis
04	DIMENSIONS Diameter Thickness	 7.70 mm to 8.10 mm 2.60 mm to 3.20 mm	Follow section V of Method of analysis
05	HARDNESS	NLT 3 kg/cm^2	Follow section VI of Method of analysis
06	FRIABILITY	NMT 1.0 %	Follow section VII of Method of analysis
07	DISINTEGRATION TIME	Not more than 15 minutes	Follow section VIII of Method of analysis
08	DISSOLUTION By HPLC Ramipril BP-5mg Hydrochlorothiazide BP-12.5mg	 Not less than 75.0 % of labeled amount. Not less than 75.0 % of labeled amount.	Follow section X of Method of analysis
09	ASSAY By HPLC **Each uncoated tablet contains:** Ramipril BP-5mg Hydrochlorothiazide BP-12.5mg	 Not Less than 90.0 % and Not more than 110.0 % Not Less than 90.0 % and Not more than 110.0 %	Follow section XII of Method of analysis

	Prepared by	Checked by	Approved by
Designation	Executive-QC	Sr. Executive-QC	Manager-QC
Signature			
Date	31/01/2024	31/01/2024	31/01/2024
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Title:	RAMITHIAZIDE 5 mg/ 12.5 mg TABLETS (Ramipril and Hydrochlorothiazide Tablets) Product Code:R09	Review Period: 3 Years Effective Date: 31/01/2024

RELEASE SPECIFICATION

S.No.	TEST	LIMIT	METHOD
01	**DESCRIPTION**	Pink coloured, flat, round, beveled edged uncoated tablet with break line on one side and plain on other side.	Follow section I of Method of analysis
02	**IDENTIFICATION (By HPLC)**		Follow section II of Method of analysis
	a. Ramipril BP	The retention time of one of the major peak in the chromatogram of sample preparation corresponds to the peak due to Ramipril in standard preparation as obtained in assay.	
	b. Hydrochlorothiazide BP	The retention time of one of the major peak in the chromatogram of sample preparation corresponds to the peak due to Hydrochlorothiazide in standard preparation as obtained in assay.	
03	**AVERAGE WEIGHT**	200.0 mg ± 5.0% (Limit:190.0 mg to 210.0 mg)	Follow section III of Method of analysis
04	**UNIFORMITY OF WEIGHT**	Not more than 2 of the individual weights deviate from the average weight by more than ± 7.5% and none deviate by more than ± 15.0%	Follow section IV of Method of analysis
05	**DIMENSIONS**		Follow section V of Method of analysis
	Diameter	7.70 mm to 8.10 mm	
	Thickness	2.60 mm to 3.20 mm	
06	**HARDNESS**	NLT 3 kg/cm^2	Follow section VI of Method of analysis
07	**FRIABILITY**	NMT 1.0 %	Follow section VII of Method of analysis
08	**DISINTEGRATION TIME**	Not more than 15 minutes	Follow section VIII of Method of analysis
09	**CONTENT UNIFORMITY By HPLC**		Follow section IX of Method of analysis
	Ramipril BP-5mg	Not less than 85.0 % and Not more than 115.0 % of labeled claim.	
	Hydrochlorothiazide BP-12.5mg	Not less than 85.0 % and Not more than 115.0 % of labeled claim.	

	Prepared by	Checked by	Approved by
Designation	Executive-QC	Sr. Executive-QC	Manager-QC
Signature			
Date	31/01/2024	31/01/2024	31/01/2024
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S.No.	TEST	LIMIT	METHOD
10	**DISSOLUTION By HPLC**		Follow section X of Method of analysis
	Ramipril BP-5mg	Not less than 75.0 % of labeled amount.	
	Hydrochlorothiazide BP-12.5mg	Not less than 75.0 % of labeled amount.	
11	**RELATED SUBSTANCES By HPLC**		Follow section XI of Method of analysis
	Impurity A	Not more than 2.0%	
	Impurity D	Not more than 6.0%	
	Impurity E	Not more than 2.0%	
	Single maximum unknown impurity	Not more than 0.5%	
	Total Impurities	Not more than 6.0%	
12	**ASSAY By HPLC** **Each uncoated tablet contains:**		Follow section XII of Method of analysis
	Ramipril BP-5mg	Not Less than 90.0 % and Not more than 110.0 %	
	Hydrochlorothiazide BP-12.5mg	Not Less than 90.0 % and Not more than 110.0 %	
13	**MICROBIOLOGICAL LIMITS**		Follow section XIII of Method of analysis
	Total Aerobic Microbial count	NMT 1000 CFU/g	
	Total Yeasts and mould counts	NMT 100 CFU/g	
	E.Coli	Should be Absent	
	Salmonella	Should be Absent	
	S.aureus	Should be Absent	
	P.aeruginosa	Should be Absent	

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Designation	Executive-QC	Sr. Executive-QC	Manager-QC
Signature			
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Department: Quality Control		Date of Issue: 31/01/2024	

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SHELF LIFE SPECIFICATION

S.No.	TEST	LIMIT	METHOD
01	DESCRIPTION	Pink coloured, flat, round, beveled edged uncoated tablet with break line on one side and plain on other side.	Follow section I of Method of analysis
02	AVERAGE WEIGHT	200.0 mg ± 5.0% (Limit:190.0 mg to 210.0 mg)	Follow section III of Method of analysis
03	HARDNESS	NLT 3 kg/cm^2	Follow section VI of Method of analysis
04	DISINTEGRATION TIME	Not more than 15 minutes	Follow section VIII of Method of analysis
05	DISSOLUTION By HPLC Ramipril BP-5mg	Not less than 75.0 % of labeled amount.	Follow section X of Method of analysis
	Hydrochlorothiazide BP-12.5mg	Not less than 75.0 % of labeled amount.	
06	RELATED SUBSTANCES By HPLC		Follow section XI of Method of analysis
	Impurity A	Not more than 2.0%	
	Impurity D	Not more than 6.0%	
	Impurity E	Not more than 2.0%	
	Single maximum unknown impurity	Not more than 0.5%	
	Total Impurities	Not more than 6.0%	
07	ASSAY By HPLC		Follow section XII of Method of analysis
	Each uncoated tablet contains:		
	Ramipril BP-5 mg	Not Less than 90.0 % and Not more than 110.0 %	
	Hydrochlorothiazide BP-12.5 mg	Not Less than 90.0 % and Not more than 110.0 %	

	Prepared by	Checked by	Approved by
Designation	Executive-QC	Sr. Executive-QC	Manager-QC
Signature			
Date	31/01/2024	31/01/2024	31/01/2024
Department: Quality Control		Date of Issue: 31/01/2024	

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S.No.	TEST	LIMIT	METHOD
08	MICROBIOLOGICAL LIMITS		Follow section XIII of Method of analysis
	Total Aerobic Microbial count	NMT 1000 CFU/g	
	Total Yeasts and mould counts	NMT 100 CFU/g	
	E.Coli	Should be Absent	
	Salmonella	Should be Absent	
	S.aureus	Should be Absent	
	P.aeruginosa	Should be Absent	

HISTORY

S. No.	Revision Number	Reason for Revision
1	Revision No.: 00	New Specification No:FPS:R09
2	Revision No.: 01	Periodic Revision
3	Revision No.: 02	Incorporated Bulk Granules Specification, Bulk product Specification.

END OF DOCUMENT

	Prepared by	Checked by	Approved by
Designation	Executive-QC	Sr. Executive-QC	Manager-QC
Signature			
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Department: Quality Control		Date of Issue: 31/01/2024	

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Title:	RAMITHIAZIDE 5 mg/12.5 mg TABLETS (Ramipril and Hydrochlorothiazide Tablets)	Review Period: 3 Years
	Product Code: R09	Effective Date: 31/01/2024

METHOD OF ANALYSIS

SECTION – I

DESCRIPTION: (By Visual Inspection)

Check physical aspects – Colour, shape and nature of tablets, presence of foreign material, mottling etc.,

SECTION – II

IDENTIFICATION

a. Ramipril

The retention time of one of the major peak in the chromatogram of sample preparation corresponds to the peak due to Ramipril in standard preparation as obtained in assay.

b.Hydrochlorothiazide

The retention time of one of the major peak in the chromatogram of sample preparation corresponds to the peak due to Hydrochlorothiazide in standard preparation as obtained in assay.

SECTION – III

AVERAGE WEIGHT

Weigh 20 tablets and note down weight in g .
Determine the average weight. Report the result of average weight in mg.

$$\text{Average weight} = \frac{\text{Weight of 20 tablets in g}}{20} \times 1000 = \_\_\_\_\_ \text{ mg}$$

SECTION – IV

UNIFORMITY OF WEIGHT

Weigh individually 20 tablets taken for average weight. Calculate the percentage of highest and lowest variation of the tablets with maximum and minimum weight from the average weight of tablets by the following expression.

	Prepared by	Checked by	Approved by
Designation	Executive-QC	Sr. Executive-QC	Manager-QC
Signature	J. Keerthi	CH	for
Date	31/01/2024	31/01/2024	31/01/2024
Department: Quality Control		Date of Issue: 31/01/2024	

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Calculation:

$$\left(\frac{\text{Lowest Wt. of Tablet}}{\text{Avg. Wt of Tablet}} \right) \times 100 - 100 = - \%$$

$$\left(\frac{\text{Highest Wt. of Tablet}}{\text{Avg. Wt. of Tablet}} \right) \times 100 - 100 = + \%$$

SECTION – V

DIMENSIONS

Measure the Diameter and Thickness of 10 tablets using Digital Vernier Calipers. Record the reading in mm.

SECTION – VI

HARDNESS

Take 10 tablets randomly from sample drawn for analysis. Place one tablet diagonally in between the space provided in the hardness tester. Operate the instrument for tablet hardness tester. Note down the reading when tablet breaks. Repeat the test for remaining 9 tablets and record the values in Kg/cm^2. Express the results as the minimum and maximum values in Kg/cm^2.

SECTION – VII

FRIABILITY

Weigh accurately about 6.5 g of tablets note down the mass in grams (a).Place weighed tablets in friability test apparatus and operate the instrument as per SOP for tablet friability test apparatus, for 100 rotations. After completion of test collect the tablets from the sample collector carefully. Remove broken particles, chipped pieces (if any) by means of gentle brushing. Weigh the tablet and record the mass in grams (b).
Calculate the weight loss (c= a-b).
Calculate the percentage as follows:
Calculation

$$\frac{c \times 100}{a} = \quad \% \text{ w/w}$$

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Signature			
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SECTION – VIII

DISINTEGRATION TIME

Determine on 6 tablets using water at 37°C ± 2°C.

Place one tablet each in six tubes of the disintegration test apparatus, add a disc and suspend the assembly in water maintained at 37 ± 2°C.Operate the apparatus till all residue passes through the mesh and note down the time taken.The time taken should not be more than the limit indicated in the product specification.If the tablets adhere to the disc repeat the test omitting the disc.

SECTION – IX

ASSAY & CONTENT UNIFORMITY

Chromatographic conditions:

Column	:	Sunniest C8, 150 mm x 4.6 mm, 5 µm or equivalent)
Flow rate	:	1.0 mL/min
Column temperature	:	25°C
LC mode	:	Isocratic
Detection wavelength	:	210 nm
Injection Volume	:	10 µL
Run time	:	10 min

Preparation of Diluent:

A mixture of 55 volume of water, 45 volume of acetonitrile and 0.1 volume of triethylamine. Adjust pH 3.0 with dilute orthophosphoric acid.

Blank:

Use diluent as blank.

Preparation of buffer:

Dissolve 12.2 g of Sodium perchlorate in 1000 mL water and adjust the pH to 2.5 with dilute orthophosphoric acid. Filter through 0.45 µ membrane filter and degas.

Preparation of mobile phase:

Mix 500 ml of buffer solution and 500 ml of acetonitrile, Sonicate and degas.

Ramipril standard stock solution:

Weigh accurately and transfer 25.0 mg of Ramipril working standard into 25 ml of volumetric flask, add 10 ml of diluent, sonicate to dissolve and dilute up to the mark with diluent and mix well.

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Hydrochlorothiazide standard stock solution:
Weigh accurately and transfer 25.0 mg of Hydrochlorothiazide working standard into 25 ml of volumetric flask, add 10 ml of diluent, sonicate to dissolve and dilute up to the mark with diluent and mix well.

Preparation of Standard solution:
Dilute 2 ml of Ramipril standard stock solution and 5 ml of Hydrochlorothiazide standard stock solution to 100 ml with diluent and mix well. (Concentration: Ramipril 0.02mg/ml & Hydrochlorothiazide 0.05mg/ml)

Preparation of Sample solution: (Assay)
Weight and powder 20 tablets. Weight accurately a quantity of powder containing about 25 mg of Ramipril (about 1000 mg sample powder) in to 250 ml volumetric flask. Add about 5 ml of water to disperse, add 150 ml of diluent and sonicate for 20 min with intermittent shaking. Cool and dilute up to the mark with diluent and mix well. Filter sufficient amount of this solution through 0.45micron syringe filter. Further dilute 5 ml of filtered solution to 25 ml with diluent, mix well and inject.
(Concentration: Ramipril 0.02mg/ml & Hydrochlorothiazide 0.05mg/ml)
Note: Prepare sample solution in duplicates.

Preparation of Sample solution (CU):
Take 1 tablet into 250 ml volumetric flask. Add about 5 ml of purified water and shake gently to disperse the tablet. Add about 150 ml of diluent, sonicate for 20 minutes with intermediate shaking, cool and dilute up to the volume with diluent. Filter the sufficient amount of this solution through 0.45micron syringe filter.
Repeat the same procedure for another 9 tablets.
(Concentration: Ramipril 0.02mg/ml & Hydrochlorothiazide 0.05mg/ml)
Procedure: Equilibrate the chromatographic system with mobile phase till a stable baseline is obtained. Separately inject equal volumes (10 µl) of solutions as per Sequence of injections into the chromatograph and record the peak area responses for the major peaks and check for the System suitability requirements.

Sequence of Injections:
1) Blank
2) Standard solution 1....5
3) Blank
4) Sample solution 1
5) Sample solution 2
6) Standard solution (B)
7) CU – 1..... 5
8) Standard solution (B)
9) CU – 6.....10
10) Standard solution (B)

	Prepared by	Checked by	Approved by
Designation	Executive-QC	Sr. Executive-QC	Manager-QC
Signature	J. Lenyd		
Date	31/01/2024	31/01/2024	31/01/2024
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System suitability requirement:

1) The Resolution between the peaks corresponding to Hydrochlorothiazide and Ramipril obtained with standard solution should not be less than 2.0
2) The tailing factor for the peak of Hydrochlorothiazide and Ramipril obtained with standard solution should not more than 2.0.
3) The column efficiency for the peak of Hydrochlorothiazide and Ramipril obtained in the chromatogram of Standard solution should not less than 2000
4) The % RSD for the peak area response of Hydrochlorothiazide and Ramipril peak obtained with the replicate injections of standard solution should not more than 2.00
5) The % RSD for the peak area response of Hydrochlorothiazide and Ramipril peak obtained with the replicate injections of standard solution and bracketing standard solution should not more than 2.00

Calculation: (Assay):

1) Calculate the content of Ramipril by using following formula,

$$= \frac{A}{B} \times \frac{W1}{25} \times \frac{2}{100} \times \frac{250}{W2} \times \frac{25}{5} \times \frac{P}{100} \times \frac{100}{5} \times \text{Average weight (mg)}$$

Where,
A = Area of Ramipril peak obtained from sample preparation.
B = Average area of Ramipril peak obtained from standard solution.
W1 = Weight of Ramipril working standard in mg.
W2 = Weight of sample in mg.
P = % Potency of Ramipril working standard on as is basis.

2) Calculate the content of Hydrochlorothiazide by using following formula,

$$= \frac{A}{B} \times \frac{W1}{25} \times \frac{5}{100} \times \frac{250}{W2} \times \frac{25}{5} \times \frac{P}{100} \times \frac{100}{12.5} \times \text{Average weight (mg)}$$

Where,
A = Area of Hydrochlorothiazide peak obtained from sample preparation.
B = Average area of Hydrochlorothiazide peak obtained from standard solution.
W1 = Weight of Hydrochlorothiazide working standard in mg.
W2 = Weight of sample in mg.
P = % Potency of Hydrochlorothiazide working standard on as is basis.

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Designation	Executive-QC	Sr. Executive-QC	Manager-QC
Signature	J.tanj		
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Department: Quality Control		Date of Issue: 31/01/2024	

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3) Calculate the average content of assay by using following formula,

$$= \frac{\text{Assay value obtained with sample 1} + \text{Assay value obtained with sample 2}}{2}$$

Reporting: Report the average assay values in % of Ramipril and Hydrochlorothiazide.

Calculation: (CU):

1)Calculate the content of Ramipril in each tablet by using following formula,

$$= \frac{A}{B} \times \frac{W1}{25} \times \frac{2}{100} \times \frac{250}{1} \times \frac{P}{100} \times \frac{100}{5}$$

Where,

A = Area of Ramipril peak obtained from sample preparation.
B = Average area of Ramipril peak obtained from standard solution.
W1 = Weight of Ramipril working standard in mg.
P = % Potency of Ramipril working standard on as is basis.

2) Calculate the content of Hydrochlorothiazide in each tablet by using following formula,

$$= \frac{A}{B} \times \frac{W1}{25} \times \frac{5}{100} \times \frac{250}{1} \times \frac{P}{100} \times \frac{100}{12.5}$$

Where,

A = Area of Hydrochlorothiazide peak obtained from sample preparation.
B = Average area of Hydrochlorothiazide peak obtained from standard solution.
W1 = Weight of Hydrochlorothiazide working standard in mg.
P = % Potency of Hydrochlorothiazide working standard on as is basis.

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Signature			
Date	31/01/2024	31/01/2024	31/01/2024
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SECTION X

DISSOLUTION:

Chromatographic conditions:

Column	:	Sunniest C8, 150 mm x 4.6 mm, 5 µm or equivalent
Flow rate	:	1.0 ml/min
Column temperature	:	25°C
LC mode	:	Isocratic
Detection wavelength	:	210 nm
Injection Volume	:	10 µl
Run time	:	10 min

Dissolution parameters:

Dissolution medium	:	0.1 N Hydrochloric acid
Volume	:	750 ml
Apparatus	:	USP Type 1 (Basket)
Speed	:	100 rpm
Time	:	45 min
Temperature	:	37°C ±0.5°C
Sampling volume	:	10 ml

Preparation of dissolution medium (0.1 N hydrochloric acid):
Dilute 8.5 ml of conc. Hydrochloric acid to 1000 ml with water and mix well.

Diluent:
Use 0.1 N hydrochloric acid as blank.

Blank:
Use diluent as blank.

Preparation of buffer:
Dissolve 12.2 g of Sodium perchlorate in 1000 ml water and adjust the pH to 2.5 with dilute orthophosphoric acid. Filter through 0.45 µ membrane filter and degas.

Preparation of mobile phase:
Mix 500 ml of buffer solution and 500 ml of acetonitrile, Sonicate and degas.

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	Product Code: R09	Effective Date: 31/01/2024

Preparation of Ramipril & Hydrochlorothiazide standard solution:
Weigh accurately and transfer 15.0 mg of Ramipril & 40.0 mg of Hydrochlorothiazide working standard into 250 mL of volumetric flask, add 150 mL of mobile phase, sonicate to dissolve and dilute up to the mark with mobile phase. Further dilute 5 ml of this solution to 50 ml with diluent. Mix well and inject .
Concentration: Ramipril 0.006 mg/ml & Hydrochlorothiazide 0.016mg/ml)

Preparation of Sample solution:
Place 750 ml of dissolution medium in the vessel of the apparatus, assemble the apparatus equilibrate the dissolution medium to 37 ±0.5°C. Place one tablet in each vessel and immediately operate the apparatus at 100 rpm. After 45 minutes withdraw sample from zone midway between the surface of dissolution medium and top of the rotating basket. Filter the sample through Whatman filter and inject.
(Concentration: Ramipril 0.006mg/ml & Hydrochlorothiazide 0.016mg/ml)

Procedure:
Equilibrate the chromatographic system with mobile phase till a stable baseline is obtained. Separately inject equal volumes (10 µl) of solutions as per Sequence of injections into the chromatograph and record the peak area responses for the major peaks and check for the System suitability requirements.

Sequence of Injections:
1) Blank
2) Standard solution 1....5
3) Blank
4) Sample solution 1.....6
5) Standard solution (B)

System suitability requirement:
1)The Resolution between the peaks corresponding to Hydrochlorothiazide and Ramipril obtained with standard solution should not be less than 2.0
2) The tailing factor for the peak of Hydrochlorothiazide and Ramipril obtained with standard solution should not more than 2.0.
3) The column efficiency for the peak of Hydrochlorothiazide and Ramipril obtained in the chromatogram of Standard solution should not less than 2000
4) The % RSD for the peak area response of Hydrochlorothiazide and Ramipril peak obtained with the replicate injections of standard solution should not more than 2.00
5) The % RSD for the peak area response of Hydrochlorothiazide and Ramipril peak obtained with the replicate injections of standard solution and bracketing standard solution should not more than 2.00

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		No.: FPSTP:R09
	FINISHED PRODUCT STANDARD TEST PROCEDURE	Revision No: 02
Title:	RAMITHIAZIDE 5 mg/12.5 mg TABLETS (Ramipril and Hydrochlorothiazide Tablets)	Review Period: 3 Years
	Product Code: R09	Effective Date: 31/01/2024

Calculation:

1) Calculate the content released of Ramipril in each tablet by using following formula,

$$= \frac{A}{B} \times \frac{W1}{250} \times \frac{5}{50} \times \frac{750}{1} \times \frac{P}{100} \times \frac{100}{5}$$

Where,

A = Area of Ramipril peak obtained from sample preparation.
B = Average area of Ramipril peak obtained from standard solution.
W1 = Weight of Ramipril working standard in mg.
P = % Potency of Ramipril working standard on as is basis.

2) Calculate the content released of Hydrochlorothiazide in each tablet by using following formula,

$$= \frac{A}{B} \times \frac{W1}{250} \times \frac{5}{50} \times \frac{750}{1} \times \frac{P}{100} \times \frac{100}{12.5}$$

Where,

A = Area of Hydrochlorothiazide peak obtained from sample preparation.
B = Average area of Hydrochlorothiazide peak obtained from standard solution.
W1 = Weight of Hydrochlorothiazide working standard in mg.
P = % Potency of Hydrochlorothiazide working standard on as is basis.

Reporting: Report the results of minimum, maximum and average value in %

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	FINISHED PRODUCT STANDARD TEST PROCEDURE	Revision No: 02
Title:	RAMITHIAZIDE 5 mg/12.5 mg TABLETS (Ramipril and Hydrochlorothiazide Tablets)	Review Period: 3 Years
	Product Code: R09	Effective Date: 31/01/2024

SECTION XI

RELATED SUBSTANCES:

Chromatographic Conditions:

LC Mode	:	Gradient
Column type	:	C18 (4.6 mm x 250 mm, 5µm) (Make: Inertsil ODS 3V column is suitable)
Flow rate	:	1.0 ml / minute.
Detector wavelength	:	210 nm.
Column oven temperature	:	25°C.
Injection volume	:	30 µl.
Run time	:	30 Minutes

Preparation of Buffer solution:

Weigh accurately about 12.2987 g of sodium perchlorate into 1000 ml glass beaker. Add about 500 ml of water, shake and sonicate to dissolve completely and finally make the solution 1000 ml with water, adjust pH 2.5 with diluted orthophosphoric acid and mix well. Filter it through 0.45µ membrane filter and degas.

Preparation of Mobile Phase:

Mobile phase A: Use buffer solution as mobile phase A

Mobile phase B: Use Acetonitrile as mobile phase B

Gradient Program:

Time (Minute)	Mobile phase A (% v/v)	Mobile phase B (%v/v)
0.0	70	30
7.0	70	30
9.0	50	50
25.0	50	50
30.0	70	30

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Preparation of Diluent:

Mix well 550 ml of water, 450 ml Acetonitrile and 1 ml Triethylamine and adjust the pH 3.0 with diluted orthophosphoric acid.

Preparation of Ramipril Standard Stock Solution:

Weigh accurately and transfer about 25 mg of Ramipril working standard into 25ml volumetric flask. Add about 10 ml of diluent, sonicate to dissolve and dilute up to mark with diluent.

Preparation of Hydrochlorothiazide Standard Stock Solution:

Weigh accurately and transfer about 25 mg of Hydrochlorothiazide working standard into 25ml volumetric flask. Add about 10 ml of diluent, sonicate to dissolve and dilute up to mark with diluent.

Preparation of Standard Solution:

Pipette out 4 ml of Ramipril Standard Stock solution and 5 ml of Hydrochlorothiazide standard stock solution and transfer into 200 ml volumetric flask and dilute to volume with diluent.
Further dilute 2 ml of this solution to 20 ml with diluent. Mix well and inject.
(Concentration: 0.002 mg / ml of Ramipril and 0.0025 mg/ml of Hydrochlorothiazide)

Preparation of Placebo solution:

Weigh accurately and transfer about 780.0 mg of placebo powder (equivalent to 20 mg of Ramipril) into 20 ml volumetric flask. Add about 12 ml of diluent and 1ml of water, sonicate for 15 minutes with intermediate shaking and dilute up to the volume with diluent and mix well. Filter the sufficient amount of this solution through 0.45micron nylon syringe filter and inject.

Preparation of Sample solution:

Weigh accurately and transfer about 800.0 g of sample powder (equivalent to 20 mg of Ramipril) into 20 ml volumetric flask. Add about 12 ml of diluent and 1ml of water, sonicate for 15 minutes with intermediate shaking and dilute up to the volume with diluent and mix well. Filter the sufficient amount of this solution through 0.45micron nylon syringe filter and inject.
(Concentration: 1 mg / ml of Ramipril)

Note: Inject all solutions freshly prepared.

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Title:	RAMITHIAZIDE 5 mg/12.5 mg TABLETS (Ramipril and Hydrochlorothiazide Tablets)	Review Period: 3 Years
	Product Code: R09	Effective Date: 31/01/2024

Procedure:

Equilibrate the chromatographic system with mobile phase till a stable baseline is obtained. Separately inject equal volumes (30 µl) of solutions as per Sequence of injections into the chromatograph and record the peak area responses for the major peaks and check for the System suitability requirements.

Sequence of Injections:

1) Blank
2) Standard Solution 1...6
3) Blank
4) Placebo solution
5) Blank
6) Sample solution
7) Standard solution (B)

System suitability requirement:

1) The theoretical plates for the peak of Ramipril obtained with the chromatogram of standard solution should not be less than 2000.
2) The % RSD for the peak area response of Ramipril peak obtained with the replicate injections of standard solution should not be more than 5.0
3) The % RSD for the peak area response of Ramipril peak obtained with the replicate injections of standard solution and bracketing standard solution should not be more than 5.0

Relative response factor for all impurities:

Name of impurity	RRT	RRF
Impurity E	0.89	22.09
Impurity A	0.91	1.15
Ramipril	1.00	-
Impurity D	1.50	1.22

Calculations:

1) Calculate the % content of known impurities by using following formula,

$$= \frac{A}{B} \times \frac{W1}{25} \times \frac{4}{200} \times \frac{2}{20} \times \frac{20}{W2} \times \frac{P}{100} \times Av. \times \frac{100}{5} \times RRF$$

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Where,
A = Peak area response of individual known impurity obtained with sample solution.

B = Average peak area response of Ramipril obtained with replicate injections of standard solution.

W1 = Weight of Ramipril standard taken in mg.

W2 = Weight of samples taken in g.

P = Purity of Ramipril standard as is in %.

Av = Average weight of sample in g.

RRF = Relative response factor of individual Impurities.

2) Calculate the % content of single maximum unknown impurity by using following formula,

$$= \frac{A}{B} \times \frac{W1}{25} \times \frac{4}{200} \times \frac{2}{20} \times \frac{20}{W2} \times \frac{P}{100} \times Av. \times \frac{100}{5}$$

Where,
A = Peak area response of single maximum unknown impurity obtained with sample solution.

B = Average peak area response of Ramipril obtained with replicate injections of standard solution.

W1 = Weight of Ramipril standard taken in mg.

W2 = Weight of samples taken in g.

P = Purity of Ramipril standard as is in %.

Av = Average weight of sample in g.

3) Calculate the % content of total unknown impurities by using following formula,

$$= \frac{A}{B} \times \frac{W1}{25} \times \frac{4}{200} \times \frac{2}{20} \times \frac{20}{W2} \times \frac{P}{100} \times Av. \times \frac{100}{5}$$

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Where,

A = Peak area response of individual unknown impurity obtained with sample solution.

B = Average peak area response of Ramipril obtained with replicate injections of standard solution.

W1 = Weight of Ramipril standard taken in mg.

W2 = Weight of samples taken in g.

P = Purity of Ramipril standard as is in %.

Av = Average weight of sample in g.

Total Impurities: Sum of % of all known impurities + Sum of % of all unknown impurities.

SECTION – XII

ASSAY

Refer to CONTENT UNIFORMITY(SECTION -IX)

SECTION-XIII

MICROBIOLOGICAL LIMITS

Refer to SOP No. QCMB 006.

HISTORY

S. No.	Revision Number	Reason for Revision
1	Revision No.: 00	New STP No:FPSTP:R09
2	Revision No.: 01	Periodic Revision
3	Revision No.: 02	Incorporated Bulk Granules Specification, Bulk product Specification

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