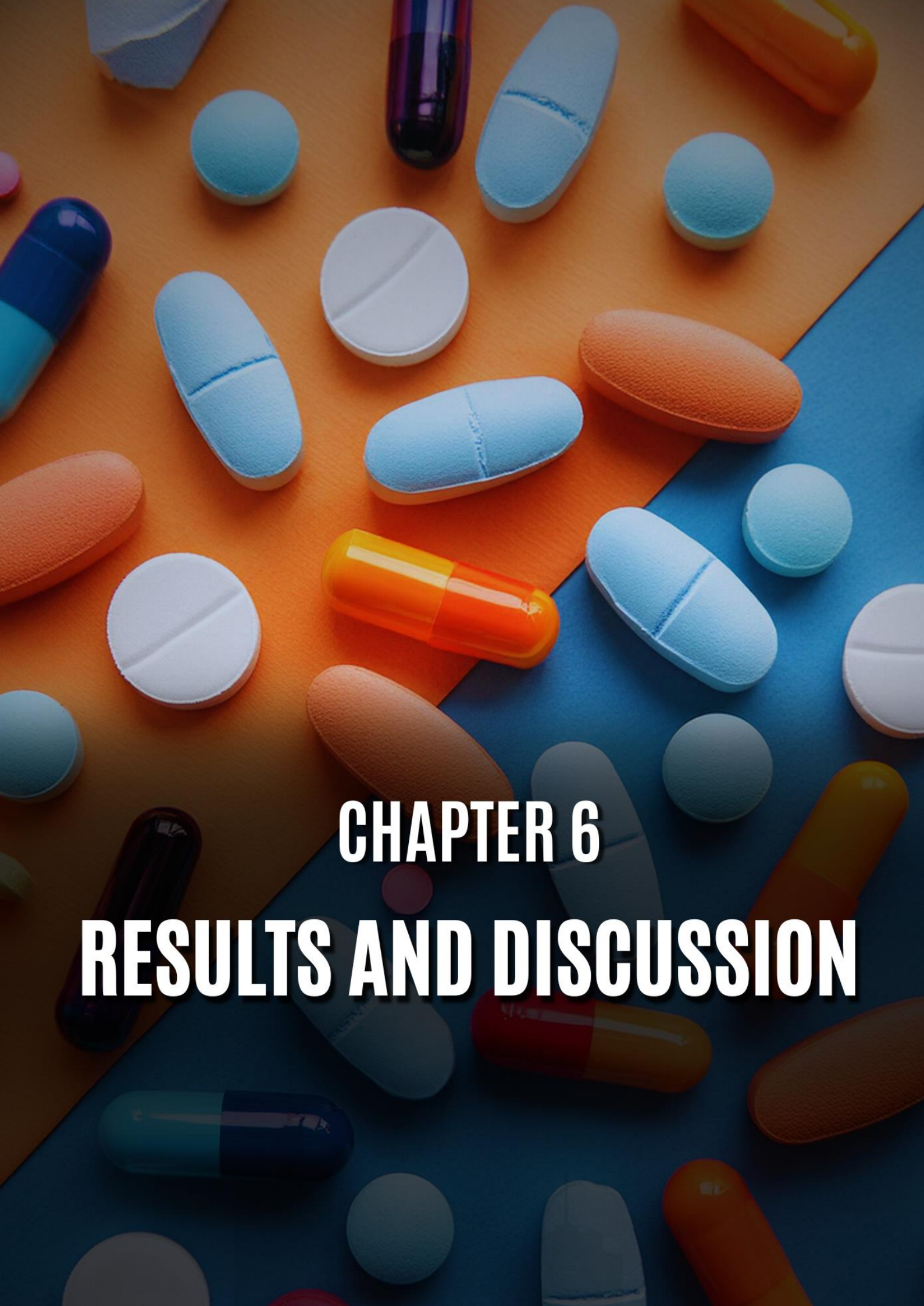

CHAPTER 6
RESULTS AND DISCUSSION

6. RESULTS AND DISCUSSION

6.1 Batch Formula

Table 6.1: Composition of batch formulation

Sr. No	Ingredients	F1	F2	F3	F4	F5	F6
	Quantity in mg per tablet						
1	Telmisartan	40	40	40	40	40	40
2	Hydrochlorothiazide	12.5	12.5	12.5	12.5	12.5	12.5
3	Avicel PH 102 (MCC)	219	201	222	211.5	221	215
4	Aerosil	1.5	1.5	1.5	1.5	1.5	1.5
5	Talc	21	21	21	21	21	21
6	Sodium Starch Glycolate	6	24	---	---	---	---
7	Croscarmellose Sodium	---	---	3	13.5	---	---
8	Crospovidone	---	---	---	---	4	10
Total		**300**	**300**	**300**	**300**	**300**	**300**

6.2 Pre Compression Parameters of Formulation Batches

Table 6.2: Results of pre compression parameters of formulation batches

Batch No.	Bulk Density (g/ml)	Tapped Density (g/ml)	Angle of Repose (Degree)	Compressibility index (%)	Hausner ratio
F1	0.45	0.625	42.27	28	1.38
F2	0.31	0.41	47.20	24.39	1.32
F3	0.33	0.625	45.56	47.2	1.89
F4	0.8	1.75	45	54.28	2.18
F5	0.35	0.55	45	36.36	1.57
F6	0.31	0.55	44.61	43.63	1.77

6.3 Post Compression Parameters of Formulation Batches

Table 6.2: Results of post compression parameters of formulation batches

Batch No.	Average weight (mg)	Average Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Disintegration Time (Second)	Dissolution Studies (% DR)	
						TEL	HCTZ
F1	297.9	6.0	3.89	0.77	40	92.26	91.44
F2	279.9	5.2	3.49	0.23	40	91.58	91.00
F3	301.5	6.0	4.29	0.16	30	91.28	89.57
F4	309.9	5.4	4.5	0.23	30	92.22	92.02
F5	299.9	5.6	4.31	0.29	40	92.55	92.26
F6	290.6	6.06	4.53	0.56	45	93.29	92.10

6.4 Regulatory Dossier

MODULE - 1

ADMINISTRATIVE AND PRODUCT INFORMATION

APPLICATION FOR DRUG REGISTRATION IN US

(TELMISARTAN AND HYDROCHOLOROTHAZIDE COMBINATION TABLET USP)

Submitted By: DADASAHEB BALPANDE COLLAGE OF PHARMAY

Near Shree Swami Samarth Dham Mandir, Manewada Road, Besa Square, Nagpur Maharashtra 440037

1.1 Table of Content

Sr. No.	CONTENT
1.1	**Table of content**
1.2	**Forms**
1.2.1	Application form: FDA form 356h
1.2.2	Annual report transmittal: FDA form 2252
1.2.3	Advertisements and promotional labeling transmittal: FDA form 2253
1.2.4	Transmittal of Labels and Circulars: FDA form 2567
1.3	**Cover letters**
1.3.1	Application letter
1.4	**Administrative information**
1.4.1	Contact/sponsor/Applicant information
1.4.2	Financial certification and disclosure
1.4.3	Patent and exclusivity
1.5	**References**
1.5.1	Letter of authorization
1.5.2	Statement of right of reference
1.6	**Labeling**

1.2 Forms

1.2.1 Application form: FDA form 356h

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

APPLICATION TO MARKET A NEW OR ABBREVIATED NEW DRUG OR BIOLOGIC FOR HUMAN USE
(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2026
See PRA Statement on page 4

FDA

1. Date of Submission *(mm/dd/yyyy)*

APPLICANT INFORMATION

2. Name of Applicant

3. Telephone Number *(Include country code if applicable and area code)*

4. Facsimile (FAX) Number *(Include country code if applicable and area code)*

5. **Applicant Address**

Address 1 *(Street address, P.O. box, company name c/o)*

Email Address

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

Applicant DUNS

City

State/Province/Region

U.S. License Number if previously issued

Country

ZIP or Postal Code

6. **Authorized U.S. Agent** *(Required for non-U.S. applicants)*

U.S. Agent Company | Prefix | First Name | Middle | Last Name | Title

Address 1 *(Street address, P.O. box, company name c/o)*

Telephone Number *(Include area code)*

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

U.S. Agent DUNS

FAX Number *(Include area code)*

City | State | ZIP Code | Email Address

PRODUCT DESCRIPTION

7. NDA, ANDA, or BLA Application Number

8. Supplement Number *(If applicable)*

9. Established Name *(e.g., proper name, USP/USAN name)*

10. Proprietary Name *(Trade Name) (If any)*

11. Chemical/Biochemical/Blood Product Name *(If any)*

12. Dosage Form | 13. Strengths | 14. Route of Administration

15A. Proposed Indication for Use

Is this indication for a rare disease *(prevalence <200,000 in U.S.)*? ☐ Yes ☐ No

Does this product have an FDA Orphan Designation for this indication?
☐ Yes ☐ No

If yes, provide the Orphan Designation number for this indication:

15B. SNOMED CT Indication Disease Term *(Use continuation page for each additional indication and respective coded disease term)*

Continuation Page for #15

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APPLICATION INFORMATION

16. Application Type *(Select one)*
- ☐ New Drug Application (NDA)
- ☐ Biologics License Application (BLA)
- ☐ Abbreviated New Drug Application (ANDA)

17. If an NDA, identify the type
- ☐ 505(b)(1)
- ☐ 505(b)(2)

18. If a BLA, identify the type
- ☐ 351(a)
- ☐ 351(k)

19. If a 351*(k), identify the biological reference product that is the basis for the submission.*

Name of Biologic:

Holder of Licensed Application:

20. If an ANDA, or 505*(b)(2), identify the listed drug product that is/are the basis for the submission.*

Name of Drug:

Application Number of Relied Upon Product:

Indicate Patent Certification: ☐ P1 ☐ P2 ☐ P3 ☐ P4 ☐ Section viii – MOU ☐ Statement of no relevant patents

21. Submission *(See instructions)*
- ☐ Original
- ☐ Efficacy Supplement
- ☐ Postmarketing Requirements or Commitments
- ☐ REMS Supplement
- ☐ REMS Assessment Methods and Study Protocols
- ☐ Human Factors *(Specify Type)*:
- ☐ Other *(Specify)*:
- ☐ Labeling Supplement
- ☐ Annual Report
- ☐ Request for Proprietary Name Review
- ☐ REMS Assessment Report
- ☐ CMC Supplement
- ☐ Product Correspondence
- ☐ Periodic Safety Report

22. Submission Sub-Type
- ☐ Presubmission
- ☐ Amendment
- ☐ Initial Submission
- ☐ Resubmission

23. If a supplement, identify the appropriate category.
- ☐ CBE
- ☐ Prior Approval (PA)
- ☐ CBE-30

24. For Originals and all Supplements, is the product a combination product *(21 CFR 3.2(e))?*
- ☐ Yes
- ☐ No

Combination Product Type *(See instructions)*

Request for Designation (RFD) Number

25. Does the submission contain:

Only Pediatric data?
- ☐ Yes
- ☐ No

Digital Health Technology (DHT) data?
- ☐ Yes
- ☐ No

26. Proposed Marketing Status *(Select one)*
- ☐ Prescription Product (Rx)
- ☐ Over-The-Counter Product (OTC)

27. Reasons for Submission

28. Establishment Information *(Full establishment information should be provided in the body of the application.)*

Establishment Name			Registration (FEI) Number
Address 1 *(Street address, P.O. box, company name c/o)*			MF Number
Address 2 *(Apartment, suite, unit, building, floor, etc.)*			Establishment DUNS Number
City	State/Province/Region	ZIP or Postal Code	Country

Is the establishment new to the application?	Is this establishment involved in the change described in this supplement?	What is the status of the establishment?
☐ Yes ☐ No	☐ Yes ☐ No	☐ Pending ☐ Active ☐ Inactive ☐ Withdrawn

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Establishment Contact Information at the site/facility

Prefix	First Name	Middle	Last Name	Title

Address 1 *(Street address, P.O. box, company name c/o)*	Telephone Number *(Include area code)*
Address 2 *(Apartment, suite, unit, building, floor, etc.)*	FAX Number *(Include area code)*
City / State/Province/Region	Email Address
Country	ZIP or Postal Code

Manufacturing Steps and/or Type of Testing

Is the site ready for inspection? ☐ Yes ☐ No ☐ N/A

If No, when will site be ready? *(mm/dd/yyyy)*

Continuation Page for #28

29. Cross References *(List related BLAs, INDs, NDAs, PMAs, 510(k)s, IDEs, MFs and DMFs referenced in the current application.)*

Continuation Page for #29

30. This application contains the following items *(Select all that apply)*

1. ☐ Index
2. ☐ Labeling (Select one):
   - ☐ Draft Labeling
   - ☐ Final Printed Labeling
3. ☐ Summary (21 CFR 314.50 (c))
4. ☐ Chemistry Section
   - A. ☐ Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
   - B. ☐ Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
   - C. ☐ Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
5. ☐ Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
6. ☐ Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
7. ☐ Clinical microbiology section (e.g., 21 CFR 314.50(d)(4))
8. ☐ Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
9. ☐ Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
10. ☐ Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
11. ☐ Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
12. ☐ Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
13. ☐ Patent information on any patent that claims the drug/ biologic (21 U.S.C. 355(b) or (c))
14. ☐ A patent certification with respect to any patent that claims the drug/ biologic (21 U.S.C. 355 (b)(2) or (j)(2)(A))
15. ☐ Establishment description (21 CFR Part 600, if applicable)
16. ☐ Debarment certification (FD&C Act 306 (k)(1))
17. ☐ Field copy certification (21 CFR 314.50 (l)(3))
18. ☐ User Fee Cover Sheet (PDUFA Form FDA 3397, GDUFA Form FDA 3794, BsUFA Form FDA 3792, or MDUFA Form FDA 3601)
19. ☐ Financial Disclosure Information (21 CFR Part 54)
20. ☐ Other (Specify):

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CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to, the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state, and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge, are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

31. Applicant's Responsible Official

Prefix	First Name	Middle	Last Name	Title

32. Date *(mm/dd/yyyy)*	33. Telephone Number *(Include country code if applicable and area code)*	34. FAX Number *(Include country code if applicable and area code)*	35. Email Address

36. Address of Applicant's Responsible Official

Address 1 *(Street address, P.O. box, company name c/o)*

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City	State/Province/Region

Country	ZIP or Postal Code

37. Signature of Applicant's Responsible Official or Other Authorized Official	38. Countersignature of Authorized U.S. Agent
Sign	Sign

THE INFORMATION BELOW APPLIES ONLY TO REQUIREMENTS OF THE PAPERWORK REDUCTION ACT OF 1995.

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"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

Department of Health and Human Services
Food and Drug Administration
Office of Operations
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

DO NOT SEND YOUR COMPLETED FORM TO THIS PRA STAFF EMAIL ADDRESS.

Form FDA 356h (07/23) (PREVIOUS EDITION OBSOLETE) **Page 4 of 4**

1.2.2 Annual report transmittal: FDA form 2252

TRANSMITTAL OF ANNUAL REPORTS FOR DRUGS AND BIOLOGICS FOR HUMAN USE
(21 CFR 314.81)

DATE SUBMITTED

Form Approved: OMB No. 0910-0001
Expiration Date: March 31, 2024
See OMB Statement on Reverse Side.

NOTE: This report is required by law (21 USC 355; 21 CFR 314.81). *Failure to report can result in withdrawal of approval of the New Drug or Biologics License Application.*

INSTRUCTIONS

Complete a transmittal for each application for which an annual report is being submitted. If submitting electronically, submit one copy of the form and annual report to FDA. If submitting in paper, submit two copies of the transmittal form along with two copies of the annual report to FDA.

If any part of the annual report applies to more than one application, list in item 8 all other applications to which such parts apply.

1. Center (Select One) ☐ CDER ☐ CBER

2. Application Type: ANDA

3. Application Number: /

Report No. *(For FDA Use Only)*

4. APPLICANT

5. PHONE NUMBER ( )

6. TYPE OF REPORT *(Check one)* ☐ ANNUAL ☐ OTHER

7. DRUG/BIOLOGIC NAME

8. OTHER APPLICATION NUMBERS *(List all numbers if any part of report applies to more than one number.)*

Application Type	Application Number
ANDA	
Choose One	

Add Row / Remove Row

9. PERIOD COVERED BY REPORT

FROM		TO	
YEAR	MONTH	YEAR	MONTH

10. NDA REPORT INFORMATION REQUIRED ***(See § 314.81 for description) (Enter type of information attached under "Identification." If you have nothing to report, enter None.) (INFORMATION IN "10b" AND "10c" IS ALWAYS REQUIRED.)***

TYPE OF INFORMATION	IDENTIFICATION *(Electronic file name or eCTD location or Volume No. (s) / Tab(s) / Page(s) of Report)*
a. SUMMARY OF SIGNIFICANT NEW INFORMATION	
b. DISTRIBUTION DATA ☐ Authorized Generic Info	
c. LABELING *(Whether or not previously submitted)*	
d. CHEMISTRY MANUFACTURING AND CONTROLS CHANGES ☐ SUPAC	
e. NONCLINICAL LABORATORY STUDIES	
f. CLINICAL DATA	
g. STATUS REPORTS OF OPEN PMRs/PMCs *(enter None if no open PMRs/PMCs to report)*	
h. STATUS OF OTHER OPEN POSTMARKETING STUDIES *(e.g., voluntary studies, CMC commitment studies, and product stability studies)*	
i. LOG OF OUTSTANDING REGULATORY BUSINESS *(Optional)*	

11. BLA REPORT INFORMATION REQUIRED *(See § 601.70 for description)*

TYPE OF INFORMATION	CONTENTS *(Check box)*
a. ANNUAL PROGRESS REPORTS OF POSTMARKETING STUDIES	☐

12. TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT
NAME
TITLE

14. SIGNATURE Sign

13. APPLICANT'S RETURN ADDRESS
Name of Sponsor / Applicant / Submitter
Address 1
Address 2
City | State | ZIP or Postal Code

FDA USE ONLY
NDA OR ANDA NUMBER
DATE OF RECEIPT

FORM FDA 2252 (07/22) Previous Edition Is Obsolete Page 1 of 2

PSC Publishing Services (301) 443-6740 EF

1.2.3 Advertisements and promotional labeling transmittal: FDA form 2253

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0001
Expiration Date: March 31, 2024
See PRA Statement on last page.

TRANSMITTAL OF ADVERTISEMENTS AND PROMOTIONAL LABELING FOR DRUGS AND BIOLOGICS FOR HUMAN USE

1. Date Submitted

2. Application Information — ☐ Single product ☐ Multiple products

Application Type:

Application Number: /

For multiple products, submit completed form and specimen of advertising/promotional materials to one application of choice, and attach separate sheet addressing items 3-5 for remainder of products. Refer to No. 3 on instruction sheet.

NOTE: Form FDA 2253 is required by law. Reports are required for approved NDAs, ANDAs (21 CFR 314.81), and BLAs (601.12(f)(4))

3. Proprietary Name

4. Established Name

Product Code No.:

5. Package Insert Date and ID Number (Latest final printed labeling)

6. Manufacturer Name

License No. (Biologics):

7. **Advertisement / Promotional Labeling Materials**

a. **Please check only one:** ☐ Professional ☐ Consumer

Material Type (use FDA codes) b.	Dissemination/ Publication Date c.	Material ID Code d.	Material Description e.	
				Delete Row

To delete a row, click the "Delete Row" button for that row (or press the enter key if you've tabbed into the button). You cannot delete the last remaining row. **Add New Row**

f. Comments

8. Applicant's (or Agent's) Return Address

Address 1 *(Street address, P.O. box, company name c/o)*

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City | State/Province/Region

Country | ZIP or Postal Code

9. Responsible Official's (or Agent's)

a. Telephone Number *(Include area code)*

b. FAX Number *(Include area code)*

c. Email Address

FORM FDA 2253 (10/21) PREVIOUS EDITION IS OBSOLETE **Page 1 of 2** PSC Publishing Services (301) 443-6740 EF

10. Typed Name and Title of Responsible Official or Agent	11. Signature of Responsible Official or Agent	12. Date
	Sign	

13. For CBER Products Only *(Check one)*

☐ Draft ☐ Final

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 2 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

FORM FDA 2253 (10/21) PREVIOUS EDITION IS OBSOLETE **Page 2 of 2**

1.2.4 Transmittal of Labels and Circulars: FDA form 2567

Form FDA 2567 is equivalent to Form FDA 2253

Form is added in section 1.2.3

1.3 Cover Letter

ON DADASAHEB BALPANDE COLLAGE OF PHARMAY, NAGPUR. Letter head.

To,

Office of Generic Drugs (HFD-600),
Centre for Drug Evaluation and Research,
Food and Drug Administrative
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Subject: Submission of Application Dossier(s) for Marketing Authorization of Tablet (Telmisartan and Hydrochlorothiazide Combination Tablets USP 300 mg)

Type of Application: New Registration for marketing authorization

Dear Sir/Madam,

Here with we are submitting the application for registration of medicinal product for marketing authorization in USFDA.

Thanking You

Yours Sincerely,

DADASAHEB BALPANDE COLLAGE OF PHARMAY, NAGPUR

1.3.1 Application letter

To,
Office of Generic Drugs (HFD-600),
Centre for Drug Evaluation and Research,
Food and Drug Administrative
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Subject: Submission of Application Dossier(s) for Marketing Authorization of Tablet (Telmisartan and Hydrochlorothiazide Combination Tablets USP 300 mg)

Type of Application: New Registration for marketing authorization

Dear Sir/Madam,
We are pleased to our submit Application Dossier (s) for a registration of human medicines that details are as follows:

Name of Medicinal Product: Telmisartan and Hydrochlorothiazide Combination Tablets USP 300 mg
Pharmaceutical Dosage Form: Uncoated Tablets
Route of Administrative: Oral

Composition

Each Uncoated Tablet Contains
Telmisartan and Hydrochlorothiazide USP……. 300 mg
Excipients…….. qs
INN/Active Pharmaceutical Ingredients (s): Telmisartan and Hydrochlorothiazide USP
Dosage Form: Uncoated Tablets
Route of Administrative: ORAL
Name of Manufacture: Dadasaheb Balpande Collage of Pharmacy, Nagpur
Address: Near Shree Swami Samarth Dham Mandir Manewada Road, Besa Chowk, Nagpur Maharashtra 440037

Applicant Name: Dadasaheb Balpande Collage of Pharmacy, Nagpur
Applicant Address: Near Shree Swami Samarth Dham Mandir Manewada Road, Besa Chowk, Nagpur Maharashtra 440037

You will find enclosed the submission dossier as specified hereafter:

√ CTD format, 2 soft copies documents format
√ VCD rom; Summaries in word format and body data in PDF format
√ We confirm that all future submissions for this specific product will be submitted in this same format
√ We confirm that the electronic submission has been checked with up-to-date and state-of-the-art antivirus software.
√ The electronic submission contains the following modules:
Module 1: Administrative information and product information
Module 2: Overview and summaries
Module 3: Quality
Module 4: Non clinical study reports
Module 5: Clinical study reports
Number of Samples Submitted:

The relevant fees have been paid.
I, the undersigned certify that all the information in this form and accompanying documentation is correct, complete and true to the best of my knowledge

Yours sincerely,

DADASAHEB BALPANDE COLLAGE OF PHARMAY, NAGPUR

1.4 Administrative information

1.4.1 Contact/sponsor/Applicant information

Site	Address
Administrative	**Dadasaheb Balpande College of Pharmacy:** Near Shree Swami Samarth Dham Mandir Manewada Road, Besa Square, Nagpur, Maharashtra 440037 **Tel:** 07103281244
Production	**Dadasaheb Balpande College of Pharmacy:** Near Shree Swami Samarth Dham Mandir Manewada Road, Besa Square, Nagpur, Maharashtra 440037 **Tel:** 07103281244
Analysis	**Dadasaheb Balpande College of Pharmacy:** Near Shree Swami Samarth Dham Mandir Manewada Road, Besa Square, Nagpur, Maharashtra 440037 **Tel:** 07103281244

1.4.2 Financial certification and disclosure

NOT APPLICABLE

Justification: Form FDA 3454, or the Financial Certification or Disclosure Statement, is used to submit information regarding clinical investigators who participated in the clinical studies. No clinical studies were performed to test this drug product. So, this section is not applicable.

1.4.3 Patent and exclusivity

In the context of pharmaceuticals and biologics, patents and exclusivity are legal mechanisms that protect the investment in drug development by granting the holder exclusive rights to market the drug for a certain period.

The first company to submit an ANDA with the FDA has the exclusive right to market the generic drug for 180 days.

1.5 References

1.5.1 Letter of authorization

[COMPANY LETTERHEAD PROVIDING COMPANY NAME, ADDRESS, AND TELEPHONE NUMBER]

[DATE]

[FDA ADDRESSEE]

Re: Letter of Authorization to Cross Reference to IND [INSERT DRUG NAME AND IND NUMBER]

Dear [NAME OF ADDRESSEE]:

This letter of authorization (LOA) authorizes [INSERT PHYSICIAN SPONSOR'S NAME] to reference and rely on [INSERT COMPANY'S NAME] IND [INSERT IND NUMBER] in connection with [INSERT PHYSICIAN SPONSOR'S NAME] individual patient expanded access IND [INSERT RELEVANT INFORMATION DESCRIBING PHYSICIAN SPONSOR'S IND].

FDA is authorized to refer to [INSERT COMPANY'S NAME] IND [INSERT IND NUMBER] for the purpose of FDA's review of the IND submitted by [INSERT PHYSICIAN SPONSOR'S NAME] and described above.

As indicated by my signature below, I am authorized to provide this LOA on behalf of [INSERT COMPANY NAME], and my full name, title, address, email address, telephone number, and facsimile number are set out below for verification.

If you have any questions, please contact me at [INSERT TELEPHONE NUMBER].

Sincerely,

[INSERT SIGNATURE OF RESPONSIBLE OFFICIAL]

[INSERT NAME OF RESPONSIBLE OFFICIAL]

[INSERT RESPONSIBLE OFFICIAL'S TITLE]

[INSERT RESPONSIBLE OFFICIAL'S FAX NUMBER]

[INSERT RESPONSIBLE OFFICIAL'S E-MAIL ADDRESS]

1.5.2 Statement of right of reference

[Company Letterhead]
Date: [Insert Date]

U.S. Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Document Control Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: Statement of Right of Reference

Dear Sir/Madam,

This letter is to formally grant [Recipient Company Name] the right of reference to the following proprietary information owned by [Owner Company Name]:

- [Detailed description of the information, such as "Clinical Study Report XYZ," "Manufacturing Data for Product ABC," etc.]

This right of reference is granted for the purpose of supporting [Recipient Company Name]'s [specific submission type, e.g., "New Drug Application (NDA)"] to the U.S. Food and Drug Administration.

The referenced information is contained in [specific submission, e.g., "ANDA Application Number XXXX," "Master File Number YYYY"].

This right of reference is valid for the duration necessary to complete the regulatory process and includes all updates and amendments to the referenced information.

If further information is required, please contact [Contact Person's Name, Title, and Contact Information].

Sincerely,
[Authorized Representative's Name]
[Title]
[Owner Company Name]
[Contact Information]

[Signature]

1.6 Labeling


Each tablet contains 40 mg of telmisartan, USP and 12.5 mg of hydrochlorothiazide, USP
Dosage: Read accompanying prescribing information.
Keep out of reach of children.
The unit-dose package is not child-resistant.
Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Manufactured for:
Dadasaheb Balpande College of Pharmacy, Nagpur
Product of India
MP/DRUGS/25/9/2010
04/22
Questions? 1 (888) 721-7115
Telmisartan and Hydrochlorothiazide Tablets, USP
40 mg/12.5 mg
NDC 68462-840-13
Telmisartan and Hydrochlorothiazide Tablets, USP
40 mg/12.5 mg
Important: Moisture sensitive tablets - do not remove from blisters until immediately before administration
Rx Only
30 Tablets (3x10 unit-dose)
Telmisartan and Hydrochlorothiazide Tablets, USP
40 mg/12.5 mg

MODULE - 2

COMMON TECHNICAL DOCUMENT SUMMARIES

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2.2 CTD Introduction

REGISTERED OFFICE OF THE ORGANISATION AND SITE OF PRODUCTION

Site	Address
Administrative	**Dadasaheb Balpande College of Pharmacy:** Near Shree Swami Samarth Dham Mandir Manewada Road, Besa Square, Nagpur, Maharashtra 440037 Tel: 07103281244
Production, Quality Control & Quality Assurance	**Dadasaheb Balpande College of Pharmacy:** Near Shree Swami Samarth Dham Mandir Manewada Road, Besa Square, Nagpur, Maharashtra 440037 Tel: 07103281244

Name of the medicinal product

Brand name: N/A
Generic name: Telmisartan and Hydrochlorothiazide Combination Tablet

Pharmacotherapeutic classification

Pharmacotherapeutic group: Angiotensin receptor blockers (ARBs)

Pharmaceutical form: Tablet
Strength: 40/12.5 mg per Tablet

Composition

Each Uncoated Tablet Contains

Telmisartan …….40 mg
Hydrochlorothiazide……...12.5 mg
Excipients……. qs

Route of administration: Oral

PACKING:

Primary packaging: Blister pack of 10 tablets such 10 blisters packed in inner carton along with package insert/leaflet.

Secondary packaging: Such 10 inner cartons are packed in outer carton and placed in a 7-ply corrugated box. Boxes are affixed with label having relevant batch details.

The cautions like
- This side up
- Not for loose handling
- Protect from water
- Avoid vigorous transportation

Shelf-life: 5 years from the date of manufacture.

Storage: Store in a cool, dry and dark place.

2.3 Quality Overall Summary (QOS)

Product brand name: N/A

Generic name: Telmisartan and Hydrochlorothiazide Combination Tablet

Strength: 40/12.5 mg per Tablets

Batch 1

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (30 Tablets in mg)	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	219 mg	NA	6,570	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Sodium Starch Glycolate	USP	6 mg	NA	180	Disintegrant

Batch 2

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (30 Tablets in mg)	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	201 mg	NA	6,030	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Sodium Starch Glycolate	USP	24 mg	NA	720	Disintegrant

Batch 3

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (30 Tablets in mg)	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	222 mg	NA	6,600	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Croscarmellose Sodium	USP	3 mg	NA	90	Disintegrant

Batch 4

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (1.00 Lac Tablets in Kg	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	211.5 mg	NA	6,345	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Croscarmellose Sodium	USP	13.5 mg	NA	405	Disintegrant

Batch 5

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (1.00 Lac Tablets in Kg	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	221 mg	NA	6,645	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Crospovidone	USP	4 mg	NA	120	Disintegrant

Batch 6

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (1.00 Lac Tablets in Kg	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	221 mg	NA	6,645	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Crospovidone	USP	4 mg	NA	120	Disintegrant

2.3.S Drug Substance

2.3.S.1 General Information

Name of drug substance: Telmisartan

Name of Manufacturer: Vasudha Pharma Chem. Limited, Hyderabad - 500 038

Name of drug substance: Hydrochlorothiazide

Name of Manufacturer: Unichem Laboratories Limited, Kolhapur - 416 236

2.3.S.2 Manufacture

Manufacturer of Telmisartan:

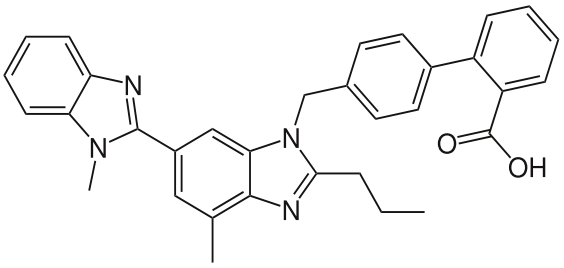
Site	Address	Responsibility
Administrative	**Vasudha Pharma Chem Limited** 78/A, Vengalrao Nagar, Hyderabad, Telangana State, India - 500 038 Phone: 91- 40 – 2381 2046, FAX: 91 – 40 - 23811576	• To arrange for raw material, solvents, chemical and engineering items required for production of bulk drug. • To arrange dispatch of goods at various places and export
Production	**Vasudha Pharma Chem Limited** 78/A, Vengalrao Nagar, Hyderabad, Telangana State, India - 500 038 Phone: 91- 40 – 2381 2046, FAX: 91 – 40 - 23811576	• Production and packing
Analysis	**Vasudha Pharma Chem Limited** 78/A, Vengalrao Nagar, Hyderabad, Telangana State, India - 500 038 Phone: 91- 40 – 2381 2046, FAX: 91 – 40 - 23811576	• Analysis of raw material, in process and finished products

Manufacturer of Hydrochlorothiazide:

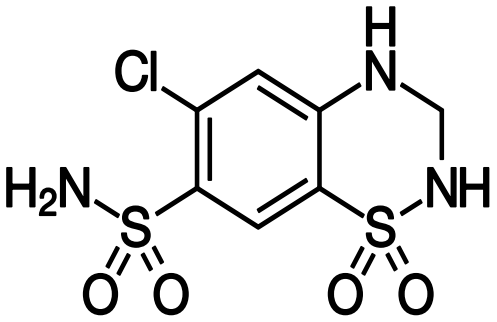
Site	Address	Responsibility
Administrative	**Unichem Laboratories Limited** Plot No T 47, 5 Star MIDC, Kolhapur, Maharashtra State, India - 416 236 Phone: 910231 - 2305221	• To arrange for raw material, solvents, chemical and engineering items required for production of bulk drug. • To arrange dispatch of goods at various places and export
Production	**Unichem Laboratories Limited** Plot No T 47, 5 Star MIDC, Kolhapur, Maharashtra State, India - 416 236 Phone: 910231 - 2305221	• Production and packing
Analysis	**Unichem Laboratories Limited** Plot No T 47, 5 Star MIDC, Kolhapur, Maharashtra State, India - 416 236 Phone: 910231 - 2305221	• Analysis of raw material, in process and finished products

2.3.S.3 Characterisation

Physico Chemical Characterization (Telmisartan):

Physical Form	: White Crystalline powder
Structural Formula	
Molecular Formula	: C33H30N4O2
Molecular weight	: 514.617 g/mol
Melting temperature	: 267°C
Solubility	: Practically insoluble in water, slightly soluble in Methanol, sparingly soluble in methylene chloride.

Physico Chemical Characterization (Hydrochlorothiazide):

Physical Form	: White Crystalline powder, odorless
Structural Formula	
Molecular Formula	: C7H8ClN3O4S2
Molecular weight	: 297.741 g/mol
Melting temperature	: 265°C
Solubility	: Soluble in acetone; sparingly soluble in ethanol (95%); very slightly soluble in water. It dissolves in dilute solution of alkali hydroxides.

2.3.S.4 Control of Drug Substance

Name of drug substance: Telmisartan

Name of Manufacturer: Vasudha Pharma Chem. Limited.

Specification of Telmisartan

	VASUDHA PHARMA CHEM LIMITED **78/A, Vengalrao Nagar, Hyderabad-500 038** **Telangana State, India** **Phone: 91-40-2381, 23711717, FAX: 91-40-2381 1576** E-Mail: vashudha@vasudhapharma.com Website: www.vashudhapharma	**Page 1 of 2**
	CERTIFICATE OF ANALYSIS	

Name of the product	:	Telmisartan IP			
Batch Number	:	BTLS/2308081-U	**Analyzed on**	:	28/08/2023
Manufacturing Date	:	JUL2023	**Retest Date**	:	JUN 2028
Quantity	:	216.00 kg	**A.R.No**	:	BFP/232609

Sr. No	Test	Specification
1.0	Description	A white to off-white crystalline powder.
2.0	Solubility	Practically insoluble in water, slightly soluble in Methanol, sparingly soluble in methylene chloride
3.0	Identification by IR	The IR absorption spectrum of the test sample should be concordant with the spectrum of working standard.
4.0	TESTS	
4.1	Appearance of solution	Not more intensely coloured than reference solution YS4
4.2	Related substances by HPLC (%)	
	Any other individual impurity	Not more than 0.2
	Total impurities	Not more than 1.0
4.3	Heavy metals (ppm)	Not more than 20
4.4	Sulphated ash (% w/w)	Not more than 0.10
4.5	Loss on Drying (% w/w)	Not more than 0.50
4.6	Assay (By HPLC, on dried basis, % w/w)	Not less than more 98.0 and Not less than more 102.0

5.0	Additional tests	
5.1	Residual solvents/Organic volatile impurities (By GC, ppm)	
	Methanol (MeOH)	Not more than 3000
	Methyl Acetate (MA)	Not more than 5000
	Methylene dichloride (MDC)	Not more than 600
	n – Butanol (NB)	Not more than 5000
	Methyl Isobutyl Ketone (MIBK)	Not more than 2250
	Toluene (TOL)	Not more than 890
5.2	Particle size (by Malvern 2000, %, um)	
	D (0.1)	For information
	D (0.5)	For information
	D (0.9)	For information

Prepared By:	Checked By:	Approved By:

DADASAHEB BALPANDE COLLEGE OF PHARMACY * BESA, NAGPUR-37 * SEAL

Name of drug substance: Hydrochlorothiazide

Name of Manufacturer: Unichem Laboratories Limited.

Specification of Hydrochlorothiazide

UNICHEM LABORATORIES LTD	Plot No T 47, 5 Star MIDC, Tal – Hatkannagle, Kagal, Kolhapur 416236		
CERTIFICATE OF ANALYSIS (Finished Product (For API))			
Product: HYDROCHOLOROTHAZIDE API			
Batch No.	KHTP200021	LIMS A.R.No.	KHFP2000139
Product Code	10000028	SAP Inspection Lot No	040000243742
Specification Id	GA/APIS/HCT01/6.00	STP No	GA/APISTP/HCT01/6.00
Mfg. Date	Jun - 2020	Date Of Release	444.18 Kg

Sr. No	TEST	SPECIFICATION
1	Description	White or almost white, crystalline powder, odourless
2	Solubility	Soluble in acetone; sparingly soluble in ethanol (95%); very slightly soluble in water. It dissolves in dilute solution of alkali hydroxides
3	Identification	
3.1	Identification by IR	The IR spectrum of sample should be concordant with the spectrum obtained with hydrochlorothiazide working standard or with the reference spectrum of hydrochlorothiazide
3.2	Identification by UV	The light absorption in the range of 230nm to 300nm of a 0.001% w/v sample solution should exhibit absorbance between 0.5 and 0.54 at a wavelength of about 273nm.the light absorption in the range 300 to 360nm of a 0.005% w/v of a sample solution should exhibit absorbance between 0.45 and 0.48 about 323nm
3.3	Identification by TLC	The principle spot in the chromatogram obtained with the test solution should correspond to that obtained with reference solution
3.4	Reaction with chromotropic acid sodium salt	A Violet colour develops
4	Acidity or Alkalinity	Sample solution is yellow and not more than 0.4ml of 0.01 M hydrochloric acid is required to change colour of the solution to red

5	Chloride (ppm)	NMT 250 ppm
6	Related substance by HPLC (%w/w)	
6.1	Any other unknown Individual Impurity	NMT 0.5%
6.2	Total Impurities	NMT 1.0%
7	Sulphated ash (%w/w)	Not more than 0.5%
8	Loss on drying	Not more than 0.5%Between 98.0% and 102.0%
9	Assay by HPLC (on dried basis) (%w/w)	Between 98.0% and 102%

Prepared by:	Checked by:	Approved by:

DADASAHEB BALPANDE COLLEGE OF PHARMACY • BESA, NAGPUR-37 • SEAL

2.3.S.5 Reference Standards or Materials

Telmisartan and Hydrochlorothiazide both are a pharmacopeial product. The sample batch is first prepared, characterized, and used as standard.

2.3.S.6 Container Closure System

API is packed in suitable clean polythene zip lock bags; 30g pack, sealed, tagged, and labelled and then packed in HDPE Drums.

The HDPE Drums are sealed and labelled. The labels give details such as:

i. Name of the product

ii. Manufacturing license number

iii. Batch number with manufacturing and expiry dates

iv. Quantity of the material packed

v. Storage conditions

vi. Name and address of the company

The labels are checked regularly for colour shade, printed matter, and size to maintain the consistency. Polythene bags, drums are also regularly checked for quality.

2.3.S.7 Stability

Proposed storage conditions and re-test period (or shelf-life, as appropriate) for Telmisartan and Hydrochlorothiazide API:

Container closure system	Storage statement	Shelf life
API is packed in suitable clean polythene zip lock bags; 30g pack, sealed, tagged, and labelled and then packed in HDPE Drums	Store in an airtight container, protected from light. Stability conditions: 40°C ± 2°C & 75 ± 5% RH 25°C ± 2°C & 60 ± 5% RH	60 Months

2.3.P Drug Product

2.3.P.1 Description and Composition of the Drug Product

Qualitative and quantitative formula

Batch 1

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (30 Tablets in mg)	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	219 mg	NA	6,570	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Sodium Starch Glycolate	USP	6 mg	NA	180	Disintegrant

Batch 2

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (30 Tablets in mg)	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	201 mg	NA	6,030	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Sodium Starch Glycolate	USP	24 mg	NA	720	Disintegrant

Batch 3

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (30 Tablets in mg)	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	222 mg	NA	6,600	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Croscarmellose Sodium	USP	3 mg	NA	90	Disintegrant

Batch 4

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (1.00 Lac Tablets in Kg	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	211.5 mg	NA	6,345	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Croscarmellose Sodium	USP	13.5 mg	NA	405	Disintegrant

Batch 5

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (1.00 Lac Tablets in Kg	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	221 mg	NA	6,645	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Crospovidone	USP	4 mg	NA	120	Disintegrant

Batch 6

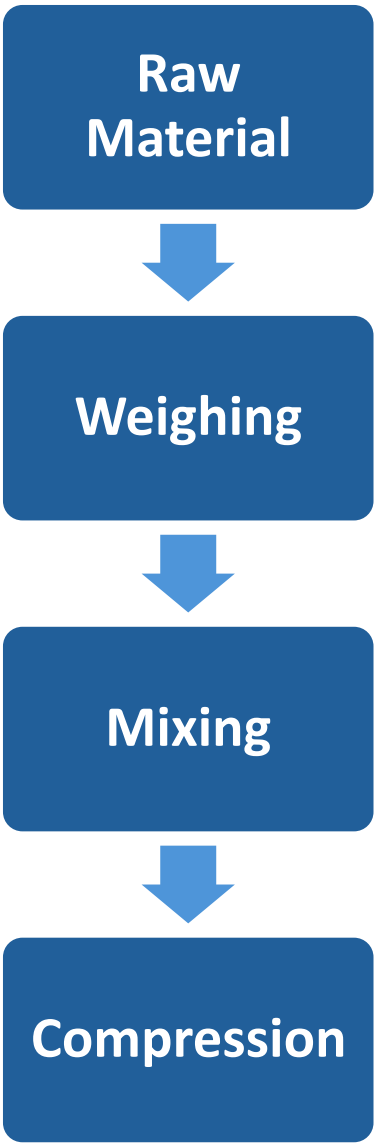
Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (1.00 Lac Tablets in Kg	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	221 mg	NA	6,645	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Crospovidone	USP	4 mg	NA	120	Disintegrant

2.3.P.2 Pharmaceutical Development

The following procedure is established for development of the product

1. Two trial batches are formulated and evaluated for all parameters.
2. Those batches who shows good results are selected.
3. Selected trial batch will be under go for further production.

Direct Compression method is used for production of further formulations. The process is as follow:



2.3.P.3 Manufacture

Information about manufacture

Site	Address
Administrative	**Dadasaheb Balpande College of Pharmacy:** Near Shree Swami Samarth Dham Mandir Manewada Road, Besa Square, Nagpur, Maharashtra 440037 **Tel:** 07103281244
Production, Quality Control & Quality Assurance	**Dadasaheb Balpande College of Pharmacy:** Near Shree Swami Samarth Dham Mandir Manewada Road, Besa Square, Nagpur, Maharashtra 440037 **Tel:** 07103281244

2.3.P.4 Control of Excipients

List of excipients used in the formulation of Telmisartan and Hydrochlorothiazide Combination tablet are as follows

Sr. No	Name of Excipients	Grade
1.	Avicel PH 102 (MCC)	USP
2.	Aerosil	USP
3.	Talc	USP
4.	Sodium Starch Glycolate	USP
5.	Croscarmellose Sodium	USP
6.	Crospovidone	USP

2.3.P.5 Control of Drug Product

	Dadasaheb Balpande Collage of Pharmacy, Nagpur	Page No 1 of 1

Quality Control Department

FINISHED PRODUCT SPECIFICATION

GENERIC NAME	TELMISARTAN AND HYDROCHOLOROTHAZIDE COMBINATION TABLET USP		
SHELF LIFE	2 YEARS		
EFFECTIVE DATE	15 MARCH 2024	**NEXT REVIEW DATE**	15 MARCH 2026
PHARMACOPIAL REFERENCE	UNITED STATE PHARMACOPIA		

LABLE CLAIM:

EACH ORAL TABLET CONTAINS
TELMISARTAN AND HYDROCHOLOROTHAZIDE TABLET USP
COLOUR: WHITE COLOURE
Excipient qs

SAMPLE QUALITY	TESTING SAMPLE: 30 TABLETS CONTROL SAMPLE: 30 TABLETS

Sr No.	TEST	STANDARD
1	Description	White colour circular, biconvex, oral tablets plain on both sides
2	Average Weight	300 mg
3	Uniformity of Weight of Tablets	± 7.5% of average weight
4	Friability	Not more than 1%
5	Thickness	4.30 mm ± 0.20 mm (4.10 – 4.50 mm)
6.	Hardness	Not less than 2.000 Kp
8.	Dissolution test	Not less than 80%
9.	Disintegration test	Not more 30 minutes

APPROVAL		
Prepared By:	**Reviewed By**	**Approved By:**

DADASAHEB BALPANDE COLLEGE OF PHARMACY * BESA NAGPUR-37 * SEAL

2.3.P.6 Reference Standards or Materials

Telmisartan and Hydrochlorothiazide is a pharmacopeial product. An an internal reference standard is prepared, characterized, and used as standard.

The COA of the latest working standard is enclosed in 3.2.S.5

2.3.P.7 Container Closure System

Telmisartan and Hydrochlorothiazide Combination 200 mg Tablets is packed in blister strip. Such 10 blister packed in white board along with leaflet and such 10 inner cartons are placed in 7-Ply corrugated box.

All the packing materials are checked for the compliance with the set in–house specification and only the material complying with the specifications are used for the packing.

2.3.P.8 Stability

Stability Study was carried out at 40°C ± 2°C/75% RH ± 5% condition for 6 months. Each piece of the tablet from the optimized formulation was packed in butter paper followed by aluminium foil. After intervals of 1, 3 and 6 months, the tablet was evaluated for the physical appearance and drug content.

2.4 Non-Clinical overview and

2.6 Non-Clinical Summary

2.5 Clinical Overview and

2.7 Clinical Summary

Non-clinical and clinical studies are not typically required for generic drugs because they are intended to be bioequivalent to the reference (innovator) drug that has already undergone extensive non-clinical testing. Generic drugs are copies of approved reference drugs that have demonstrated safety and efficacy through clinical trials and non-clinical studies during the original drug's development.

Telmisartan and Hydrochlorothiazide Combination Tablets USP is a generic drug application so this part is **NOT APPLICABLE.**

MODULE - 3
QUALITY

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3.2.S.1.2	Structure
3.2.S.1.3	General properties
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3.2.S.2.2	Description of manufacturing process and process controls
3.2.S.2.3	Control of materials
3.2.S.2.4	Controls of critical steps and intermediates
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3.2.S.3.1	Elucidation of Structure and other Characteristics
3.2.S.3.2	Impurities
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3.2.S.4.5	Justification of specification
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3.2.S.7.1	Stability summary and conclusion
3.2.S.7.2	Post approval stability protocol and stability commitment
3.2.S.7.3	Stability data
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3.2.P.2.1.2	Excipients
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3.2.P.3.3	Description of manufacturing process and process controls
3.2.P.3.4	Controls of critical steps and intermediates
3.2.P.3.5	Process validation and/or evaluation
3.2.P.4	**Control of excipients**
3.2.P.4.1	Specifications

3.2.P.4.2	Analytical procedures
3.2.P.4.3	Validation of analytical procedures
3.2.P.4.4	Justifications of specifications
3.2.P.4.5	Excipients of human or animal origin
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3.2.P.5	**Control of drug product**
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3.2.P.5.2	Analytical procedures
3.2.P.5.3	Validation of analytical procedures
3.2.P.5.4	Batch analyses
3.2.P.5.5	Characterisation of impurities
3.2.P.5.6	Justification of specification(s)
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3.2.P.8	**Stability**
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3.2.A.2	Adventitious agents safety evaluation
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3.2.R.1.2	Master production documents
3.2.R.2	Analytical procedures and validation information

3.2. Body of Data

3.2.S Drug Substance

3.2.S.1 General Information

Name of drug substance: Telmisartan

Name of Manufacturer: Vasudha Pharma Chem. Limited, Hyderabad - 500 038

Name of drug substance: Hydrochlorothiazide

Name of Manufacturer: Unichem Laboratories Limited, Kolhapur – 416 236

3.2.S.1.1 Nomenclature

Drug Name: Telmisartan

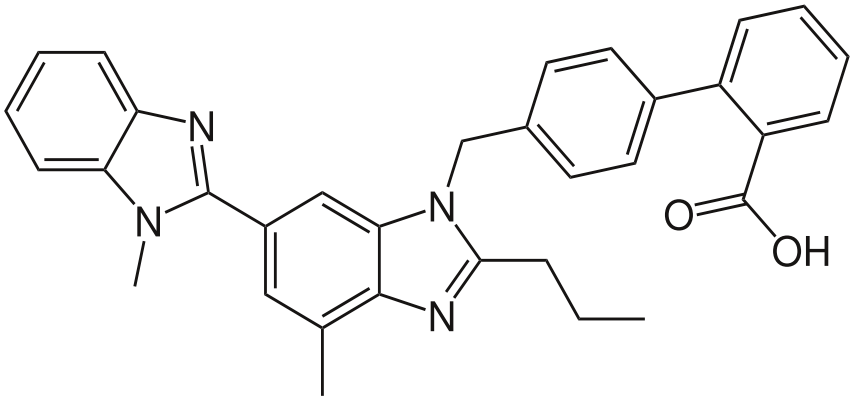
Recommended international non-proprietary (rINN)	Telmisartan
IUPAC	2-(4-{[4-Methyl-6-(1-methyl-1H-1,3-benzodiazol-2-yl)-2-propyl-1H-1,3-benzodiazol-1-yl] methyl} phenyl) benzoic acid
CAS No	144701-48-4

Drug Name: Hydrochlorothiazide

Recommended international non-proprietary (rINN)	Hydrochlorothiazide
IUPAC	6-chloro-1,1-dioxo-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide
CAS No	58-93-5

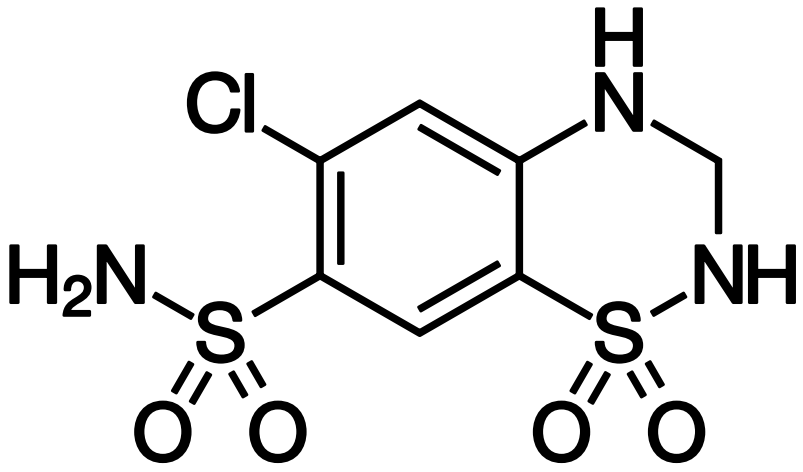
3.2.S.1.2 Structure

Structure of Telmisartan



Molecular Formula	C33H30N4O2
Molecular weight	514.617 g/mol
Therapeutic category	Angiotensin II receptor antagonists

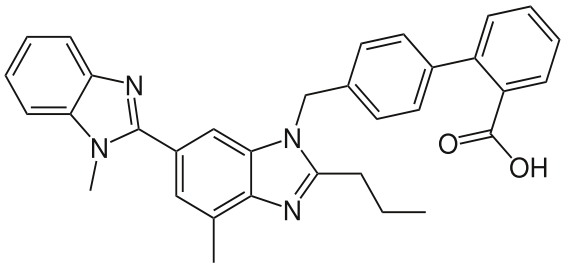
Structure of Hydrochlorothiazide



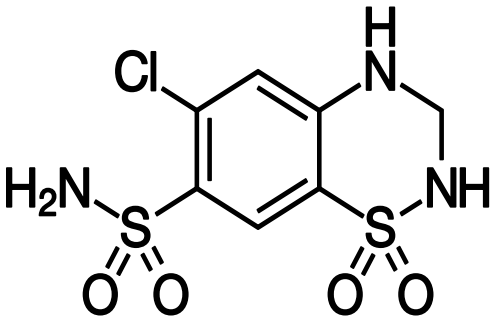
Molecular Formula	C7H8ClN3O4S2
Molecular weight	297.741 g/mol
Therapeutic category	Thiazide-type diuretic

3.2.S.1.3 General Properties

Physico Chemical Characterization (Telmisartan):

Physical Form	: White Crystalline powder
Structural Formula	
Molecular Formula	: C33H30N4O2
Molecular weight	: 514.617 g/mol
Melting temperature	: 267°C
Solubility	: Practically insoluble in water, slightly soluble in Methanol, sparingly soluble in methylene chloride.

Physico Chemical Characterization (Hydrochlorothiazide):

Physical Form	: White Crystalline powder, odorless
Structural Formula	
Molecular Formula	: C7H8ClN3O4S2
Molecular weight	: 297.741 g/mol
Melting temperature	: 265°C
Solubility	: Soluble in acetone; sparingly soluble in ethanol (95%); very slightly soluble in

water. It dissolves in dilute solution of alkali hydroxides.

3.2.S.2 Manufacture

Name of drug substance: Telmisartan

Name of Manufacturer: Vasudha Pharma Chem. Limited, Hyderabad - 500 038

Name of drug substance: Hydrochlorothiazide

Name of Manufacturer: Unichem Laboratories Limited, Kolhapur – 416 236

3.2.S.2.1 Manufacturer(s)

Manufacturer of Telmisartan:

Site	Address	Responsibility
Administrative	**Vasudha Pharma Chem Limited** 78/A, Vengalrao Nagar, Hyderabad, Telangana State, India - 500 038 Phone: 91- 40 – 2381 2046, FAX: 91 – 40 - 23811576	• To arrange for raw material, solvents, chemical and engineering items required for production of bulk drug. • To arrange dispatch of goods at various places and export
Production	**Vasudha Pharma Chem Limited** 78/A, Vengalrao Nagar, Hyderabad, Telangana State, India - 500 038 Phone: 91- 40 – 2381 2046, FAX: 91 – 40 - 23811576	• Production and packing
Analysis	**Vasudha Pharma Chem Limited** 78/A, Vengalrao Nagar, Hyderabad, Telangana State, India - 500 038 Phone: 91- 40 – 2381 2046, FAX: 91 – 40 - 23811576	• Analysis of raw material, in process and finished products

Manufacturer of Hydrochlorothiazide:

Site	Address	Responsibility
Administrative	**Unichem Laboratories Limited** Plot No T 47, 5 Star MIDC, Kolhapur, Maharashtra State, India - 416 236 Phone: 910231 - 2305221	• To arrange for raw material, solvents, chemical and engineering items required for production of bulk drug. • To arrange dispatch of goods at various places and export
Production	**Unichem Laboratories Limited** Plot No T 47, 5 Star MIDC, Kolhapur, Maharashtra State, India - 416 236 Phone: 910231 - 2305221	• Production and packing
Analysis	**Unichem Laboratories Limited** Plot No T 47, 5 Star MIDC, Kolhapur, Maharashtra State, India - 416 236 Phone: 910231 - 2305221	• Analysis of raw material, in process and finished products

3.2.S.2.2 Description of Manufacturing Process and Process Controls

API is not manufactured within the industry, it is outsourced. Details are as follows;

Name of drug substance: Telmisartan

Name of Manufacturer: Vasudha Pharma Chem. Limited, Hyderabad - 500 038

Name of drug substance: Hydrochlorothiazide

Name of Manufacturer: Unichem Laboratories Limited, Kolhapur – 416 236

3.2.S.2.3 Control of Materials

List of raw material (s),

Sr. No.	Raw Material (s)
1	Avicel PH 102 (MCC)
2	Talc
3	Aerosil
4	Sodium Starch Glycolate
5	Croscarmellose sodium
6	Crospovidone

All the raw materials used in the manufacturing process are checked for the quality as per the set specifications. All the raw materials are procured from authentic source and from validated vendors only.

3.2.S.2.4 Controls of Critical Steps and Intermediates

During the manufacturing process the critical process parameter like mixing the material, compression and temperature as these parameters can affect the quality or yield of the product they are identified, studied, and controlled to maintain the quality and yield of the product.

During the scale up these critical process parameters are studied again and are duly revised to get consistent quality and yield.

3.2.S.2.5 Process Validation and/or Evaluation

NOT APPLICABLE

Justification: This section contains details about how the process validation and Evaluation. As we have purchased the API's and raw materials from the other company. So, this section is not applicable.

3.2.S.2.6 Manufacturing Process Development

NOT APPLICABLE

Justification: This section contains details about how the manufacturing process of drug substance. As we have purchased the API's and raw materials from the other company. So, this section is not applicable.

3.2.S.3 Characterisation

3.2.S.3.1 Elucidation of Structure and other Characteristics

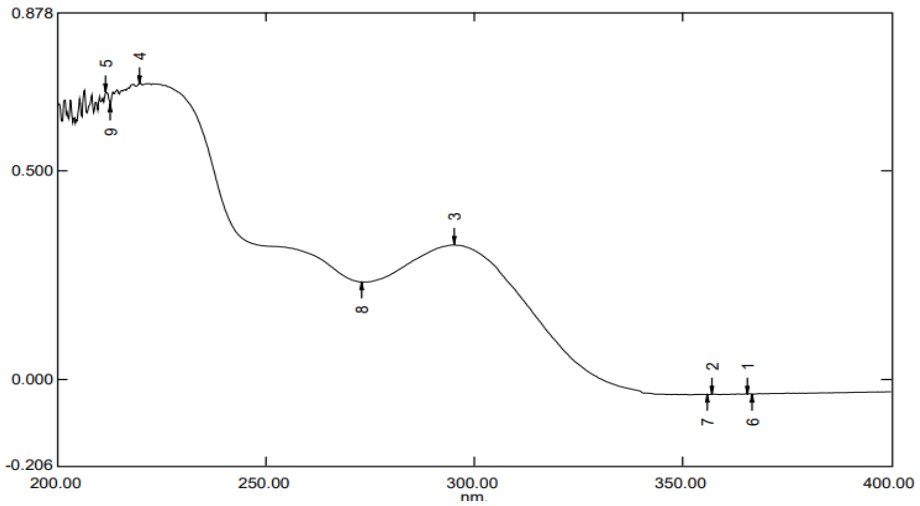
Evidence of chemical structure

The elucidation of structure of Telmisartan and Hydrochlorothiazide is based on appropriate physical and chemical test results.

1. UV spectrum
2. IR spectrum

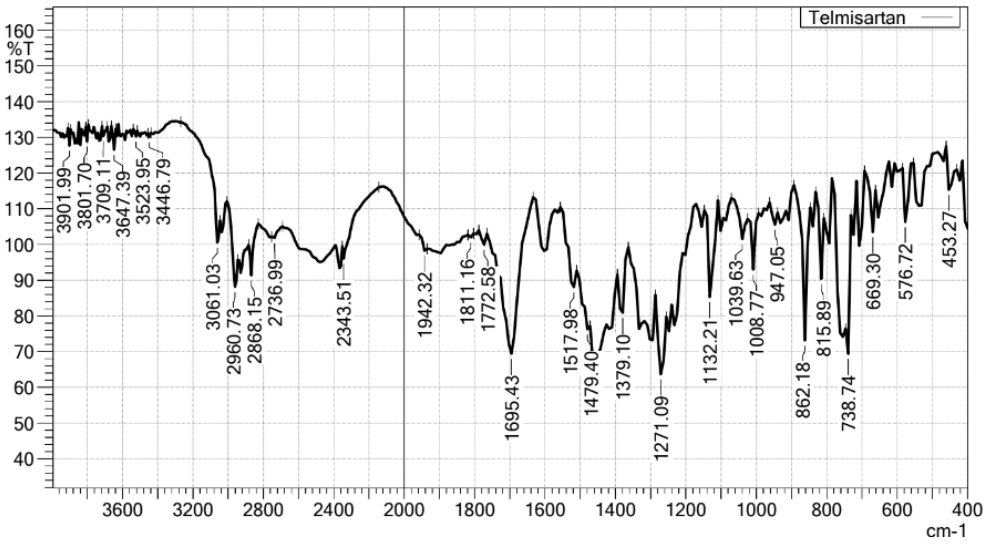
3.2.S.3.1.1 UV Analysis of Telmisartan

Instrument: The UV spectrum was generated using a SHIMADZU UV-1800 Spectrophotometer



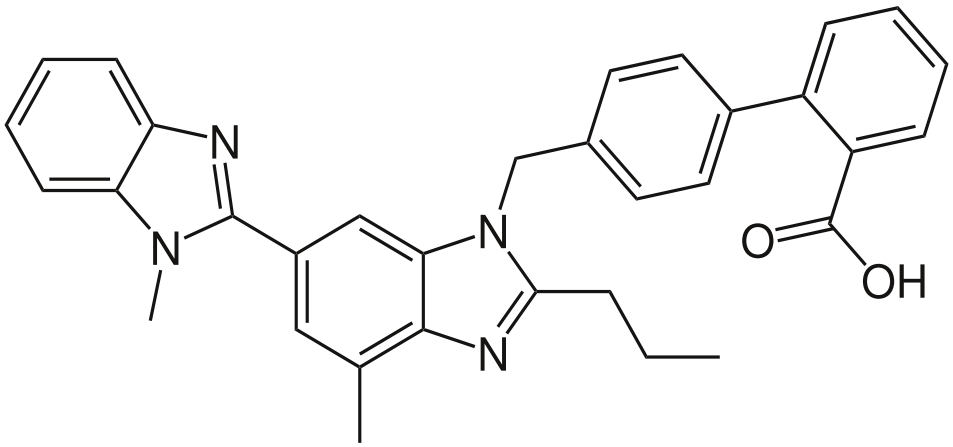
3.2.S.3.1.2 IR Spectrum of Telmisartan

Instrument: The IR spectrum of Telmisartan is recorded on FT-IR DRS 800.



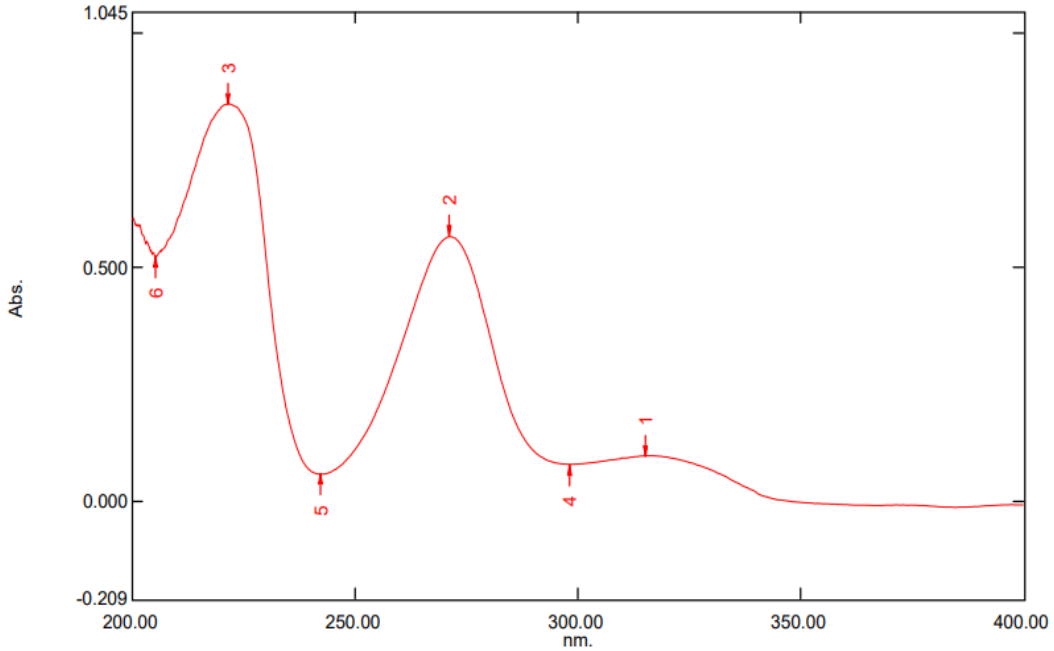
Conclusion:

The UV analysis of Telmisartan is in close agreement with the theoretically excepted values. The wavelength of Telmisartan sample obtained by UV analysis matches with the wavelength of Telmisartan standard confirming the identity of the compound. Based on the analytical data above, it understands that the Telmisartan sample has the structure as following.



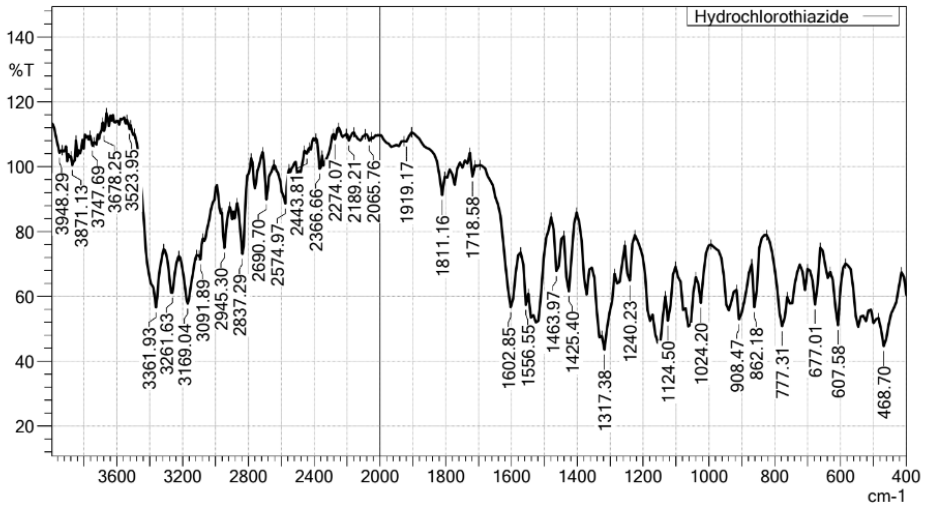
3.2.S.3.1.3 UV Analysis of Hydrochlorothiazide

Instrument: The UV spectrum was generated using a SHIMADZU UV-1800 Spectrophotometer



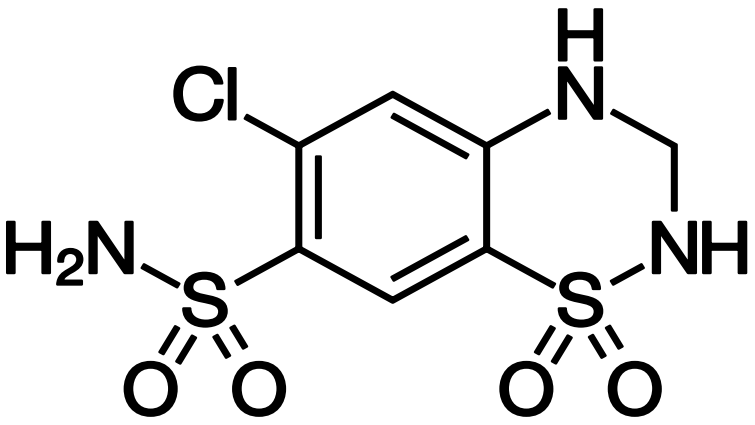
3.2.S.3.1.4 IR Spectrum of Hydrochlorothiazide

Instrument: The IR spectrum of Hydrochlorothiazide is recorded on FT-IR DRS 800.



Conclusion:

The UV analysis of Hydrochlorothiazide is in close agreement with the theoretically excepted values. The wavelength of Hydrochlorothiazide sample obtained by UV analysis matches with the wavelength of Hydrochlorothiazide standard confirming the identity of the compound. Based on the analytical data above, it understands that the Hydrochlorothiazide sample has the structure as following.



3.2.S.3.2 Impurities

NO APPLICABLE

Justification: This section contains the results of impurities present in the drug substances. As we have purchased the API's and raw materials from the other company. So, this section is not applicable.

3.2.S.4 Control of Drug Substance

3.2.S.4.1 Specification

Name of drug substance: Telmisartan

Name of Manufacturer: Vasudha Pharma Chem. Limited, Hyderabad - 500 038

Specification of Telmisartan

	VASUDHA PHARMA CHEM LIMITED 78/A, Vengalrao Nagar, Hyderabad-500 038 Telangana State, India Phone: 91-40-2381, 23711717, FAX: 91-40-2381 1576 E-Mail: vashudha@vasudhapharma.com Website: www.vashudhapharma	Page 1 of 2
	CERTIFICATE OF ANALYSIS	

Name of the product	:	Telmisartan IP			
Batch Number	:	BTLS/2308081-U	**Analyzed on**	:	28/08/2023
Manufacturing Date	:	JUL2023	**Retest Date**	:	JUN 2028
Quantity	:	216.00 kg	**A.R.No**	:	BFP/232609

Sr. No	Test	Specification
1.0	Description	A white to off-white crystalline powder.
2.0	Solubility	Practically insoluble in water, slightly soluble in Methanol, sparingly soluble in methylene chloride
3.0	Identification by IR	The IR absorption spectrum of the test sample should be concordant with the spectrum of working standard.
4.0	TESTS	
4.1	Appearance of solution	Not more intensely coloured than reference solution YS4
4.2	Related substances by HPLC (%)	
	Any other individual impurity	Not more than 0.2
	Total impurities	Not more than 1.0
4.3	Heavy metals (ppm)	Not more than 20
4.4	Sulphated ash (% w/w)	Not more than 0.10
4.5	Loss on Drying (% w/w)	Not more than 0.50
4.6	Assay (By HPLC, on dried basis, % w/w)	Not less than more 98.0 and Not less than more 102.0

5.0	Additional tests	
5.1	Residual solvents/Organic volatile impurities (By GC, ppm)	
	Methanol (MeOH)	Not more than 3000
	Methyl Acetate (MA)	Not more than 5000
	Methylene dichloride (MDC)	Not more than 600
	n – Butanol (NB)	Not more than 5000
	Methyl Isobutyl Ketone (MIBK)	Not more than 2250
	Toluene (TOL)	Not more than 890
5.2	Particle size (by Malvern 2000, %, um)	
	D (0.1)	For information
	D (0.5)	For information
	D (0.9)	For information

Prepared By:	Checked By:	Approved By:

DADASAHEB BALPANDE COLLEGE OF PHARMACY * BESA, NAGPUR-37 * SEAL

Name of drug substance: Hydrochlorothiazide

Name of Manufacturer: Unichem Laboratories Limited, Kolhapur – 416 236

Specification of Hydrochlorothiazide

UNICHEM LABORATORIES LTD	Plot No T 47, 5 Star MIDC, Tal – Hatkannagle, Kagal, Kolhapur 416236		
CERTIFICATE OF ANALYSIS (Finished Product (For API))			
Product: HYDROCHOLOROTHAZIDE API			
Batch No.	KHTP200021	LIMS A.R.No.	KHFP2000139
Product Code	10000028	SAP Inspection Lot No	040000243742
Specification Id	GA/APIS/HCT01/6.00	STP No	GA/APISTP/HCT01/6.00
Mfg. Date	Jun - 2020	Date Of Release	444.18 Kg

Sr. No	TEST	SPECIFICATION
1	Description	White or almost white, crystalline powder, odourless
2	Solubility	Soluble in acetone; sparingly soluble in ethanol (95%); very slightly soluble in water. It dissolves in dilute solution of alkali hydroxides
3	Identification	
3.1	Identification by IR	The IR spectrum of sample should be concordant with the spectrum obtained with hydrochlorothiazide working standard or with the reference spectrum of hydrochlorothiazide
3.2	Identification by UV	The light absorption in the range of 230nm to 300nm of a 0.001% w/v sample solution should exhibit absorbance between 0.5 and 0.54 at a wavelength of about 273nm.the light absorption in the range 300 to 360nm of a 0.005% w/v of a sample solution should exhibit absorbance between 0.45 and 0.48 about 323nm
3.3	Identification by TLC	The principle spot in the chromatogram obtained with the test solution should correspond to that obtained with reference solution
3.4	Reaction with chromotropic acid sodium salt	A Violet colour develops
4	Acidity or Alkalinity	Sample solution is yellow and not more than 0.4ml of 0.01 M hydrochloric acid is required to change colour of the solution to red

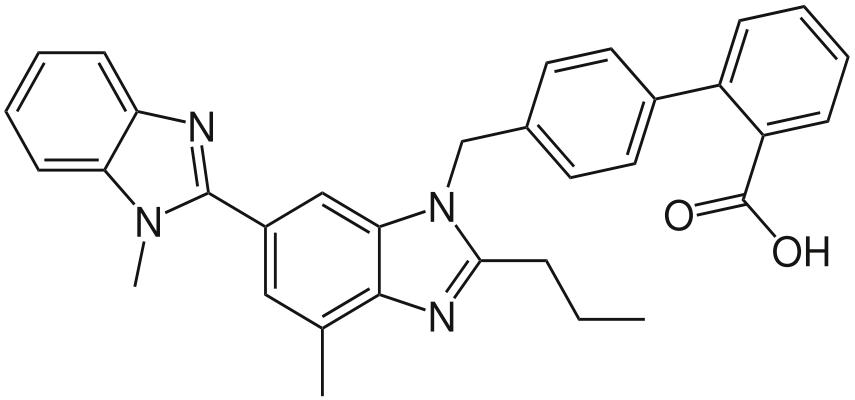
5	Chloride (ppm)	NMT 250 ppm
6	Related substance by HPLC (%w/w)	
6.1	Any other unknown Individual Impurity	NMT 0.5%
6.2	Total Impurities	NMT 1.0%
7	Sulphated ash (%w/w)	Not more than 0.5%
8	Loss on drying	Not more than 0.5%Between 98.0% and 102.0%
9	Assay by HPLC (on dried basis) (%w/w)	Between 98.0% and 102%

Prepared by:	Checked by:	Approved by:

DADASAHEB BALPANDE COLLEGE OF PHARMACY * BESA, NAGPUR-37 *
SEAL

3.2.S.4.2 Analytical Procedures

3.2.S.4.2.1 Analytical Procedures for Telmisartan



Chemical Formula: $C_{33}H_{30}N_4O_2$ Molecular Weight: 514.62 g/mol

1,1-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'- propyl [2,6'-bi-1H-benzimidazol]-1-yl)methyl-]; 4-[[4-Methyl-6-(1-methyl-2-benzimidazolyl)-2-propyl-1- benzimidazolyl]methyl]-2-biphenylcarboxylic acid [144701-48-4].

DEFINITION:

Telmisartan contains NLT 98.0% and NMT 101.0% of C33H30N4O2, calculated on the dried basis.

Identification:

Change to read

A. SPECTROSCOPIC IDENTIFICATION TESTS (197), Infrared Spectroscopy:

197K (CN 1-May-2020): USP Telmisartan RS[NOTE-Heating the solution may be necessary for complete dissolution.) Cool the solution in an ice bath, filter the crystals, and dry at 105°.

B. The retention time of the major peak from the Sample solution corresponds to that from the Standard solution, as obtained in the test for Organic Impurities.

ASSAY

PROCEDURE (See Titrimetry (541).)

Sample solution: 190 mg of Telmisartan in 5 ml. of anhydrous formic acid. Dilute with 75 mL of acetic anhydride.

Analysis: Titrate with 0.1 M perchloric acid versus a blank determination under the same conditions. Each mL of 0.1 M perchloric acid is equivalent to 25.73 mg Of C33H30N4O2

Acceptance criteria: 98.0%-101.0% on the dried basis

IMPURITIES

RESIDUE ON IGNITION (281); NMT 0.1%. A 1-g sample is used.

ORGANIC IMPURITIES

[NOTE-Freshly prepare sample solutions, and protect from light.]

Solution A: 2.0 g of monobasic potassium phosphate and 3.8 g of sodium 1-pentanesulfonate in 1 L'of water. Adjust with 1 M phosphoric acid to a pH of 3.0.

Solution B: Acetonitrile and methanol (4:1)

Mobile phase: See Table 1.

Table 1: Mobile Phase

Time (Min)	Solution A %	Solution B %
0	70	30
2	70	30
27	20	80
32	20	80
32.1	70	30
37	70	30

System suitability solution:

Dissolve USP Telmisartan RS and USP Telmisartan Related Compound B RS in methanol (0.2 mL/mg of USP Telmisartan RS) and 100 µl of 1 M sodium hydroxide solution. Sonicate to dissolve. The final concentration is 2.5 mg/mL of the USP Telmisartan RS and 2.5 µg/mL of USP Telmisartan Related Compound B RS in methanol.

Standard solution:

Dissolve USP Telmisartan RS in methanol (0.2 mL/mg of USP Telmisartan RS) and 100 µε of 1 M sodium hydroxide solution. Sonicate to dissolve. The final concentration is 0.025 mg/mL.

Sample Solution:

Dissolve Telmisartan in methanol (0.2 mL/mg of Telmisartan) and 100 µL of 1 M sodium hydroxide solution. Sonicate to dissolve. The final concentration is 2.5 mg/ml.

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 230 nm

Column: 4.0-mm x 12.5-cm; 5-µm packing L1

Column temperature: 40"

Flow rate: 1 ml/min

Injection size: 2 µL

System suitability sample: System suitability solution and Standard solution

Suitability Requirement Resolution: NLT 3.0 between telmisartan and telmisartan related compound B, system suitability solution

Tailing factor: Between 0.9 and 1.5 for telmisartan related compound B, System suitability solution

Relative Standard deviation: NMT 5.0% for the telmisartan peak, standard solution

Analysis Samples: Standard solution and Sample solution calculate the percentage of any individual impurity in the portion of telmisartan taken:

$$\text{Result} = (r_u/r_s) \times (C_u/C_s) \times 100$$

Were,

r_u: peak response of each impurity from the Sample solution.
r_s: Peak response of telmisartan from the standard solution
c_s: Concentration of USP telmisartan RS in the standard solution
c_u: Concentration of telmisartan in the sample solution

Acceptance criteria:

See Table 2. [NOTE-Calculate the total impurities from the sum of all impurity peaks greater than or equal to 0.05%.]

Table 2: Acceptance Criteria

Name	Relative Retention Time	Acceptance Criteria NMT%
Telmisartan related compound A[a]	0.3	0.1
Telmisartan amide[b]	0.7	0.1
Telmisartan related compound B[C]	0.9	0.1
Telmisartan diacide[d]	0.67	0.1
Telmisartan tert-butyl ester[e]	1.7	0.2
Telmisartan unknown impurity	1.8	0.2
Any other individual impurity	-	0.1
Total impurities	-	1.0

SPECIFIC TESTS

LOSS ON DRYING (731):

Dry 1.0 g of the sample at 105° to constant weight: it loses NMT 1.5%.

Additional requirement

Packaging And Storage: Preserve in tight containers, and protect from light

USP References (11): USP Telmisartan RS

USP Telmisartan Related Compound B RS

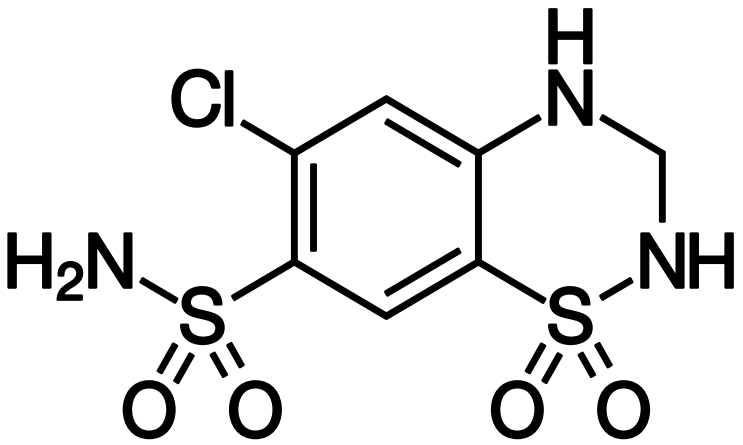
4'-[(1,7'-Dimethyl-2'-propyl-1H,1'H-2,5'-bibenzo[d] imidazol-1'-yl) methyl] biphenyl-2-carboxylic acid.

Molecular Formula: $C_{33}H_{30}N_4O_2$

Molecular Weight: 514.62

3.2.S.4.2.2 Analytical Procedures for Hydrochlorothiazide

Structure



Molecular Formula: C7H8ClN3O4S2 Molecular Weight: 514.617 g/mol

DEFINITION

Hydrochlorothiazide contains NLT 98.0% and NMT 102.0% solution of hydrochlorothiazide (C7H8ClN3O4S2), calculated on the Analysis dried basis.

IDENTIFICATION

(C7H8ClN3O4S2) in the portion of Hydrochlorothiazide

A. INFRARED ABSORPTION

Sample: Potassium bromide–hydrochlorothiazide mixture, previously heated at 105° for 2 h

Acceptance criteria: Meets the requirements

B. ULTRAVIOLET ABSORPTION ⟨197U⟩

Sample: 25 mL Sample solution: 10 µg/mL in methanol Blank: 25 mL water.

Acceptance criteria: Meets the requirement

ASSAY

Procedure

Buffer: 2.76 g of monobasic sodium phosphate in a Endpoint detection: 1000-mL volumetric flask. Add 990 mL of water. Adjust Visual Analysis: Place Sample in a conical flask, add methyl with phosphoric acid to a pH of 2.7 ± 0.1, and dilute with water to volume.

Diluent: Acetonitrile and Buffer (3:7)

Solution A: Acetonitrile and methanol (3:1)

Solution B: Anhydrous formic acid in water (5 in 1000)

Mobile phase: See Table 1.

Table 1: Mobile Phase

Time (Min)	Solution (A)	Solution (B)
0	3	97
5	3	97
14	36	64
18	3	97
20	3	97

System suitability solution:

0.32 mg/mL of USP Hydrochlorothiazide RS, 0.0032 mg/mL of USP Chlorothiazide RS, and 0.0032 mg/mL of USP Benzothiadiazide Related Compound A RS in Diluent; sonicate if necessary to dis-solve. Pass a portion through a filter of 0.45-µm or finer pore size.

Standard Solution:

0.32 mg/mL of USP Hydrochlorothiazide RS in Diluent. Sonicate if necessary to dissolve Pass a portion through a filter of 0.45-µm or finer pore size.

Sample solution:

0.32 mg/ml of Hydrochlorothiazide in diluent, prepared as follows. Transfer 32 mg of Hydrochlorothiazide into a 100 ml volumetric flask. Add 70 ml of diluent, sonicate for 10 min if necessary to dissolve and allow to cool to ambient temperature. Dilute with diluent to volume. Pass a portion through a filter of 0.045 -µm or fine pore size.

Chromatographic System

(See Chromatography 621, System Suitability)

Mode: LC

Detector: UV 275 nm

Column: 4.6-mm × 5-cm; 3.5-µm packing L1

Column temperature: 35°

Flow rate: 1 mL/min

Injection volume: 10 µL System suitability

Samples: System suitability solution and Standard solution

NOTE - See Table 2 for the relative retention times.] Chromatograph the Diluent to check for interference by system-related peaks.

Suitability requirements

Resolution: NLT 2.0 between benzothiadiazine related compound A and chlorothiazide and NLT 1.5 between chlorothiazide and hydrochlorothiazide, System suitability solution

Tailing factor: NMT 1.5 for the peaks for benzothiadiazine related compound A, chlorothiazide, and hydrochlorothiazide, System suitability solution

Relative standard deviation: NMT 1.0%, Standard solution

Analysis

Samples: Standard solution and Sample solution Calculate the percentage of hydrochlorothiazide ($C_2H_2ClN_3O_4S_2$) in the portion of Hydrochlorothiazide taken:

$$\text{Result} = (r_u/r_s) \times (C_s/C_u) \times 100$$

r_u = peak response of hydrochlorothiazide from the Sample solution

r_s = peak response of hydrochlorothiazide from the Standard solution

C_s = concentration of USP Hydrochlorothiazide RS in the Standard solution (mg/mL)

C_u = concentration of Hydrochlorothiazide in the Sample solution (mg/mL)

Acceptance criteria: 98.0%-102.0% on the dried basis

IMPURITIES

RESIDUE ON IGNITION (281): NMT 0.1%

Chloride and Sulfate, Chloride (221)

Sample solution: Shake 0.50 g with 40 mL of water for 5 min, and filter.

Acceptance criteria: 0.035%; the filtrate shows no more chloride than corresponds to 0.25 mL of 0.020 N hydrochloric acid.

Selenium (291)

Sample: 200 mg

Acceptance criteria: NMT 30 ppm

ADDITIONAL REQUIRMENTS

Packaging and Storage: Preserve in well-closed containers

USP Reference Standards:

USP Benzothiadiazine Related Compound A RS

4-Amino-6-chloro-1,3-benzenedisulfonamide.

Molecular Formula: C6H8CIN3O4S2 Molecular Weight: 285.73

USP Chlorothiazide RS

USP Hydrochlorothiazide RS

3.2.S.4.3 Validation of Analytical Procedures

NOT APPLICABLE

Justification: The analytical procedure followed are those that are specified in the monograph of the United State Pharmacopeia. The methods followed are also exactly those of the United States Pharmacopeia. So, there is no need to validate the analytical procedure.

3.2.S.4.4 Batch Analyses

Batch analytical results of drug substances are provided below:

3.2.S.4.4.1 Certificate of Analysis of Telmisartan

VASUDHA PHARMA CHEM. LIMITED

VASUDHA PHARMA CHEM LIMITED
78/A, Vengalrao Nagar, Hyderabad-500 038,
Telangana State, India
Phone: 91-40-2381 2046, 2371 1717, FAX: 91-40-2381 1576
E-Mail: vasudha@vasudhapharma.com,
Website:www.vasudhapharma.com

Page 1 of 2

CERTIFICATE OF ANALYSIS — QUALITY ASSURANCE RELEASE

Customer Name:

Dispatch Quantity: 215.00 Kg Sign.&Date 9/11/23

Name of the product	:	TELMISARTAN IP	Analyzed on	:	28/08/2023
Batch Number	:	BTLS/2308081-U	Retest Date	:	JUN 2028
Manufacturing Date	:	JUL 2023	A.R.No	:	BFP/232609
Quantity	:	216.00 Kg			

S.No	TEST	RESULT	SPECIFICATION
1.0	Description	White crystalline powder	A white to off-white crystalline powder.
2.0	Solubility	Complies	Practically insoluble in Water, slightly soluble in Methanol, sparingly soluble in methylene chloride.
3.0	Identification by IR	Complies	The IR absorption spectrum of the test sample should be concordant with the spectrum of working standard.
4.0	TESTS		
4.1	Appearance of solution	Complies	Not more intensely coloured than reference solution YS4
4.2	Related Substances by HPLC (%)		
	Any other individual impurity	0.05	Not more than 0.2
	Total impurities	0.21	Not more than 1.0
4.3	Heavy metals (ppm)	Less than 20	Not more than 20
4.4	Sulphated ash (%, w/w)	0.05	Not more than 0.10
4.5	Loss on drying (%, w/w)	0.20	Not more than 0.50
4.6	Assay (By HPLC, on dried basis, %, w/w)	98.8	Not less than 98.0 and Not more than 102.0

	Prepared By	Checked By	Approved By
Signature	P.Es 29/08/2023	Bmme 29/08/23	K.S.R 29/08/2023
Name	P.Eswara Rao	B.Murali Mohana Rao	K.Satyadora
Designation	Executive (QC)	Jr.Manager (QC)	Asst.Manager (QC)

Works: Vasudha Pharma Chem Ltd, Unit-II, Plot No. 79, Jawaharlal Nehru Pharma City, Thanam village ,Parawada (M), Anakapalli-531019, Andhra Pradesh, India.

Format No.: CQA/002/F05/01

VASUDHA PHARMA CHEM. LIMITED

VASUDHA PHARMA CHEM LIMITED
78/A, Vengalrao Nagar, Hyderabad-500 038,
Telangana State, India
Phone: 91-40-2381 2046, 2371 1717, FAX: 91-40-2381 1576
E-Mail: vasudha@vasudhapharma.com
Website:www.vasudhapharma.com

Page 2 of 2

CERTIFICATE OF ANALYSIS

QUALITY ASSURANCE RELEASE
Customer Name:
Dispatch Quantity: 215.00 Kg Sign & Date 05/10/23

Name of the product	:	TELMISARTAN IP			
Batch Number	:	BTLS/2308081-U	Analyzed on	:	28/08/2023
Manufacturing Date	:	JUL 2023	Retest Date	:	JUN 2028
Quantity	:	216.00 Kg	A.R.No	:	BFP/232609

S.No	TEST	RESULT	SPECIFICATION
5.0	Additional tests		
5.1	Residual solvents / Organic volatile impurities (By GC, ppm)		
	Methanol (MeOH)	13	Not more than 3000
	Methyl Acetate (MA)	15	Not more than 5000
	Methylene dichloride (MDC)	Not Detected	Not more than 600
	n-Butanol (NB)	Not Detected	Not more than 5000
	Methyl Isobutyl Ketone (MIBK)	Not Detected	Not more than 2250
	Toluene (TOL)	Not Detected	Not more than 890
5.2	Particle size (by Malvern 2000,%,µm)		
	D(0.1)	1.1	For Information
	D(0.5)	3	For Information
	D(0.9)	11	For Information

REMARKS: The material Complies as per the IP specification.

	Prepared By	Checked By	Approved By
Signature	P.Eswara Rao 29/08/2023	B.Murali Mohana Rao 29/08/23	K.Satyadora 29/08/2023
Name	P.Eswara Rao	B.Murali Mohana Rao	K.Satyadora
Designation	Executive (QC)	Jr.Manager (QC)	Asst.Manager (QC)

Works: Vasudha Pharma Chem Ltd, Unit-II, Plot No. 79, Jawaharlal Nehru Pharma City, Thanam village ,Parawada (M), Anakapalli-531019, Andhra Pradesh, India.

Format No.: CQA/002/F05/01

EFFECTIVE DATE: 01/01/2021

3.2.S.4.4.1 Certificate of Analysis of Hydrochlorothiazide

UNICHEM LABORATORIES LIMITED

Plot No T 47, 5 Star MIDC,
Tal – Hatkannagle, Kagal, Kolhapur 416236

CERTIFICATE OF ANALYSIS
(Finished Product(For API))

Product: HYDROCHLOROTHIAZIDE IP			
Batch No.	KHTP200021	**LIMS A.R. No.**	KHFP2000139
Product Code	10000028	**SAP Inspection Lot No**	040000243742
Specification Id	GA/APIS/HCT01/6.00	**STP No.**	GA/APISTP/HCT01/6.00
Mfg. Date	Jun-2020	**Date Of Release**	Aug 11 2020 6:41PM
Exp. Date/Re-test Date	May-2025	**Batch Quantity**	444.18 Kg

S. No.	TEST	SPECIFICATION	RESULT
1	Description	White or almost white, crystalline powder, odorless	White crystalline powder, odorless
2	Solubility	Soluble in acetone; sparingly soluble in ethanol (95%); very slightly soluble in water. It dissolves in dilute solution of alkali hydroxides	Soluble in acetone; sparingly soluble in ethanol (95%); very slightly soluble in water. It dissolves in dilute solution of alkali hydroxides
3	Identification		
3.1	Identification by IR	The IR spectrum of sample should be concordant with the spectrum obtained with Hydrochlorothiazide working standard or with the reference spectrum of Hydrochlorothiazide	Test tidentification by IR not performed since identification by UV and reaction with chromotropic acid sodium salt is performed
3.2	Identification by UV	The light absorption in the range of 230nm to 300nm of a 0.001% w/v sample solution should exhibit absorbance between 0.5 and 0.54 at a wavelength of about 273nm.The light absorption in the range 300 to 360nm of a 0.005% w/v of a sample solution should exhibit absorbance between 0.45 and 0.48 about 323nm	The light absorption in the range of 230nm to 300nm of a 0.001% w/v sample solution exhibit absorbance 0.536 at a wavelength of 273.25nm.The light absorption in the range 300 to 360nm of a 0.005% w/v of a sample solution exhibit absorbance 0.461 at a wavelength 322.75nm
3.3	Identification by TLC	The principle spot in the chromatogram obtained with the test solution should correspond to that obtained with reference solution	The principle spot in the chromatogram obtained with the test solution correspond to that obtained with reference solution
3.4	Reaction with Chromotropic acid sodium salt	A Violet colour develops	A Violet colour develops
4	Acidity or Alkalinity	Sample solution is yellow and not more than 0.4ml of 0.01M hydrochloric acid is required to change colour of the solution to red	Sample solution is yellow and 0.27ml of 0.01M hydrochloric acid is required to change colour of the solution to red
5	Chloride (ppm)	NMT 250 ppm	Less than 250 ppm

Remarks: APPROVED (Sample Conforms to above Specification)			
Comment(s): Approved			
Checked By	Kiran.Pisat (Sr.Executive-QC)	Approved By	Sandip.Kale (Manager)
Checked On	Aug 11 2020 6:29PM	Approved On	Aug 11 2020 6:41PM
Printed by: Anand.Potdar		**Printed on: Aug 19 2020 4:03PM**	
Copy No.: 1		Page No.: 1 of 2	
Note : This document has been generated electronically and is valid without signature.			
Form No.LIMS/ACOA-010/01			

UNICHEM LABORATORIES LIMITED

Plot No T 47, 5 Star MIDC,
Tal – Hatkannagle, Kagal, Kolhapur 416236

CERTIFICATE OF ANALYSIS
(Finished Product(For API))

Product: HYDROCHLOROTHIAZIDE IP			
Batch No.	KHTP200021	LIMS A.R. No.	KHFP2000139
Product Code	10000028	SAP Inspection Lot No	040000243742
Specification Id	GA/APIS/HCT01/6.00	STP No.	GA/APISTP/HCT01/6.00
Mfg. Date	Jun-2020	Date Of Release	Aug 11 2020 6:41PM
Exp. Date/Re-test Date	May-2025	Batch Quantity	444.18 Kg

6	Related substance by HPLC (%w/w)		
6.1	Any other unknown Individual Impurity	NMT 0.5%	0.10%
6.2	Total Impurities	NMT 1.0%	0.11%
7	Sulphated ash (%w/w)	Not more than 0.1%	0.05 %
8	Loss on drying (%w/w)	Not More than 0.5%	0.22 %
9	Assay by HPLC (on dried basis) (%w/w)	Between 98.0% and 102.0%	99.9 %

Test Plan Remarks: -

Remarks: APPROVED (Sample Conforms to above Specification)

Comment(s): Approved

Checked By	Kiran.Pisat (Sr.Executive-QC)	Approved By	Sandip.Kale (Manager)
Checked On	Aug 11 2020 6:29PM	Approved On	Aug 11 2020 6:41PM
Printed by: Anand.Potdar		Printed on: Aug 19 2020 4:03PM	
Copy No.: 1		Page No.: 2 of 2	

Note : This document has been generated electronically and is valid without signature.

Form No.LIMS/ACOA-010/01

20/12/2020 22/12/2020

3.2.S.4.5 Justification of Specification

The specifications followed in analyzing these materials are those specified in the monograph of the United State Pharmacopeia. The methods followed are also exactly those of the United States Pharmacopeia.

This justifies appropriateness of the specification.

3.2.S.5 Reference Standards or Materials

Telmisartan and Hydrochlorothiazide both are a pharmacopeial product. The sample batch is first prepared, characterized, and used as standard.

3.2.S.6 Container Closure System

API is packed in suitable clean polythene zip lock bags; 30g pack, sealed, tagged, and labelled and then packed in HDPE Drums.

The HDPE Drums are sealed and labelled. The labels give details such as:

i. Name of the product

ii. Manufacturing license number

iii. Batch number with manufacturing and expiry dates

iv. Quantity of the material packed

v. Storage conditions

vi. Name and address of the company

The labels are checked regularly for colour shade, printed matter, and size to maintain the consistency. Polythene bags, drums are also regularly checked for quality.

3.2.S.7 Stability

3.2.S.7.1 Stability Summary and Conclusions

Stability Study was carried out at 40°C ± 2°C/75% RH ± 5% condition for 6 months. Each piece of the tablet from the optimized formulation was packed in butter paper followed by aluminium foil. After intervals of 1, 3 and 6 months, the tablet was evaluated for the physical appearance and drug content.

Conclusion:

There was no significant statistical difference observed when the % drug content of various formulations of Telmisartan and Hydrochlorothiazide combination tablet stored at ambient temperatures were compared with the initial % drug content.

3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment

After approval of the product following stability studies will be performed:

Every six months, one batch from production will be subjected to stability studies at Room Temperature till the expiry of the product.

The protocol for the same will be same as that described above for the initial batches. Further, if there are any process modifications then first three batches manufactured by the modified process are subjected to the stability program as given above.

3.2.S.7.3 Stability Data

Below table give stability data of the drug substance when stored at 40°C ± 2°C/75% RH ± 5%

Initial drug content (%)		**40°C ± 2°C/75% RH ± 5 %**					
		1 Month		**3 Month**		**6 Month**	
TEL	HCTZ	TEL	HCTZ	TEL	HCTZ	TEL	HCTZ
93.89	93.73	93.81	93.65	93.78	93.74	93.71	93.68

3.2.P DRUG PRODUCT

Name of FPP Manufacturer: Dadasaheb Balpande Collage of Pharmacy, Nagpur

Name of FPP: Telmisartan - Hydrochlorothiazide Combination Tablet

Dosage Form: Oral Tablets

3.2.P.1 Description and Composition of the Drug Product

Description: White coloured circular tablet plain on both the sides.

Label Claim

Composition

Each Tablet Contains

Telmisartan …….40 mg
Hydrochlorothiazide……...12.5 mg
Excipients……. qs
Colour……..White

Qualitative and quantitative formula (Batch 1)

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (30 Tablets in mg)	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	219 mg	NA	6,570	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Sodium Starch Glycolate	USP	6 mg	NA	180	Disintegrant

USP= United State Pharmacopoeia

Qualitative and quantitative formula (Batch 2)

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (30 Tablets in mg)	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	201 mg	NA	6,030	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Sodium Starch Glycolate	USP	24 mg	NA	720	Disintegrant

USP= United State Pharmacopoeia

Qualitative and quantitative formula (Batch 3)

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (30 Tablets in mg)	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	222 mg	NA	6,600	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Croscarmellose Sodium	USP	3 mg	NA	90	Disintegrant

USP= United State Pharmacopoeia

Qualitative and quantitative formula (Batch 4)

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (1.00 Lac Tablets in Kg	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	211.5 mg	NA	6,345	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Croscarmellose Sodium	USP	13.5 mg	NA	405	Disintegrant

USP= United State Pharmacopoeia

Qualitative and quantitative formula (Batch 5)

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (1.00 Lac Tablets in Kg	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	221 mg	NA	6,645	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Crospovidone	USP	4 mg	NA	120	Disintegrant

USP= United State Pharmacopoeia

Qualitative and quantitative formula (Batch 6)

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (1.00 Lac Tablets in Kg	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	221 mg	NA	6,645	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Crospovidone	USP	4 mg	NA	120	Disintegrant

USP= United State Pharmacopoeia

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

- **Batch 1**

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (30 Tablets in mg)	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	219 mg	NA	6,570	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Sodium Starch Glycolate	USP	6 mg	NA	180	Disintegrant

USP = United State Pharmacopoeia

- **Batch 2**

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (30 Tablets in mg)	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	201 mg	NA	6,030	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Sodium Starch Glycolate	USP	24 mg	NA	720	Disintegrant

USP = United State Pharmacopoeia

- **Batch 3**

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (30 Tablets in mg)	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	222 mg	NA	6,600	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Croscarmellose Sodium	USP	3 mg	NA	90	Disintegrant

USP = United State Pharmacopoeia

- **Batch 4**

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (1.00 Lac Tablets in Kg	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	211.5 mg	NA	6,345	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Croscarmellose Sodium	USP	13.5 mg	NA	405	Disintegrant

USP = United State Pharmacopoeia

- **Batch 5**

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (1.00 Lac Tablets in Kg	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	221 mg	NA	6,645	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Crospovidone	USP	4 mg	NA	120	Disintegrant

USP = United State Pharmacopoeia

- **Batch 6**

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (1.00 Lac Tablets in Kg	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	221 mg	NA	6,645	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Crospovidone	USP	4 mg	NA	120	Disintegrant

USP = United State Pharmacopoeia

3.2.P.2.1.1 Drug Substance

The excipients used in this formulation are compatible with the drug substance Telmisartan and Hydrochlorothiazide and is established during trials taken for development of formulation.

Physiochemical properties of Telmisartan

A white to off white crystalline powder, insoluble in water slightly soluble in methanol, sparingly soluble in methylene chloride.

Physiochemical properties of Hydrochlorothiazide

A white to off white crystalline powder, soluble in acetone; sparingly soluble in ethanol (95%) very slightly soluble in water. It dissolves in dilute solution of alkali hydroxides.

3.2.P.2.1.2 Excipients

Name of FPP Manufacturer: Dadasaheb Balpande Collage of Pharmacy, Nagpur

Name of FPP: Telmisartan - Hydrochlorothiazide Combination Tablet

Dosage Form: Oral tablets

Table: Excipients used in FPP

Sr. No	Name of Excipients	Function
1.	Avicel PH 102 (MCC)	Diluent/Binder
2.	Aerosil	Glidant
3.	Talc	Lubricant
4.	Sodium Starch Glycolate	Disintegrant
5.	Croscarmellose Sodium	Disintegrant
6.	Crospovidone	Disintegrant

All above excipients used are inert in nature and do not interfere with the drug product while the microcrystalline cellulose and sodium starch glycolate enhances the disintegration of tablet which helps in fast release of drug.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

At Dadasaheb Balpande Collage of Pharmacy, Nagpur, the basic selection of excipients and designing of manufacturing process and operating parameters are developed and finalized on a

laboratory scale before the technology is scaled-up on a commercial scale, trials conducted to optimize several operating parameters.

After the successful manufacturing at laboratory scale critical process parameters were identified and the process was validated.

The complete chemistry of manufacturing process was understood and the process was scaled up.

3.2.P.2.2.2 Overages

No overages are added in this formulation

3.2.P.2.2.3 Physicochemical and Biological Properties

White coloured circular biconvex tablet plain on both the sides, with average wt. of 300 mg per tablet, thickness 3.89 mm, hardness of tablets must not be less than 2 kP, the disintegration time is less than 15 min in water and drug release should not be less than 75% of labeled amount in 45 min. The microbiological attributes must comply with the United States Pharmacopoeia.

3.2.P.2.3 Manufacturing Process Development

At Dadasaheb Balpande Collage of Pharmacy, Nagpur, the basic selection of excipients and designing of manufacturing process and operating parameters are developed and finalized on a laboratory scale before the technology is scaled-up on a commercial scale, trials conducted to optimize several operating parameters.

After the successful manufacturing at laboratory scale critical process parameters were identified and the process was validated.

The complete chemistry of manufacturing process was understood and the process was scaled up.

3.2.P.2.4 Container Closure System

Primary packing: 10 tablets are packed in the PVC-ALU Blister. Well printed aluminum foil of 0.25 µ thickness is used as lead foil and 25Ø PVC foil used as base foil for blister formation of 9 mm diameter and 4.7 ± 0.2 mm depth. The lead foil and base foils are thermally sealed.

Secondary packing: 300 gsm white board is used for printed cartons which contains 10 strips of 10 tablets blister. Which are over printed for batch numbers, manufacturing date, and expiry date.

Tertiary packing: 7 ply corrugated boxes are used to pack 100 Shrinks of 10 cartons. Which are finally sealed with BOPP tape and two straps.

3.2.P.2.5 Microbiological Attributes

NOT APPLICABLE

Justification: Microbial studies of finish product is not possible at organization level.

3.2.P.2.6 Compatibility

This oral dosage is formulated in tablet form and no need reconstituted with any diluents are not to be consumed with any device hence no need to discuss on this point.

3.2.P.3 Manufacture

Name of FPP Manufacturer: Dadasaheb Balpande Collage of Pharmacy, Nagpur,

Name of FPP: Telmisartan - Hydrochlorothiazide Combination Tablet

Dosage Form: Oral Tablets

3.2.P.3.1 Manufacturer(s)

Site	Address
Administrative	**Dadasaheb Balpande College of Pharmacy:** Near Shree Swami Samarth Dham Mandir Manewada Road, Besa Square, Nagpur, Maharashtra 440037 **Tel:** 07103281244
Production, Quality Control & Quality Assurance	**Dadasaheb Balpande College of Pharmacy:** Near Shree Swami Samarth Dham Mandir Manewada Road, Besa Square, Nagpur, Maharashtra 440037 **Tel:** 07103281244

3.2.P.3.2 Batch Formula

Description: White coloured circular tablet plain on both the sides.

Label Claim

Each Tablet Contains

Telmisartan …….40 mg

Hydrochlorothiazide……...12.5 mg

Excipients……. qs

Colour……..White

- **Batch 1**

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (30 Tablets in mg)	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	219 mg	NA	6,570	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Sodium Starch Glycolate	USP	6 mg	NA	180	Disintegrant

USP= United State Pharmacopoeia

- **Batch 2**

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (30 Tablets in mg)	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	201 mg	NA	6,030	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant

6.	Sodium Starch Glycolate	USP	24 mg	NA	720	Disintegrant

USP= United State Pharmacopoeia

- **Batch 3**

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (30 Tablets in mg)	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	222 mg	NA	6,600	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Croscarmellose Sodium	USP	3 mg	NA	90	Disintegrant

USP= United State Pharmacopoeia

- **Batch 4**

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (1.00 Lac Tablets in Kg	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	211.5 mg	NA	6,345	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant

5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Croscarmellose Sodium	USP	13.5 mg	NA	405	Disintegrant

USP= United State Pharmacopoeia

- **Batch 5**

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (1.00 Lac Tablets in Kg	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	221 mg	NA	6,645	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant
5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Crospovidone	USP	4 mg	NA	120	Disintegrant

USP= United State Pharmacopoeia

- **Batch 6**

Sr. No	Ingredients	Specification	Qty/ Tablet (In mg)	Overages Added (In %)	STD B. Size (1.00 Lac Tablets in Kg	Reason for function
1.	Telmisartan	USP	40 mg	NA	1,200	Active
2.	Hydrochlorothiazide	USP	12.5 mg	NA	375	Active
3.	Avicel PH 102 (MCC)	USP	221 mg	NA	6,645	Diluent/ Binder
4.	Aerosil	USP	1.5 mg	NA	45	Glidant

5.	Talc	USP	21 mg	NA	630	Lubricant
6.	Crospovidone	USP	4 mg	NA	120	Disintegrant

USP= United State Pharmacopoeia

3.2.P.3.3 Description of Manufacturing Process and Process Controls

Manufacturing process

Step No.	Manufacturing Procedure
1.	**Weighing**
1.1	All the active pharmaceutical ingredient (API), diluents, binders, disintegrants, lubricants, and any other excipients are weighed as per the formulation requirements.
1.2	Calibrated weighing balance was used to ensure precision.
2.	**Mixing**
2.1	All the weighed raw materials are transferred into a mortar and pestle.
2.2	All the materials were blended for a specified time to ensure uniform distribution of the API and excipients.
3.	**Compression**
3.1	The blended mixture was added into the hopper of the tablet compression machine.
3.2	The compression machine parameters, including punch pressure, tablet weight, and speed are set based on the formulation requirements.
3.3	The tablet blend was compressed.

3.2.P.3.4 Controls of Critical Steps and Intermediates

Following are the In-process quality control tests performed during compression

Sr. No	Parameter	Frequency of in process checks	Specification
1	Appearance	Initially and after 30 tablets	White coloured, circular, biconvex tablets plain on both sides.

2	Average weight	Initially and after 30 tablets	300 mg
3	Thickness	Initially and after 30 tablets	4.30 mm ± 0.20 mm
4	Hardness	Initially and after 30 tablets	Not less than 2.000 Kp

3.2.P.4 Control of Excipients

List of excipients used in the formulation of Telmisartan and Hydrochlorothiazide combination tablet are as follows

Sr. No	Name of Excipients	Grade
1.	Avicel PH 102 (MCC)	USP
2.	Aerosil	USP
3.	Talc	USP
4.	Sodium Starch Glycolate	USP
5.	Croscarmellose Sodium	USP
6.	Crospovidone	USP

3.2.P.4.1 Specifications

- **COA of Avicel 102 (MCC)**

Certificate Of Analysis

NAME OF MATERIAL	: Microcrystalline Cellulose IP PH-102 (Chem Field)	MFG DATE	: Apr-2024
CONTROL NO	: 00032/RMSAMP/24-25	EXP. DATE	: Mar-2029
BATCH NO	: 2404029-C	DATE OF ANALYSIS	: 02-May-2024
QTY RECEVIED	: 200.00 Kg	DATE OF REPORT	: 02-May-2024
QTY SAMPLED	: 0.020 Kg	A.R.No.	: RM24/28
DATE OF SAMPLING	: 30 - Apr – 2024		
SAMPLED BY	: Ms. Ankita Mankar		

Sr. No.	TEST	STANDARD	RESULT
1.	Description	A fine granular, white or almost white powder, odour less	Complies
2.	Solubility	Practically insoluble in water, in acetone, in ethanol	Complies
3.	Identification A	A red colour is produced	Complies
4.	pH	Valid Rang Between 5.00 to 7.50	6.52
5.	Starch & Dextrin	No blue or brownish red coloured produced	Complies
6.	Water soluble substance	Valid range not more than 0.20%	0.12%
7.	Organic Impurity	Not red coloured is produced	Complies
8.	Arsenic	The strain produced on mercuric bromide paper of test solution is not more intense than the stest solution is not more intense than the stain produced on mercuric bromide paper of standard solution	Complies
9.	Heavy Metals	The colour produced with the test solution is not more intense than that produced with the standard solution	Complies

10.	Loss on drying	Valid range not more than 6.00%	2.12%
11.	Sulphated Ash	Valid range not more than 0.2%	0.10%
12.	Assay	Valid range not less than 97.00% and not more than 102.00% on dried basis	98.12%

Prepared By	Checked By	Approved by

- **COA of Aerosil**

Certificate of Analysis

NAME OF MATERIAL	: Aerosil	**MFG DATE**	: Apr-2024
CONTROL NO	: 00384/RMSAMP/23-24	**EXP. DATE**	: Mar-2029
BATCH NO	: 2309336	**DATE OF ANALYSIS**	: 02-May-2024
QTY RECEVIED	: 50.00 KGS	**DATE OF REPORT**	: 02-May-2024
QTY SAMPLED	: 0.008 KGS	**A.R.No.**	: RM24/28
DATE OF SAMPLING	: 24 - Nov – 2023		
SAMPLED BY	: Ms. Pranjali Lute		

Sr. No.	TEST	STANDARD	RESULT
1.	Description	A light fine, white, amorphous powder. It has a practical size of about 15nm	Complies
2.	Solubility	Practically insoluble in water and in mineral acids with the exception of hydrofluoric acid. Dissolves in hot solution of alkali hydroxides. When 1g is shaken vigorously with 20ml of carbon tetrachloride for 3 minutes a transparent gel is produced.	Complies
3.	Identification	Gives reaction of silicates.	Complies
4.	pH	Valid Rang Between 3.50 to 5.50	4.21
5.	Arsenic	Mercuric chloride paper is not more intense than that obtained by treating standard	Complies
6.	Heavy Metals	Colour produced with the test solution is not more intense than that produced with the standard solution	Complies
7.	Chlorides	Opalescence produced is not more intense than standard.	Complies
8.	Loss on ignition	Valid range not more than 5.00%	1.23%
9.	Assay	Valid range not less than 99.00% and not more than 100.5% on ignite basis	100.25%

Prepared By	Checked By	Approved By

SEAL

- **COA of Talc**

Certificate of Analysis

NAME OF MATERIAL	: Purified Talc	MFG DATE	: Oct-2021
CONTROL NO	: 00037/RMSAMP/22-23	EXP. DATE	: Sep-2026
BATCH NO	: H-1227	DATE OF ANALYSIS	: 24-April-2022
QTY RECEVIED	: 500.00 KGS	DATE OF REPORT	: 29-Apr-2022
QTY SAMPLED	: 0.036 KGS	A.R.No.	: RM22/D/38
DATE OF SAMPLING	: 23 - Apr – 2022		
SAMPLED BY	: Ms.Madhavi jambutkar		

Sr. No.	TEST	STANDARD	RESULT
1.	Description	A white or almost white powder, free from Grittiness; readily adheres to the skin, unctuous to the touch, odorless	Complies
2.	Solubility	Practically insoluble in water, and in dilute solution of acids and in alkali hydroxides	Complies
3.	Identification A	Infrared spectroscopy	Complies
4.	Acidity or Alkalinity	Solutions is not acid and requires not more than 0.3 ml of 0.1 M hydrochloric acid to make it acid	Complies
5.	Iron	Any colour produced is not more intense than standard solution.	Complies
6.	Acid soluble substance	NMT 2.0%	1.98%
7.	Carbonates	No effervescence produced	Complies
8.	Chlorides	Opalescence produced is not more intense than standard solution	Complies
9.	Organic Compound	Residue obtained in LOD is not more slightly yellow or grey	Complies
10.	Loss on drying	Not more than 1.0%	0.56%
11.	Microbial Contamination	The total viable aerobic count is not more than 1000 bacteria and not more than 100 fungi per gram	Complies
12.	Heavy Metals	The resulting solution complies with the limit test for heavy metals	Complies
13.	Water soluble matter	Not more than 10 mg	1.14 mg

Prepared By	Checked By	Approved By

DADASAHEB BALPANDE COLLEGE OF PHARMACY SEAL

- **COA of Sodium Starch Glycolate**

Certificate of Analysis

NAME OF MATERIAL	: Sodium Starch Glycolate	**MFG DATE**	: Jan-2024
CONTROL NO	: 00508/RMSAMP/23-24	**EXP. DATE**	: Dec-2028
BATCH NO	: PR/P/SG-0025/24	**DATE OF ANALYSIS**	: 18-Feb-2024
QTY RECEVIED	: 250.00 Kg	**DATE OF REPORT**	: 22-Feb-2024
QTY SAMPLED	: 0.022 Kg	**A.R.No.**	: RM24/B/29
DATE OF SAMPLING	: 18 - Feb – 2024		
SAMPLED BY	: Ms. Pranjali Lute		

Sr. No.	TEST	STANDARD	RESULT
1.	Description	A very fine, white or off- white, free flowing powder, odourless or almost odourless	Complies
2.	Solubility	Practically insoluble in water, insoluble in most organic solvents.	Complies
3.	Identification A	By infrared spectroscopy	Complies
4.	Identification B	A dark blue colour is produced.	Complies
5.	Identification C	Gives reaction of sodium salts	Complies
4.	pH	Valid Rang not less than 5.5 and not more than 7.5	6.45
9.	Heavy Metals	Colour produced with the test solution is not more intense than that produced with the standard solution	Complies
10.	Iron	Any colour produced is not more intense than standard solution	Complies
	Microbial Contamination	Freely from Escherichia coli and shigella, salmonellae	Absent
10.	Loss on drying	Valid range not more than 10.00%	2.14%
12.	Assay	Valid range not less than 2.800% and not more than 4.50% on dried basis	3.21%

Prepared By	Checked By	Approved By

SEAL

- **COA Of Croscarmellose Sodium**

Certificate of Analysis

NAME OF MATERIAL	: Cross Carmellose Sodium	**MFG DATE**	: Jan-2024
CONTROL NO	: 00512/RMSAMP/23-24	**EXP. DATE**	: Dec-2028
BATCH NO	: PR/P/CR-0077/24	**DATE OF ANAYLYSIS**	: 22-Feb-2024
QTY RECEVIED	: 200.00 KGS	**DATE OF REPORT**	: 22-Feb-2024
QTY SAMPLED	: 0.012 KGS	**A.R.No.**	: RM24/B/28
DATE OF SAMPLING	: 18 - Feb – 2024		
SAMPLED BY	: Ms. Pranjali Lute		

Sr. No.	TEST	STANDARD	RESULT
1.	Description	A white free flowing powder.	Complies
2.	Solubility	Soluble in water insoluble in ethanol, ether, acetone and in another organic solvents	Complies
3.	Identification A	The substance under examination absorbs the methylene blue and settles as a blue fibrous mass.	Complies
4.	pH	Valid Rang Between 5.0 to 7.0	6.15
5.	Heavy Metals	The colour produced with the test solution is not more intense than that produced with the standard solution	Complies
6.	Microbial Contamination-Total microbial count	Valid range not more than 1000 cfu per g.	25 cfu per g
7.	Microbial Contamination-Total fungal count	Valid range not more than 100 cfu per g	00 cfu per g
8.	Microbial Contamination-E. coli	Should be Absent in 1 g	Absent
9.	Sulphated Ash	Valid range between 14.0% to 28.0%	17.21%
10.	Loss on drying	Valid range not more than 10.00%	2.37%

Prepared By	Checked By	Approved By

SEAL

- **COA of Crospovidone**

Certificate of Analysis

NAME OF MATERIAL	: Cross Povidone	**MFG DATE**	: Jan-2024
NAME OF MATERIAL	: 00503/RMSAMP/23-24	**EXP. DATE**	: Dec-2028
BATCH NO	: PR/P/CRP-0005/24	**DATE OF ANALYSIS**	: 23-Feb-2024
QTY RECEVIED	:100.00 KGS	**DATE OF REPORT**	: 23-Feb-2024
QTY SAMPLED	: 0.012 KGS	**A.R.NO.**	: RM24/B/27
DATE OF SAMPLING	: 18 – Feb - 2024		
SAMPLED BY	: Ms. Pranjali Lute		

Sr. No.	TEST	STANDARD	RESULT
1.	Description	A white to creamy white hygroscopic powder, faint odour.	Complies
2.	Solubility	Insoluble in ethanol (95%), ether & other organic solvent.	Complies
3.	Identification A	IR	Complies
4.	Identification B	No blue colour develops.	Complies
4.	pH	5.0-8.0	6.71
5.	Water	NMT 5.0 %	2.31%
9.	Heavy Metals	Colour of sample solution not more intense than standard solution.	Complies
12.	Water-Insoluble matter	NMT 1.8%	1.34%

Prepared By	Checked By	Approved By

SEAL

3.2.P.4.2 Analytical Procedures

- **Avicel PH 102 (MCC)**

DEFINITION

Microcrystalline Cellulose is purified, partially depolymerized cellulose prepared by treating alpha cellulose, obtained as a pulp from fibrous plant material, with mineral acids**.**

IDENTIFICATION

A. INFRARED ABSORPTION á197Kñ or á197Añ:

[NOTE—Disregard any peak between 800 and 825 cm−1 as well as those between 950 and 1000 cm−1.]

B. Iodinated zinc chloride solution:

Iodinated zinc chloride solution: Dissolve 20 g of zinc chloride and 6.5 g of potassium iodide in 10.5 mL of water. Add 0.5 g of iodine, and shake for 15 min.
Sample: 10 mg
Analysis: Place the Sample on a watch glass, and disperse in 2 mL of Iodinated zinc chloride solution.
Acceptance criteria: The substance takes on a violet-blue colour.

C. Sample: 1.3 g of Microcrystalline Cellulose, accurately weighed to 0.1 mg.

Analysis: Transfer the Sample to a 125-mL conical flask. Add 25.0 mL of water and 25.0 mL of 1.0 M cupriethylenediamine hydroxide solution. Immediately purge the solution with nitrogen, insert the stopper, and shake on a wrist-action shaker, or other suitable mechanical shaker, until completely dissolved. Transfer an appropriate volume of the sample solution to a calibrated number 150 Cannon-Fenske, or equivalent, viscometer. Allow the solution to equilibrate at 25 ± 0.1° for NLT 5 min. Time the flow between the 2 marks on the viscometer, and record the flow time, t1, in seconds. Calculate the kinematic viscosity, (KV)1, of Microcrystalline Cellulose taken:

$$\text{Result} = t_1 \times k_1$$

t_1 = flow time (s)
k_1 = viscometer constant

Obtain the flow time, t2, for 0.5 M cupriethylenediamine hydroxide solutions using a number 100 CannonFenske, or equivalent, viscometer. Calculate the kinematic viscosity, (KV)2, of the solvent:

$$\text{Result} = t_2 \times k_2$$

t_2 = flow time for 0.5 M cupriethylenediamine hydroxide solutions (s)
k_2 = viscometer constant

Determine the relative viscosity, ηrel, of the Microcrystalline Cellulose specimen taken:

$$\text{Result} = (KV)_1/(KV)_2$$

$(KV)_1$ = kinematic viscosity of Microcrystalline Cellulose taken
$(KV)_2$ = kinematic viscosity of the solvent.

Determine the intrinsic viscosity, [η]c, by interpolation, using the Intrinsic Viscosity Table in the Reference Tables section.

Calculate the degree of polymerization, P:

Result = [(95) × [η]c / {WS × [(100 − %LOD)/100]}

[η]c = intrinsic viscosity

WS = weight of Microcrystalline Cellulose taken (g)

%LOD = value obtained from the test for Loss on Drying

Acceptance criteria: The degree of polymerization is NMT 350.

IMPURITIES

INORGANIC IMPURITIES

• **Residue on Ignition á281ñ:** NMT 0.1%

SPECIFIC TESTS

• **MICROBIAL ENUMERATION TESTS á61ñ and TESTS FOR SPECIFIED MICROORGANISMS á62ñ:**

The total aerobic microbial count does not exceed 103 cfu/g, and the total combined molds and yeasts count does not exceed 102 cfu/g. It meets the requirements of the tests for absence of Staphylococcus aureus and Pseudomonas aeruginosa and for the absence of Escherichia coli and Salmonella species.

• **CONDUCTIVITY**

Sample: 5 g

Analysis: Shake the Sample with 40 mL of water for 20 min, and centrifuge. Retain the supernatant for use in the pH test. Using an appropriate conductivity meter that has been standardized with a potassium chloride conductivity calibration standard having a conductivity of 100 µS/cm, measure the conductivity of the supernatant after a stable reading is obtained, and measure the conductivity of the water used to prepare the test specimen.

Acceptance criteria: The conductivity of the supernatant does not exceed the conductivity of the water by more than 75 µS/cm.

• **pH á791ñ:** 5.0–7.5 in the supernatant obtained in the Conductivity test.

• **LOSS ON DRYING á731ñ**

Analysis: Dry a sample at 105° for 3 h.

Acceptance criteria: NMT 7.0% NF 1-Dec-2019 or some other lower percentage, or is within a percentage range, as specified in the labelling.

• **BULK DENSITY**

Analysis: Use a volumeter that has been fitted with a 10- mesh screen. The volumeter is freestanding of the brass or stainless-steel cup, which is calibrated to a capacity of 25.0 ± 0.05 mL and has an inside diameter of 30.0 ± 2.0 mm. Weigh the empty cup, position it under the chute, and slowly pour the powder from a height of 5.1 cm (2 in) above the funnel through the volumeter, at a rate suitable to prevent clogging, until the cup overflows. Level the excess powder, and weigh the filled cup. Calculate the bulk density by dividing the weight of the powder in the cup by the volume of the cup.

Acceptance criteria: The bulk density is within the labelled specification.

PARTICLE SIZE DISTRIBUTION

Where the labeling states the particle size distribution, determine the particle size distribution as directed in Particle Size Distribution Estimation by Analytical Sieving á786ñ, or by a suitable validated procedure.

• WATER-SOLUBLE SUBSTANCES

Sample: 5.0 g

Analysis: Shake the Sample with 80 mL of water for 10 min, and pass with the aid of a vacuum through filter paper (Whatman No. 42 or equivalent) into a vacuum flask. Transfer the filtrate to a tared beaker, evaporate to dryness without charring, dry at 105° for 1 h, cool in a desiccator, and weigh.

Acceptance criteria: The difference between the weight of the residue and the weight obtained from a blank determination does not exceed 12.5 mg (0.25%).

ETHER-SOLUBLE SUBSTANCES

Sample: 10.0 g

Analysis: Place the Sample in a chromatographic column having an internal diameter of about 20 mm, and pass 50 mL of peroxide-free ether through the column. Evaporate the eluate to dryness in a previously dried and tared evaporating dish with the aid of a current of air in a fume hood. After all the ether has evaporated, dry the residue at 105° for 30 min, cool in a desiccator, and weigh. Acceptance criteria: The difference between the weight of the residue and the weight obtained from a blank determination does not exceed 5.0 mg (0.05%).

ADDITIONAL REQUIREMENTS

PACKAGING AND STORAGE: Preserve in tight containers**.**

LABELING: The labelling indicates the nominal loss on drying, bulk density, and degree of polymerization values. Degree of polymerization compliance is determined using Identification. Where the particle size distribution is stated in the labelling, proceed as directed in the test for Particle Size Distribution. The labelling indicates with which technique the particle size distribution was determined if a technique other than analytical sieving was used; and the labelling indicates the d10, d50, and d90 values and the range for each.

• **USP REFERENCE STANDARDS**: USP Microcrystalline Cellulose RS

- **Aerosil**

DEFINITION

Colloidal Silicon Dioxide is a sub microscopic fumed silica prepared by the vapor-phase hydrolysis of a silicon compound. When ignited at 1000° for 2 h, it contains NLT 99.0% and NMT 100.5% of SiO_2.

IDENTIFICATION

A. PROCEDURE

Analysis: Transfer 5 mg to a platinum crucible, and mix with 200 mg of anhydrous potassium carbonate. Ignite at a red heat over a burner for 10 min, and cool. Dissolve the melt in 2 mL of freshly distilled water, warming if necessary, and slowly add 2 mL of ammonium molybdate TS to the solution.

Acceptance criteria: A deep yellow colour is produced.

B. PROCEDURE

Analysis: Place 1 drop of the yellow silicomolybdate solution from Identification test A on a filter paper, and evaporate the solvent. Add 1 drop of a saturated solution of o-tolidine in glacial acetic acid to reduce the silicomolybdate to molybdenum blue, and place the paper over ammonium hydroxide.

Acceptance criteria: A greenish blue spot is produced.

ASSAY

PROCEDURE

Sample: 500 mg

Analysis: Ignite the Sample in a tared platinum crucible at 1000±25° for 2 h, cool in a desiccator, and weigh. Add 3 drops of sulfuric acid, and add enough alcohol to just mois- ten the sample completely. Add 15 mL of hydrofluoric acid, and in a well-ventilated hood evaporate on a hot plate to dryness, using medium heat (95°-105°) and taking care that the sample does not spatter as dryness is approached. Heat the crucible to a red color with the aid of a Bunsen burner. Ignite the residue at 1000 ± 25° for 30 min, cool in a desi-cator, and weigh. If a residue remains, repeat the Analysis, beginning with "Add 15 mL of hydrofluoric acid". The weight lost by the assay specimen, previously ignited at 1000 ± 25°, represents the weight of SiO2 in the portion taken.

Acceptance criteria: 99.0%-100.5% on the previously ig-nited basis.

IMPURITIES

Inorganic Impurities

LOSS ON IGNITION (733):

Ignite the portion of Colloidal Silicon Dioxide, retained from the test for Loss on Drying, at 1000 ± 25° to constant weight: the previously dried Colloidal Silicon Dioxide loses NMT 2.0% of its weight.

ARSENIC, Method 1

Sample solution: To 2.5 g add 50 mL of 3 N hydrochloric acid, and reflux for 30 min using a water condenser. Cool, filter with the aid of suction, and transfer the filtrate to a 100-mL volumetric flask. Wash the filter and flask with several portions of hot water, and add the washings to the flask. Cool, and dilute with water to volume.

Analysis: A 15.0-mL portion of Sample solution, to which 3 mL of hydrochloric acid has been added, meets the requirements of the test, the addition of the 7 N sulfuric acid being omitted.

Acceptance criteria: NMT 8 ppm

SPECIFIC TESTS

• **PH ⟨791⟩:** 3.5–5.5, in a (1 in 25) dispersion

• **LOSS ON DRYING ⟨731⟩:** Dry in a tared platinum crucible at .105° for 2 h: it loses NMT 2.5% of its weight. Retain the dried specimen in the crucible for the test for Loss on Ignition.

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers.

Simethicone: Simethicone General Monographs

Simethicone Emulsion: Simethicone. Emulsion General Monograph

Soda Lime: Soda Lime is a mixture of Calcium Hydroxide and Sodium or Potassium Hydroxide or both. It may contain an indicator that is inert toward aesthetic gases such as Ether, Cyclopropane, and Nitrous Oxide, and that changes color when the Soda Lime no longer can absorb Carbon Dioxide.

Identification:

A: Place a granule of it on a piece of moistened red litmus paper: the paper turns blue immediately.

B: A solution in 6 N acetic acid responds to the tests for Calcium (191). It also imparts a yellow color to a nonluminous flame that, when viewed through cobalt glass, may show a violet color.

Loss on drying (731)-

Weigh accurately, in a tared weighing bottle, about 10 g, and dry at 105° for 2 hours: it loses between 12.0% and 19.0% of its weight.

Moisture absorption-Place about 10 g in a tared, 50-mL weighing bottle, having a diameter of 50 mm and a height of 30 mm, and weigh. Then place the bottle, with cover removed, for 24 hours in a closed container in which the atmosphere is maintained at 85% relative humidity by being in equilibrium with sulfuric acid having a specific gravity of 1.16. Weigh again: the increase in weight is not more than 7.5%.

Hardness-Screen 200 g on a mechanical sieve shaker (see Particle Size Distribution Estimation by Analytical Sieving (786)) having a frequency of oscillation of 285 ± 3 cycles per minute, for 3 minutes, to remove granules both coarser and finer than the labelled particle size. Proceed as directed in the test for Hardness under Barium Hydroxide Lime, beginning with "Weigh 50 g of the granules." The percentage of Soda Lime retained on the screen is not less than 75.0, and represents the hardness.

Carbon dioxide absorbency-Proceed as directed in the test for Carbon dioxide absorbency under Barium Hydroxide Lime. The increase in weight is not less than 19.0% of the weight of Soda Lime used for the test.

Other requirements-It meets the requirements for Packaging and storage, Labelling, and Size of granules under Barium Hydroxide Lime.

- **Talc**

DEFINITION

Talc is a powdered, selected, natural, hydrated magnesium silicate. Pure talc has the formula $Mg_3Si_4O_{10}(OH)_2$. It may contain variable amounts of associated minerals among which chlorites (hydrated aluminium and magnesium silicates), magnesite (magnesium carbonate), calcite (calcium carbonate), and dolomite (calcium and magnesium carbonate) are predominant.

IDENTIFICATION:

A. INFRARED ABSORPTION: The IR spectrum of a potassium bromide dispersion of it exhibits maxima at 3677 ± 2 cm-1, at 1018±2cm-1, and at 669 ± 2 cm-1.

B. PROCEDURE

Sample: 100 mg

Analysis: Mix about 200 mg of anhydrous sodium car- bonate and 2 g of anhydrous potassium carbonate, and melt in a platinum crucible. To the melt add the Sam- ple, and continue heating until fusion is complete. Cool, and transfer the fused mixture to a dish or beaker with the aid of about 50 mL of hot water. Add hydrochloric acid to the liquid until effervescence ceases, then add 10 mL more of the acid, and evaporate the mixture on a steam bath to dryness. Cool, add 20 mL of water, boil, and filter the mixture. Save the insoluble residue for use in Identification test C. To 5 mL of the filtrate add 1 mL of 6 N ammonium hydroxide and 1 mL of ammonium chloride TS. Filter, if necessary, and add 1 mL of dibasic sodium phosphate TS to the filtrate.

Acceptance criteria: A white, crystalline precipitate of magnesium ammonium phosphate is formed.

ASSAY

CONTENT OF MAGNESIUM

lanthanum chloride solution: To 5.9 g of lanthanum oxide slowly add 10 mL of hydrochloric acid, and heat to boiling. Allow to cool, and dilute with water to 100 mL.

Magnesium standard stock solution: 10 µg/mL of magnesium, prepared by diluting an 8.365 mg/mL solution of magnesium chloride in diluted hydrochloric acid with water (1 in 100)

Magnesium standard solutions: Into four identical 100-mL volumetric flasks, each containing 10.0 mL of hydrochloric acid and 10 mL of Lanthanum chloride solu- tion, transfer respectively 2.5, 3.0, 4.0, and 5.0 mL of Magnesium standard stock solution, and dilute with water to volume.

Sample stock solution: [Caution Perchlorates mixed with heavy metals are known to be explosive. Take proper precautions while performing this analysis.] Weigh 500 mg of Talc in ene dish. Add 5 a 100-mL polytetrafluoroethylene- mL of hydrochloric acid, 5 mL of lead- free nitric acid, and 5 mL of perchloric acid. Stir gently, then add 35 mL of hydrofluoric acid, and evaporate slowly on a hot plate to moist dryness (until about 0.5 mL remains). To the residue, add 5 mL of hydrochloric acid, cover with a watch glass, heat to boiling, and allow to cool. Rinse the watch glass and the dish with water, transfer to a 50-mL volumetric flask, and dilute with water to volume.

Sample solution: Dilute the Sample stock solution with water (1 in 200). Transfer 4.0 mL of this solution to a 100-mL volumetric flask, add 10.0 mL of hydrochloric acid and 10 mL of Lanthanum

chloride solution, and di- lute with water to volume. Instrumental conditions T (See Spectrophotometry and Light-Scattering (851).)

Mode: Atomic absorption spectrophotometry Analytical wavelength: Magnesium emission line at 285.2 nm

Lamp: Magnesium hollow-cathode

Flame: Air-acetylene

Analysis Samples: Magnesium standard solutions and Sample solution Concomitantly determine the absorbance of the solutions.

Acceptance criteria: 17.0%-19.5%

IMPURITIES

WATER-SOLUBLE SUBSTANCES

Sample: 10.0 g

Analysis: To the Sample add 50 mL of carbon dioxide- free water, heat to boiling, and boil under a reflux con- denser for 30 min. Allow to cool, filter, and dilute with carbon dioxide-free water to 50.0 mL. Test with litmus paper. Evaporate 25.0 mL of the filtrate to dryness, dry at 105° for 1 h, and weigh the residue.

Acceptance criteria: The filtrate is neutral to litmus pa- per, and the weight of the residue is NMT 5 mg (0.1%)

LIMIT OF IRON: Iron standard stock solution: 250 µg/mL of iron from 4.840 g ferric chloride in a 150 g/L solution of hydro- chloric acid in water. Prepare immediately before use.

Iron standard solutions: Into four 100-mL volumetric flasks, each containing 50.0 mL of 0.5 N hydrochloric acid, transfer respectively 2.0, 2.5, 3.0, and 4.0 mL of the Standard iron stock solution, and dilute each flask with water to volume.

Sample stock solution: Transfer 10.0 g of Talc to a conical flask fitted with a reflux condenser. Gradually add 50 mL of 0.5 N hydrochloric acid while stirring, and heat on a water bath for 30 min. Allow to cool. Transfer the mixture to a beaker, and allow the undissolved material to settle. Filter the supernatant into a 100-mL volumetric flask, retaining as much as possible of the insoluble material in the beaker. Wash the residue and the beaker with three 10-mL portions of hot water. Wash the filter with 15 mL of hot water, allow the filtrate to cool, and dilute with water to 100.0 mL.

Sample solution: Transfer 2.5 mL of the Sample stock solution to a 100-mL volumetric flask, add 50.0 mL of 0.5 N hydrochloric acid, and dilute with water to volume.

Instrumental conditions

Analytical wavelength: Iron emission line at 248.3 nm

Lamp: Iron hollow-cathode

Flame: Air-acetylene

Analysis Samples: Iron standard solutions and Sample solution Concomitantly determine the absorbance of the solutions. Make any correction using a deuterium lamp.

Acceptance criteria: NMT 0.

LIMIT OF LEAD

Sample solution: Use the Sample stock solution as di- rected in the test for Limit of Iron.

Diluent: Nitric acid in water (1 in 100)

Lead standard stock solution: 10 µg/mL of lead pre- pared as follows. Dissolve 160 mg of lead nitrate in 100 mL of Diluent, and dilute with water to 1000 mL. Dilute this solution with water (1 in 10).

Lead standard solutions: Into four identical 100-mL volumetric flasks, each containing 50.0 mL of 0.5 N hydrochloric acid, transfer respectively 5.0, 7.5, 10.0, and 12.5 mL of Lead standard stock solution, and dilute with water to volume.

Instrumental conditions

Mode: Atomic absorption spectrophotometry

Analytical wavelength: Lead emission line at 217.0 nm

Lamp: Lead hollow-cathode

Flame: Air-acetylene

Analysis Samples: Lead standard solutions and Sample solution Concomitantly determine the absorbance of the solutions.

Acceptance criteria: NMT 10 ppm

LIMIT OF CALCIUM

Lanthanum chloride solution: Prepare as directed in the Assay.

Calcium standard stock solution: 100 µg/mL of cal- cium, prepared immediately before use by diluting a 3.67 mg/mL solution of calcium chloride dihydrate in diluted hydrochloric acid with water (1 in 10)

Calcium standard solutions: Into four identical 100-mL volumetric flasks, each containing 10.0 mL of hydro- chloric acid and 10 mL of Lanthanum chloride solution, transfer respectively 1.0, 2.0, 3.0, and 4.0 mL of Calcium standard stock solution, and dilute each solution with water to volume.

Sample stock solution: Prepare as directed in the Assay.

Sample solution: Transfer 5.0 mL of the Sample stock solution to a 100-mL volumetric flask, add 10.0 mL of hydrochloric acid and 10 mL of Lanthanum chloride solution, and dilute with water to volume.

Instrumental conditions

Mode: Atomic absorption spectrophotometry

Analytical wavelength: Calcium emission line at 422.7 nm

Lamp: Calcium hollow-cathode

Flame: Nitrous oxide-acetylene

Analysis Samples: Calcium standard solutions and Sample solution Concomitantly determine the absorbance of the solutions.

Acceptance criteria: NMT 0.9%

LIMIT OF ALUMINUM

Cesium chloride solution: 25.3 mg/mL of cesium chloride in water.

Aluminium standard stock solution: 100 µg/mL of aluminium, prepared immediately before use by diluting an 8.947 mg/mL solution of aluminium chloride in water with water (1 in 10)

Aluminium standard solutions: Into four identical 100- mL volumetric flasks, each containing 10.0 mL of hydro- chloric acid and 10 mL of Cesium chloride solution, trans- fer respectively 5.0, 10.0, 15.0, and 20.0 mL of Aluminium standard stock solution, and dilute with water to volume.

Sample stock solution: Proceed as directed in the As- say. Transfer 5 mL of the Cesium chloride solution to the 50-mL flask prior to transfer of the residue, and dilute with water to volume.

Sample solution: Transfer 5.0 mL of the Sample stock solution to a 100-mL volumetric flask, add 10 mL of the Cesium chloride solution and 10.0 mL of hydrochloric acid, and dilute with water to volume. Instrumental conditions

Mode: Atomic absorption spectrophotometry

Analytical wavelength: Aluminium emission line at 309.3 nm

Lamp: Aluminium hollow-cathode

Flame: Nitrous oxide–acetylene

Samples: Aluminium standard solutions and Sample solution Concomitantly determine the absorbance of the solutions.

Acceptance criteria: NMT 2.0%

ABSENCE OF ASBESTOS

1: Infrared Absorption

The IR absorption spectrum of a potassium bromide dispersion of Talc at the absorption band at 758 ±1 cm^{-1}, using scale expansion, may indicate the presence of tremolite or chlorite. If the absorption band remains after ignition of the substance at 850° for at least 30 min, it indicates the

presence of tremolite. In the range 600 cm^{-1} to 650 cm^{-1} using scale expansion, any ab- sorption band or shoulder may indicate the presence of serpentines**.**

2: Procedure 2: Use the following conditions (see X-Ray Diffraction (941)):

Cu Kα monochromatic 40 kV radiation, 24–30 mA; the incident slit is set at 1°; the detection slit is set at 0.2°; the goniometer speed is 1/10° 20/min; the scanning range is 10°-13° 20 and 24°-26° 20; the sample is not oriented. Prepare a random sample, and place on the sample holder. Pack and smooth its surface with a polished glass microscope slide. Record the diffractograms: the presence of amphiboles is detected by a diffraction peak at 10.5 ± 0.1° 20, and the presence of serpentines is detected by diffraction peaks at 24.3 ± 0.1° 20 to 12.1 ± 0.1° 20.

3: Procedure 3:

The presence of asbestos is shown if there is a range of length to width ratios of 20:1 to 100:1, or higher for fibres longer than 5 μm; if there is a capability of splitting into very thin fibrils; and if there are two or more of the following four criteria: (1) parallel fibres occurring in bundles, (2) fibre bundles displaying frayed ends, (3) fibres in the form of thin needles, and (4) matted masses of individual fibres and/or fibres showing curvature.

SPECIFIC TESTS

MICROBIAL Enumeration TESTS (61) and TESTS FOR SPECI-FIED MICROORGANISMS (62) Intended for topical administration Total aerobic microbial count: NMT 100 cfu/g

Total combined molds and yeasts count: NMT 50 cfu /g Intended for oral administration

Total aerobic microbial count: NMT 1000 cfu/g

Total combined molds and yeasts count: NMT 100 cfu/g

ACIDITY AND ALKALINITY:

Boil 2.5 g of Talc with 50 mL of carbon dioxide-free water under reflux. Filter under vacuum. To 10 mL of the filtrate, add 0.1 mL of bromothymol blue TS. Add 0.01 N hydrochloric acid un- til the indicator changes colour. To a second 10 mL of the filtrate, add 0.1 mL of phenolphthalein TS. Add 0.01 N sodium hydroxide until the indicator turns pink.

Acceptance criteria: NMT 0.4 mL of 0.01 N hydrochloric acid is required to change the colour of the bromothymol blue indicator. NMT 0.3 mL of 0.01 N sodium hydroxide is required to change the colour of the phenolphthalein indicator to pink.

LOSS ON IGNITION (733)

Sample: 1 g

Analysis: Ignite at 1075 ± 25° to constant weight.

Acceptance criteria: It loses NMT 7.0% of its weight.

ADDITIONAL REQUIREMENTS

PACKAGING AND STORAGE:

Preserve in well-closed containers. No storage requirements specified.

LABELING: The label states, where applicable, that the substance is suitable for oral or topical administration. The certificate of analysis states the absence of asbestos. It also indicates that Talc is not derived from deposits that are known to contain associated asbestos, and which method specified in the test for Absence of Asbestos was used for analysis.

LABELING: The label states, where applicable, that the substance is suitable for oral or topical administration. The certificate of analysis states the absence of asbestos. It also indicates that Talc is not derived from deposits that are known to contain associated asbestos, and which method specified in the test for Absence of Asbestos was used for analysis.

- **Sodium Starch Glycolate**

DEFINITION

Sodium Starch Glycolate is the sodium salt of a carboxy- methyl ether of starch or of a cross-linked carboxymethyl ether of starch. It may contain NMT 7.0% of Sodium Chloride. The pH and assay requirements for Type A and Type B are set forth in the accompanying table.

Type	pH		% Sodium, Combined for as Sodium Starch pH Glycolate	
	Min.	Max.	Min.	Max.
A	5.5	7.5	2.8	4.2
B	3.0	5.0	2.0	3.4

IDENTIFICATION

A. INFRARED ABSORPTION

B. An acidified solution of it 2s (NF32) is coloured blue to violet by the addition of iodine and potassium iodide T.

C. PROCEDURE

Potassium pyroantimonate solution: Dissolve 2s (NF32) 2 g of potassium pyroantimonate in 85 25 (NF32) mL of hot 25 (NF32) water. Cool 25 (NF32) quickly, and add 10 mL of a solution of potassium hydroxide (3 in 20). Allow to stand for 24 h,25 (NF32) filter, and dilute with water to 100 mL.25 (NF32) Analysis: To a 2-mL portion of the Sample solution pre- pared for the test for Limit of Iron, add 2mL of 15% potassium carbonate, and heat to boiling. No precipitate is formed. Add 25 (NF32) 4 mL of Potassium pyroan timonate solution, and heat to boiling. Allow to cool in ice water and, if 25 (NF32) necessary, rub the inside of the test tube with a glass rod.

Acceptance criteria: A dense 2s (NF32) precipitate is formed**.**

D. Sodium Starch Glycolate imparts an intense Sample solution: Transfer 200 mg to a 100-mL beaker. yellow colour to a nonluminous flame.

ASSAY

PROCEDURE

Sample: 1 g

Analysis: Transfer the Sample to a conical flask, add 20 mL of 80% alcohol, stir for 10 min, and filter. Re- peat the extraction until the chloride has been completely extracted, as shown by a test with silver nitrate. Dry the insoluble portion at 105° to constant weight, and transfer an accurately weighed portion (700 mg) of the dried 80% alcohol-insoluble portion to a suitable flask. Add 80 mL of glacial acetic acid, and heat the mixture under reflux on a boiling water bath for 2 h. Cool

to room temperature, and titrate with 0.1 N per- chloric acid VS, determining the endpoint potentiometrically

Calculate the percentage of sodium combined in the form of sodium starch glycolate:

$$\text{Result} = 100 \times (22.99) \times V \times N/W$$

V = volume of perchloric acid consumed (mL)
N = normality of the perchloric acid
W = weight of the dried alcohol-insoluble residue taken for the Assay (mg)

Acceptance criteria: 2.8%-4.2% for Type A; 2.0%-3.4% for Type B

THER COMPONENTS

LIMIT OF SODIUM CHLORIDE

Sample: 500 mg of Sodium Starch Glycolate Titrimetric system

Mode: Direct titration

Titrant: 0.1 N silver nitrate VS

Endpoint detection: Potentiometric Electrodes

Indicator: Suitable silver-based

Reference: Double junction electrode containing a 10% potassium nitrate filling solution in the outer jacket, and a standard filling solution in the inner jacket

Analysis: Transfer the Sample to a beaker, and suspend in 100 mL of water. Add 1 mL of nitric acid. Titrate with the Titrant. Each mL of 0.1 N silver nitrate is equivalent to 5.844 mg of sodium chloride.

Acceptance criteria: NMT 7.0%

LIMIT OF SODIUM GLYCOLATE

Solution A: 0.1 mg/mL of 2,7-dihydroxynaphthalene in sulfuric acid; allow to stand until decolorized, and use within 2 days.

Standard solution: Transfer 310 mg of glycolic acid, previously dried over phosphorus pentoxide in a desiccator at room temperature overnight, to a 500-mL volumetric flask. 2S (NF32) Dissolve in and dilute with water to volume. Transfer 5.0 mL of this solution to a 100-mL beaker, add 4 mL of 6 N acetic acid, and allow to stand for about 30 min. Add 50 mL of acetone and 1 g of sodium chloride, mix, and pass-through fast filter paper moistened with acetone into a 100-mL volumetric flask. Rinse the beaker and the filter paper with acetone. Combine the filtrate and washings, dilute with acetone to volume, and mix. Allow to stand for 24 h without shaking. Use the clear supernatant as the standard solution.

Sample solution: Transfer 200 mg to a 100-mL beaker. Add 4 mL of 6 N acetic acid and 5 mL of water. Stir until dissolution is complete (about 10 min). Add 50 mL of acetone and 1 g of sodium chloride, mix, 2S (NF32) and pass-through fast filter paper moistened with acetone into a 100-mL volumetric flask. Rinse the beaker and filter paper with acetone. Combine the filtrate and washings,25 (NF32) dilutes with acetone to volume, and mix. 25 (NF32) Allow to stand for 24 h without shaking. Use the clear supernatant as the Sample solution.

Analysis: Treat the Sample solution and the Standard solution as follows. Heat 2.0 mL of the solution on a water bath for 20 min to remove the acetone. Cool to room temperature. Add 20.0 mL of Solution A to the solution under test, mix, and heat on heat on a water bath for 20 min. Cool under running water, and quantitatively transfer to a 25-mL volumetric flask. Maintain the flask under running water, and dilute with sulfuric acid to volume. Within 10 min, determine the absorbance of the solution at 540 nm with a suitable spectrophotometer, using water as the blank.

Acceptance criteria: The absorbance of the Sample solution is NMT that of the Standard solution (2.0%).

IMPURITIES:

Heavy Metals: 20 ppm

LIMIT OF IRON

Standard solution: Dissolve 863.4 mg of ferric ammonium sulphate [$FeNH4(SO4)2\ 12H_2O$] in water, add 25 mL of 2N sulfuric acid, dilute with water to 500.0 mL, and mix. Pipet 10 mL of this solution into a 100-mL volumetric flask, dilute with water to volume, and mix. Pipet 5 mL of this solution into a 100-mL volumetric flask, dilute with water to volume, and mix. This solution contains the equivalent of 1.0 µg/mL of iron.

Sample solution: Place 2.5 g in a silica or platinum crucible, and add 2 mL of 10 10N sulfuric acid. Heat on a water bath, then cautiously raise the temperature progressively over an open flame. Ignite, preferably in a muffle furnace, at 600 ± 25°. Continue heating until all black particles have disappeared. Cool, add a few drops of 2 N sulfuric acid, and heat and ignite as above. Add a few drops of 2 M ammonium carbonate, evaporate to dryness, and ignite as above. Cool, dis- solve the residue in 50 mL of water, and mix.

Analysis: Treat the Sample solution and the Standard solution as follows. Transfer 10 mL of the solution to a suitable beaker, add 2 mL of citric acid solution (1 in 5) and 0.1 mL of thioglycolic acid, and mix. Render the solution alkaline, using litmus paper as an external indicator, by the addition of ammonium hydroxide. Dilute with water to 20 mL, and mix. Allow the solutions to stand for 5 min.

Acceptance criteria: The color of the solution from the Sample solution is a shade of pink no deeper than that of the solution from the Standard solution (0.002%).

SPECIFIC TESTS

MICROBIAL ENUMERATION TESTS (61) and TESTS FOR SPECI- FIED MICROORGANISMS (62): It meets the requirements of the tests for absence of Salmonella species and Escherichia coli.

pH (791): Disperse 1 g in 30 mL of water. The pH of the resulting suspension is either 5.5-7.5 for Type A or 3.0-5.0 for Type B.

LOSS ON DRYING (731): Analysis: Dry at 130° for 90 min. Acceptance criteria: NMT 10.0%

ADDITIONAL REQUIREMENTS

Packaging and storage: Preserve in well - closed containers, preferably protected from wire variation in temperature and humidity, which may cause caking.

LABELING: Label it to indicate the botanical source of the starch from which it was derived, the cross- linking agent (if used), the pH range, and whether it is Type A or Type B 2S (NF32)

USP REFERENCE STANDARDS

USP Sodium Starch Glycolate Type A RS

USP Sodium Starch Glycolate Type B RS

- **Croscarmellose Sodium**

DEFINITION

Croscarmellose Sodium is the sodium salt of a cross-linked, partly O-(carboxymethylated) cellulose.

IDENTIFICATION

A. Mix 1 g with 100 mL of methylene blue solution (1 in 250,000), stir the mixture, and allow it to settle. The Croscarmellose Sodium absorbs the methylene blue and settles as a blue, fibrous mass.

B. Mix 1 g with 50 mL of water. Transfer 1 mL of the mixture to a small test tube, and add 1 mL of water and 5 drops of 1-naphthol TS. Incline the test tube, and carefully add 2 mL of sulfuric acid down the side so that it forms a lower layer: a reddish-violet colour develops at the interface.

C. A portion of the mixture of Croscarmellose Sodium with water, prepared as directed in Identification test B, meets the requirements of the flame test for Identification Tests-General (191), Sodium.

IMPURITIES

Inorganic Impurities **RESIDUE** ON IGNITION (281): 14.0%-28.0%, calculated on the dried basis. Use 1.0 g for the test, and use sufficient sulfuric acid to moisten the entire residue after the initial charring step, and additional sulfuric acid if an excessive amount of carbonaceous material remains after the initial complete vol- atilization of white fumes.

HEAVY METALS, Method II (231): 10 ppm

SODIUM CHLORIDE and SODIUM GLYCOLATE

Sodium chloride

Sample: 5 g of Croscarmellose Sodium

Analysis:

Transfer the Sample to a 250-mL beaker. Add 50 mL of water and 5 mL of 30% hydrogen peroxide, and heat on a steam bath for 20 min, stirring occasion- ally to ensure hydration. Cool, and add 100 mL of water and 10 mL of nitric acid. Titrate with 0.05 N silver nitrate VS, determining the endpoint potentiometrically, using asilver-based indicator electrode and a double-junction reference electrode containing 10% potassium nitrate filling solution in the outer jacket and a standard filling solution in the inner jacket, and stirring constantly Calculate the percentage of sodium chloride in the specimen taken:

Result = (F x V x N)/[(100 - b) x W]

F = equivalence factor for sodium chloride, 584.4
V = volume of the silver nitrate (mL)
N = normality of the silver nitrate
b = percentage of Loss on Drying, determined separately
W = weight of the specimen (g)

Sodium glycolate

Sample solution: Transfer 500 mg to a 100-mL beaker. Moisten thoroughly with 5 mL of glacial acetic acid, followed by 5 mL of water, and stir with a glass rod to ensure proper hydration (usually about 15 min). Slowly add 50 mL of acetone while stirring, then add 1 g of sodium chloride, and stir for several min to ensure complete precipitation of the carboxymethylcellulose. Filter through a soft, open-textured paper, previously wetted with a small amount of acetone, and collect the filtrate in a 100-mL volumetric flask. Use an additional 30 mL of acetone to facilitate the transfer of the solids and to wash the filter cake, then dilute with acetone to volume, and mix.

Standard stock solution: Transfer 100 mg of glycolic acid, previously dried in a desiccator at room temperature overnight, to a 100-mL volumetric flask. Dissolve in and dilute with water to volume, and mix. [NOTE-Use this solution within 30 days.]

Standard solution A: Transfer 1.0 mL of the Standard stock solution to a 100-mL volumetric flask. Add water to make 5 mL, then add 5 mL of glacial acetic acid. Dilute with acetone to volume, and mix.

Standard solution B: Transfer 2.0 mL of the Standard stock solution to a 100-mL volumetric flask. Add water to make 5 mL, then add 5 mL of glacial acetic acid. Dilute with acetone to volume, and mix.

Standard solution C: Transfer 3.0 mL of the Standard stock solution to a 100-mL volumetric flask. Add water to make 5 mL, then add 5 mL of glacial acetic acid. Dilute with acetone to volume, and mix.

Standard solution D: Transfer 4.0 mL of the Standard stock solution to a 100-mL volumetric flask. Add water to make 5 mL, then add 5 mL of glacial acetic acid. Dilute with acetone to volume, and mix.

Analysis

Samples: Sample solution, Standard solution A, Standard solution B, Standard solution C, and Standard solution D Transfer 2.0 mL of the Sample solution and 2.0 mL of each Standard solution to separate 25-mL volumetric flasks, and prepare a blank flask containing 2.0 mL of a solution containing 5% each of glacial acetic acid and water in acetone. Place the uncovered flasks in a boiling water bath for 20 min to remove the acetone. Remove from the bath, and cool. Add to each flask 5.0 mL of 2,7-dihydroxynaphthalene TS, mix, add an additional 15 mL, and again mix. Cover the mouth of each flask with a small piece of aluminium foil. Place the flasks upright in a boiling water bath for 20 min, then remove from the bath, cool, dilute with sulfuric acid to volume, and mix. Determine the absorbance of each solution at 540 nm, with a suitable spectrophotometer,

against the blank, and prepare a standard curve using the absorbances obtained from the Standard solutions. Calculate the percentage of sodium glycolate in the specimen taken:

$$\text{Result} = (F \times W_1)/ [(100 – b) \times W2]$$

F = factor converting glycolic acid to sodium glycolate, 12.9
W_1 = weight of glycolic acid in the specimen (mg), determined from the standard curve and the absorbance of the Sample solution
b= percentage of Loss on Drying, determined separately
W_2 = weight of the specimen taken (g) Acceptance criteria: The sum of the percentages of sodium chloride and sodium glycolate is NMT 0.5%.

SPECIFIC TESTS

CONTENT OF WATER-SOLUBLE MATERIAL

Analysis: Disperse 10 g in 800 mL of water, and stir for 1 min every 10 min during the first 30 min. Allow to stand for an additional h, or centrifuge, if necessary. Decant 200 mL of the aqueous slurry rry onto a rapid-filtering filter paper in a vacuum filtration funnel, apply vacuum, and collect about 150 mL of the filtrate. Pour the filtrate into a tared 250-mL beaker, weigh, and calculate the weight, in g, of the filtrate, W3, by difference. Concentrate on a hot plate to a volume, but not to dryness; dry at 105° for 4 small h; again weigh; and calculate the weight, in g, of residue W_1, by difference. Calculate the percentage of water-soluble material in the specimen, on the dried basis, taken:

$$\text{Result} = [100 \times W1 \times (800 + W2)]/(W2 \times W3 \times [1 - (0.01 \times b)])$$

W_1 = weight of residue by difference (g)
W_2= weight of the specimen taken (g)
W_3 = weight of the filtrate by difference (g)
b = percentage Loss on Drying of the specimen taken

Acceptance criteria: NMT 10.0%

DEGREE OF SUBSTITUTION

Sample: 1 g

Analysis: Transfer the Sample to a glass-stoppered, 500-mL conical flask. Add 300 mL of sodium chloride solution (1 in 10), then add 25.0 mL of 0.1 N sodium hydroxide VS. Insert the stopper, and allow to stand for 5 min with intermittent shaking. Add 5 drops of m-cresol purple TS, and from a burette add 15 mL of 0.1 N hydrochloric acid VS. Insert the stopper in the flask, and shake. If the solution is violet, add 0.1 N hydrochloric acid VS in 1-mL portions until the solution becomes yellow, shaking after each addition. Titrate with 0.1 N sodium hydroxide VS to a violet endpoint. Calculate the net number of milliequivalents, M, of base required for the neutralization of 1 g of

Croscarmellose Sodium, on the dried basis. Calculate the degree of acid carboxymethyl substitution, A:

$$\text{Result} = 1150 \times M/[7102- (412 \times M) - (80 \times C)]$$

M = milliequivalents
C = percentage of Residue on Ignition of the Croscarmellose Sodium as determined in the test for Residue on Ignition Calculate the degree of sodium carboxymethyl substitution, S:

$$\text{Result} = [162 + (58 \times A)] \times C/ [7102 - (80 \times C)]$$

A = degree of acid carboxymethyl substitution, as determined above
C = percentage of Residue on Ignition of the Croscarmellose Sodium as determined in the test for Residue on Ignition The degree of substitution is the sum of A + S.

Acceptance criteria: The degree of substitution is 0.60-0.85, on the dried basis

LOSS ON DRYING (731): Dry a sample at 105° for 6 h: it loses NMT 10.0% of its weight.

MICROBIAL ENUMERATION TESTS (61) and TESTS FOR SPECIFIED MICROORGANISMS (62):

The total aerobic microbial count does not exceed 1000 cfu/g, and the total combined molds and yeasts count does not exceed 100 cfu/g. It meets the requirements of the tests for absence of Escherichia coli.

PH (791): The pH of the dispersion is 5.0-7.0. Mix 1 g with 100 mL of water for 5 min.

SETTLING VOLUME

Analysis: To 75 mL of water in a 100-mL graduated cylinder, add 1.5 g of it in 0.5-g portions, shaking vigorously after each addition. Add water to make 100 mL, shake again until all of the powder is homogeneously distributed, and allow to stand for 4 h. Note the volume of the settled mass.

Acceptance criteria: The volume of the settled mass is 10.0-30.0 mL

ADDITIONAL REQUIREMENTS

PACKAGING AND STORAGE: Preserve in well-closed containers. No storage requirements specified.

- **Crospovidone**

DEFINITION

Crospovidone is a water-insoluble synthetic cross-linked homo- polymer of N-vinyl-2-pyrrolidinone. It contains NLT 11.0% and NMT 12.8% of nitrogen (N), calculated on the dried basis. Two types of Crospovidone are available, depending on the particle size: Type A and Type B.25 (NF29)

IDENTIFICATION

A. INFRARED ABSORPTION (197K): Previously dried in a vac- uum at 105° for 1 h.

B. Sample: 1 g

Analysis: Suspend the Sample in 10 ml of water, add 0.1 mL of 0.1 N iodine, and shake for 30 s. Add 1 mL of starch TS, and shake.

Acceptance criteria: No blue color develop

C. To 10 mL of water add 0.1 g and shake. A suspension is formed and no clear solution is obtained within 15 min.25

D. Sample: 20 g of the dried substance

Analysis: Clean and dry the analytical sieves used in the analysis by washing the sieves in hot water. Allow to dry overnight in a drying cabinet at 105°. Place the Sample in a 1000-mL conical flask, add 500 mL of water, and shake the suspension for 30 min. Pour the suspension through a 63- µm analytical sieve, previously tared, and rinse the sieve with water until the filtrater is clear. Dry the sieve and sample residue at 105° for 5 min a drying cabinet without circulating air. Cool in a desiccator for 30 min, and weigh. Calculate the percentage sieving residue fraction of sample particles having a diameter of more than 63 µm:

Result = $[(m_1 m3) \times 100]/m2$

m_1 = mass of the sieve and sample residue, after drying for 5 h (g)
m_3= mass of the sieve (g)
m_2 = initial mass of the sample, calculated on a dried basis (g)

Acceptance criteria: If the sieving residue fraction is more than 15%, the substance is classified as Type A; if the sieving residue fraction is NMT 15%, the substance is classified as Type B.25 (NF29)

ASSAY

NITROGEN DETERMINATION, Method II (461)

Sample: 0.1 g

Analysis: Proceed as directed, using the Sample. In the procedure, omit the use of hydrogen peroxide, and use 5 g of a powdered mixture of potassium sulfate, cupric sulfate, and titanium dioxide (33:1:1), instead of potassium sulfate and cupric sulfate (10:1). Heat until a clear, light

green solution is obtained. Heat for an additional 45 min, and proceed as directed for Procedure, beginning with "Cautiously add to the digestion mixture 70 mL of water".

Acceptance criteria: 11.0%-12.8% on the dried 25 (NF29) basis

IMPURITIES

RESIDUE ON IGNITION (281): NMT 0.1%, determined on 1.0 g 25 (NF29)

HEAVY METALS, Method II (231): NMT 10 ppm.

PEROXIDES

Sample suspension A: 40 mg/mL in water. To 25 mL of this suspension add 2 mL of titanium trichloride-sulfuric acid TS. Allow to stand for 30 min, and filter.

Sample suspension B: 16 mg/mL in water. To 25 mL of this suspension add 2 mL of titanium trichloride-sulfuric acid TS. Allow to stand for 30 min, and filter.

Compensation liquid A: 40 mg/mL in water. Filter, take 25 mL, and add 2 mL of a 13% solution of sulfuric acid. Compensation liquid B: 16 mg/mL in water. Filter, take 25 mL, and add 2 mL of a 13% solution of sulfuric acid.

Analysis: Measure the absorbance of the filtrate at 405 nm against the appropriate compensation liquid. Acceptance criteria: NMT 0.35. For Type A, this corresponds to NMT 400 ppm expressed as H2O2; for Type B, this corresponds to NMT 1000 ppm expressed as H2O2-25 (NF29)

VINYLPYRROLIDINONE

Mobile phase: Acetonitrile and water (1:9)

Sample solution: 25 mg/mL suspension in methanol. Shake for 60 min. Leave the bulk to settle, and pass through a filter of 0.2-µm pore size.

Reference stock solution A: 5 µg/mL of vinyl pyrrolidinone in methanol

Reference stock solution B: 100 µg/mL of vinylpyrrolidone- none and 5 mg/mL of vinyl acetate in methanol

Reference solution A: A 1 in 20 solution of Reference stock solution A in Mobile phase

Reference solution B: A 1 in 100 solution of Reference stock solution B in Mobile phase

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC
Detector: UV
Detection wavelength: 235 nm
Precolumn: 4-mm × 2.5-cm; 5-µm packing L1

Column: 4-mm × 25-cm; 5-µm packing L1
Column temperature: 40°
Flow rate: 1 mL/min
Injection size: 50 µL. [NOTE-After each injection of the Sample solution, wash the precolumn by passing the Mobile phase backwards, at the same flow rate as applied in the test, for 30 min.]

System suitability

Samples: Reference solution A and Reference solution B Suitability requirements

Resolution: NLT 2.0 between vinylpyrrolidone and vinyl acetate, Reference solution B

Relative standard deviation: NMT 2.0% for 6 injections, Reference solution A

Analysis Samples: Sample solution and Reference solution A Record the chromatograms, and measure the responses for the vinyl pyrrolidinone peak.

Acceptance criteria: The area of the peak from the Sample solution is NMT the area of the principal peak from Reference solution A (NMT 10 ppm).25 (NF29)

SPECIFIC TESTS

PH (791): 5.0-8.0, in an aqueous suspension (1 in 100) 25 (NF29)

WATER DETERMINATION, Method | (921): NMT 5.0% 25 (NF29)

LOSS ON DRYING (731): Dry 0.5 g at 105° to constant weight; it loses NMT 5.0% of its weight.25 (NF29)

WATER-SOLUBLE SUBSTANCES

Sample: 25.0 g

Analysis: Transfer the Sample to a 400-mL beaker, add 200 mL of water, and stir on a magnetic stirrer, using a 5-cm stirring bar, for 1 h. Transfer to a 250-mL volumetric flask with the aid of 25 mL of water. Add water to volume. Allow the bulk of the solids to settle. Pass 100 mL of the relatively clear supernatant through a membrane filter of 0.45-µm pore size, protected against clogging by superimposing a membrane filter of 3-um pore size. While filtering, stir the solution above the filter manually or with a mechanical stir- rer, taking care not to physically damage the membrane fil- ter. Transfer 50.0 mL of the clear filtrate to a tared 100-mL beaker, evaporate to dryness, and dry at 110° for 3 h. Acceptance criteria: The weight of the residue does not exceed 75 mg (1.5%). -(NF29)

ADDITIONAL REQUIREMENTS

PACKAGING AND STORAGE: Preserve in tight containers.

LABELING: The label states the type (Type A or Type B). +25 (NF29)

USP REFERENCE STANDARDS (11)

USP Crospovidone RS.

3.2.P.4.3 Validation of Analytical Procedures

As the excipients are mentioned in US pharmacopoeia so there is no need to provide validation of analytical procedures.

3.2.P.4.4 Justification of Specifications

The specifications followed in analyzing these materials are those specified in the US. The results obtained are within specified limit. It indicates that they possess the require quality standards and purity. Hence, it is not required to justify specification of excipients additionally.

3.2.P.4.5 Excipients of Human or Animal Origin

There are no excipients used are derived from human or animal origin. The product is produced in facility where no animal, animal by-products, veterinary vaccines or animal pathogens are maintained and are packed.

3.2.P.4.6 Novel Excipients

No novel excipients are used in the manufacturing process

3.2.P.5 Control of Drug Product

3.2.P.5.1 Specification(s)

	Dadasaheb Balpande Collage of Pharmacy, Nagpur		Page No 1 of 1
Quality Control Department			
FINISHED PRODUCT SPECIFICATION			
GENERIC NAME	TELMISARTAN AND HYDROCHOLOROTHAZIDE COMBINATION TABLET USP		
SHELF LIFE	2 YEARS		
EFFECTIVE DATE	15 MARCH 2024	**NEXT REVIEW DATE**	15 MARCH 2026
PHARMACOPIAL REFERENCE	UNITED STATE PHARMACOPIA		
LABLE CLAIM: EACH ORAL TABLET CONTAINS TELMISARTAN AND HYDROCHOLOROTHAZIDE TABLET USP **COLOUR**: WHITE COLOURE Excipient qs			
SAMPLE QUALITY	TESTING SAMPLE: 30 TABLETS CONTROL SAMPLE: 30 TABLETS		

Sr No.	TEST	STANDARD
1	Description	White colour circular, biconvex, oral tablets plain on both sides
2	Average Weight	300 mg
3	Uniformity of Weight of Tablets	± 7.5% of average weight
4	Friability	Not more than 1%
5	Thickness	4.30 mm ± 0.20 mm (4.10 – 4.50 mm)
6.	Hardness	Not less than 2.000 Kp
8.	Dissolution test	Not less than 80%
9.	Disintegration test	Not more 30 minutes

APPROVAL		
Prepared By:	**Reviewed By**	**Approved By:**

SEAL

3.2.P.5.2 Analytical Procedures

FINISHED PRODUCTS CONTROL METHOD
Telmisartan and Hydrochlorothiazide Combination Tablet USP

Sr. No	Parameters	Limits
1	**Description**	**Procedure:** Take 20 tablets on a clean and dry petri dish against white background and observe against requirements. **Limit:** White coloured, circular, biconvex tablets plain on both side
2	**Average weight**	**Instrument:** Analytical balance **Procedure:** Weigh 30 tablets and calculate the average weight. **Calculation:** $\frac{Weight\ of\ 30\ Tablets}{30}$
3	**Uniformity of weight**	**Instrument:** Analytical balance **Procedure:** Determine the average weight on 30 tablets and determine individual weights of 30 tablets and record the deviation from the average. **Limit:** ± 7.5% of average weight
4	**Tablet Dimensions**	**Instrument:** Tablet Tester **Procedure:** Thickness and diameter of the tablets were measured using a "Tablet Tester" (Model: ULH-3P, UL UNIVERSAL). It was determined by checking three tablets from each formulation. It is expressed in mm.
5	**Hardness**	**Instrument:** Tablet Tester **Procedure:** Hardness of the prepared formulations was determined using "Tablet Tester" (Model: ULH-3P, UL UNIVERSAL). It was expressed in kp. Three tablets were selected and hardness was measured **Limit:** Not less than 2.00 kp

6	**Friability**	**Instrument:** Roche Friabilator **Procedure:** Pre- weighed sample of tablets was placed in the friability tester, which was then operated for 25 revolutions for 4 min, tablets were dedusted and reweighed. **Calculation:** $\mathrm{F}\ (\%) = \frac{Initial\ Weight\ -\ Final\ Weight}{Initial\ Weight} \times 100$ **Limit:** Not more than 1%
7	**Disintegration**	**Instrument:** Disintegration apparatus USP (Electrolab) **Procedure:** In vitro disintegration test was carried out at 37 ± 2˚C in 900 ml by using disintegration media i.e., water. Six tablets of each formulation were taken and placed in 6 tubes of disintegration apparatus. The time for disintegration of each tablet is recorded. **Limit:** Not more than 30 minutes
8	**In–vitro dissolution studies**	**Instrument:** Dissolution Tester (USP) TDT-08L **Procedure:** In-vitro dissolution studies for all the fabricated tablets were carried out using USP apparatus type II at 75 rpm. The dissolution medium used was (7.5 phosphate buffer and 0.1 M HCL, 900 ml) maintained at 37 ± 0.5ºC. Aliquots of dissolution media were withdrawn (5ml) at different intervals and content of Telmisartan and hydrochlorothiazide was measured by determining absorbance at 295 nm and 221 nm. **Limit:** Not less than 80%

3.2.P.5.3 Validation of Analytical Procedures

All the analytical procedures are mentioned and performed as per the US pharmacopoeia, so there is no need to provide validation of Analytical procedures.

3.2.P.5.4 Batch Analyses

Batch 1

PRODUCT: TELMISARTAN AND HYDROCHLOROTHIAZIDE COMBINATION TABLET USP	
Batch No: 1	Batch Size: 30 Tablets
Mfg. Date: 1 March 2024	Date of Analysis: 02/03/2024
Expiry Date: 1 February 2026	Date of Report: 04/03/2024
Sampled Quantity: 30 X 30 Tablets	Mfg. By: DBCOP

TEST	LIMIT	RESULTS	
Description	White colour circular, biconvex, oral tablets plain on both sides.	White colour circular, biconvex, oral tablets plain on both sides.	
Average Weight of Tablets	300 mg	297.9 mg	
Friability	Not more than 1%	0.77 %	
Uniformity of Weight of Tablets	± 7.5% of average weight	Complies	
Hardness	Not less than 2.000 Kp	6 Kp	
Thickness	4.30 mm ± 0.20 mm (4.10 – 4.50 mm)	3.89 mm	
Disintegration Test	Not more 30 minutes	40 Sec	
Dissolution Test	Not less than 80%	Telmisartan	HCTZ
		92.26 %	91.44 %
Content uniformity	75% to 115%	Complies	

APPROVAL		
Prepared By:	**Reviewed By**	**Approved By:**

SEAL

Batch 2

PRODUCT: TELMISARTAN AND HYDROCHOLOROTHAZIDE COMBINATION TABLET USP	
Batch No: 2	Batch Size: 30 Tablets
Mfg. Date: 5 March 2024	Date of Analysis: 6/03/2024
Expiry Date: 5 February 2026	Date of Report: 09/03/2024
Sampled Quantity: 30 X 30 Tablets	Mfg. By: DBCOP

TEST	**LIMIT**	**RESULTS**	
Description	White colour circular, biconvex, oral tablets plain on both sides.	White colour circular, biconvex, oral tablets plain on both sides.	
Average Weight of Tablets	300 mg	279.7 mg	
Friability	Not more than 1%	0.23 %	
Uniformity of Weight of Tablets	± 7.5% of average weight	Complies	
Hardness	Not less than 2.000 Kp	5.2 Kp	
Thickness	4.30 mm ± 0.20 mm (4.10 – 4.50 mm)	3.49 mm	
Disintegration Test	Not more 30 minutes	40 Sec	
Dissolution Test	Not less than 80%	Telmisartan	HCTZ
		91.58 %	91.00 %
Content uniformity	75% to 115%	Complies	

APPROVAL		
Prepared By:	**Reviewed By**	**Approved By:**

DADASAHEB BALPANDE COLLEGE OF PHARMACY SEAL BESA, NAGPUR-37

Batch 3

PRODUCT: TELMISARTAN AND HYDROCHOLOROTHAZIDE COMBINATION TABLET USP	
Batch No: 3	Batch Size: 30 Tablets
Mfg. Date: 10 March 2024	Date of Analysis: 11/03/2024
Expiry Date: 10 February 2026	Date of Report: 14/03/2024
Sampled Quantity: 30 X 30 Tablets	Mfg. By: DBCOP

TEST	LIMIT	RESULTS	
Description	White colour circular, biconvex, oral tablets plain on both sides.	White colour circular, biconvex, oral tablets plain on both sides.	
Average Weight of Tablets	300 mg	301.5 mg	
Friability	Not more than 1%	0.16 %	
Uniformity of Weight of Tablets	± 7.5% of average weight	Complies	
Hardness	Not less than 2.000 Kp	6.0 Kp	
Thickness	4.30 mm ± 0.20 mm (4.10 – 4.50 mm)	4.29 mm	
Disintegration Test	Not more 30 minutes	30 Sec	
Dissolution Test	Not less than 80%	Telmisartan	HCTZ
		91.28 %	89.57 %
Content uniformity	75% to 115%	Complies	

APPROVAL		
Prepared By:	**Reviewed By**	**Approved By:**

SEAL

Batch 4

PRODUCT: TELMISARTAN AND HYDROCHOLOROTHIAZIDE COMBINATION TABLET USP	
Batch No: 4	Batch Size: 30 Tablets
Mfg. Date: 15 March 2024	Date of Analysis: 16/03/2024
Expiry Date: 15 February 2026	Date of Report: 19/03/2024
Sampled Quantity: 30 X 30 Tablets	Mfg. By: DBCOP

TEST	LIMIT	RESULTS	
Description	White colour circular, biconvex, oral tablets plain on both sides.	White colour circular, biconvex, oral tablets plain on both sides.	
Average Weight of Tablets	300 mg	309.9 mg	
Friability	Not more than 1%	0.23 %	
Uniformity of Weight of Tablets	± 7.5% of average weight	Complies	
Hardness	Not less than 2.000 Kp	5.4 Kp	
Thickness	4.30 mm ± 0.20 mm (4.10 – 4.50 mm)	4.5 mm	
Disintegration Test	Not more 30 minutes	30 Sec	
Dissolution Test	Not less than 80%	Telmisartan	HCTZ
		92.22 %	92.02 %
Content uniformity	75% to 115%	Complies	

APPROVAL		
Prepared By:	**Reviewed By**	**Approved By:**

SEAL

Batch 5

PRODUCT: TELMISARTAN AND HYDROCHLOROTHAZIDE COMBINATION TABLET USP	
Batch No: 5	Batch Size: 30 Tablets
Mfg. Date: 20 March 2024	Date of Analysis: 21/03/2024
Expiry Date: 20 February 2026	Date of Report: 24/03/2024
Sampled Quantity: 30 X 30 Tablets	Mfg. By: DBCOP

TEST	LIMIT	RESULTS	
Description	White colour circular, biconvex, oral tablets plain on both sides.	White colour circular, biconvex, oral tablets plain on both sides.	
Average Weight of Tablets	300 mg	2.99.9 mg	
Friability	Not more than 1%	0.29 %	
Uniformity of Weight of Tablets	± 7.5% of average weight	Complies	
Hardness	Not less than 2.000 Kp	5.6 Kp	
Thickness	4.30 mm ± 0.20 mm (4.10 – 4.50 mm)	4.31 mm	
Disintegration Test	Not more 30 minutes	40 Sec	
Dissolution Test	Not less than 80%	Telmisartan	HCTZ
		92.55 %	92.26 %
Content uniformity	75% to 115%	Complies	

APPROVAL		
Prepared By:	**Reviewed By**	**Approved By:**

SEAL

Batch 6

PRODUCT: TELMISARTAN AND HYDROCHOLOROTHAZIDE COMBINATION TABLET USP	
Batch No: 6	Batch Size: 30 Tablets
Mfg. Date: 25 March 2024	Date of Analysis: 26/03/2024
Expiry Date: 25 February 2026	Date of Report: 29/03/2024
Sampled Quantity: 30 X 30 Tablets	Mfg. By: DBCOP

TEST	LIMIT	RESULTS	
Description	White colour circular, biconvex, oral tablets plain on both sides.	White colour circular, biconvex, oral tablets plain on both sides.	
Average Weight of Tablets	300 mg	290.6 mg	
Friability	Not more than 1%	0.56 %	
Uniformity of Weight of Tablets	± 7.5% of average weight	Complies	
Hardness	Not less than 2.000 Kp	6.06 Kp	
Thickness	4.30 mm ± 0.20 mm (4.10 – 4.50 mm)	4.53 mm	
Disintegration Test	Not more 30 minutes	45 Sec	
Dissolution Test	Not less than 80%	Telmisartan	HCTZ
		93.29 %	92.10 %
Content uniformity	75% to 115%	Complies	

APPROVAL		
Prepared By:	**Reviewed By**	**Approved By:**

SEAL

3.2.P.5.5 Characterisation of Impurities

NOT APPLICABLE

Justification: This section contains the information about the characterisation of the impurities present in the finish drug product. These studies are critical to perform at organization level.

3.2.P.5.6 Justification of Specification(s)

The specification followed in analysing (Telmisartan and Hydrochlorothiazide Combination Tablets USP) are specified in USP. The results obtained from this method are within specified limit. The USP test method is based on the requirements of various customers & this is acceptable by regulatory authorities. This justifies appropriateness of the specification.

3.2.P.6 Reference Standards or Materials

Telmisartan and Hydrochlorothiazide is a pharmacopeial product. An internal reference standard is prepared, characterized, and used as standard.

3.2.P.7 Container Closure System

Primary packing: 10 tablets are packed in the PVC-ALU Blister. Well printed aluminium foil of 0.25 µ thickness is used as lead foil and 25Ø PVC foil used as base foil for blister formation of 9 mm diameter and 4.7 ± 0.2 mm depth. The lead foil and base foils are thermally sealed.

Secondary packing: 300 gsm white board is used for printed cartons which contains 10 strips of 10 tablets blister. Which are over printed for batch numbers, manufacturing date, and expiry date.

Tertiary packing: 7 ply corrugated boxes are used to pack 100 Shrinks of 10 cartons. Which are finally sealed with BOPP tape and two straps.

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

Stability Study was carried out at 40°C ± 2°C/75% RH ± 5% condition for 6 months. Each piece of the tablet from the optimized formulation was packed in butter paper followed by aluminium foil. After intervals of 1, 3 and 6 months, the tablet was evaluated for the physical appearance and drug content.

Conclusion:

There was no significant statistical difference observed when the % drug content of various formulations of Telmisartan and Hydrochlorothiazide combination tablet stored at ambient temperatures were compared with the initial % drug content.

3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment

After approval of the product following stability studies will be performed:

Every six months, one batch from commercial production will be subjected to stability studies at Room Temperature till the expiry of the product.

The protocol for the same will be same as that described above for the initial batches. Further, if there are any process modifications then first three batches manufactured by the modified process are subjected to the stability program as given above.

3.2.P.8.3 Stability Data

Table No. I give stability data of the drug substance when stored at 40°C ± 2°C/75% RH ± 5%

Table: Results of stability studies

Initial drug content (%)		**40°C ± 2°C/75% RH ± 5 %**					
		1 Month		**3 Month**		**6 Month**	
TEL	HCTZ	TEL	HCTZ	TEL	HCTZ	TEL	HCTZ
93.89	93.73	93.81	93.65	93.78	93.74	93.71	93.68

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

The equipment's and facilities used in formulation are listed below

Table: List of machineries and equipment's required

Sr. No	Name of Equipment's	Make	Model	Equipment Code
1	Weighing Balance	SHIMAZZU	ATY224	DBCP/CIR/DB/SHIMADZU/ 001/18-19
2	Tap Density Tester	ELECTROLAB		DBCP/CIR/TDT/001/17-18
3	FT-IR	SHIMAZZU	FT-IR- DRS 800	DBCP/CIR/IR/001/18-19
4	UV Spectrophotom eter	SHIMAZZU	UV-1800	DBCP/CIR/UVVIS/002/11-12
5	Dissolution Test Apparatus	ELECTROLAB	Dissolution Tester (USP) TDT-08L	DBCP/CIR/TDISA/001/12-13
6	Disintegration Test Apparatus	ELECTROLAB	----------	DBCP/CIR/DT/001/15-16
7	Tablet Tester	UL UNIVERSAL	ULH-3P	DBCP/MR/TT/001/21-22
8	Friability Tester	ELECTROLAB	----------	DBCP/CIR/FIRA/001/15-16
9	Tablet Compressing Machin Mini Press - II	----------	----------	DBCP/MR/TBM/001/11-12

3.2.A.2 Adventitious Agents Safety Evaluation

None of the ingredients used in the drug product (Telmisartan and Hydrochlorothiazide Combination Tablets USP) is derived from animal or human origin.

3.2.A.3 Excipients

No novel excipients are used in the manufacturing process of (Telmisartan and Hydrochlorothiazide Combination Tablets USP)

MODULE - 4

Non Clinical Study Reports

4.1 Table of Content of Module 4

MODULE 4 NONCLINICAL STUDY REPORTS	
4.1	**Table of contents**
4.2	**Study Reports**
4.2.1	**Pharmacology**
4.2.1.1	Primary Pharmacodynamics
4.2.1.2	Secondary Pharmacodynamics
4.2.1.3	Safety Pharmacology
4.2.1.4	Pharmacodynamics Drug Interactions
4.2.2	**Pharmacokinetics**
4.2.2.1	Analytical Methods and Validation Reports
4.2.2.2	Absorption
4.2.2.3	Distribution
4.2.2.4	Metabolism
4.2.2.5	Excretion
4.2.2.6	Pharmacokinetic Drug Interactions
4.2.2.7	Other Pharmacokinetic studies
4.2.3	**Toxicology**
4.2.3.1	Single-Dose Toxicity
4.2.3.2	Repeate-Dose Toxicity
4.2.3.3	Genotoxicity
4.2.3.3.1	In vitro
4.2.3.3.2	In vivo
4.2.3.4	Carcinogenicity
4.2.3.4.1	Long term studies
4.2.3.4.2	Short term or medium term studies
4.2.3.4.3	Other studies

4.2.3.5	Reproductive and Developmental Toxicity
4.2.3.5.1	Fertility and early embryonic development
4.2.3.5.2	Embryo-fetal development
4.2.3.5.3	Prenatal and postnatal development, including maternal Function
4.2.3.5.4	Studies in which the offspring are dosed and /or further Evaluated
4.2.3.6	Local Tolerance
4.2.3.7	Other Toxicity studies (If available)
4.3	**Literature References**

Non-Clinical Study:

The term "non-clinical study of a drug" refers to the preclinical phase of drug development. It involves a series of laboratory-based experiments and studies conducted prior to the initiation of human clinical trials. Non-clinical studies are designed to assess the safety, pharmacology, and toxicology of a drug candidate, as well as its potential efficacy, using in vitro (cell-based) and/or in vivo (animal-based) models.

Non-clinical studies are not typically required for generic drugs because they are intended to be bioequivalent to the reference (innovator) drug that has already undergone extensive non-clinical testing. Generic drugs are copies of approved reference drugs that have demonstrated safety and efficacy through clinical trials and non-clinical studies during the original drug's development.

Telmisartan and Hydrochlorothiazide Combination Tablet USP is a generic drug application so this part is **NOT APPLICABLE.**

MODULE - 5

Clinical Study Reports

5.1 Table of Content of Module 5

MODULE 5 CLINICAL STUDY REPORTS	
5.1	**Table of contents for clinical study reports**
5.2	**Tabular listing of all clinical studies**
5.3	**Clinical Study Reports**
5.3.1	**Reports of Biopharmaceutics Studies**
5.3.1.1	Bioavailability Study Reports
5.3.1.2	Comparative BA and Bioequivalence (BE) study Reports
5.3.1.3	In vitro-In vivo Correlation Study Reports
5.3.1.4	Reports of Bioanalytical and Analytical Methods for Human Studies
5.3.2	**Reports of studies Pertinent to Pharmacokinetics using Human Biomaterials**
5.3.2.1	Plasma Protein Binding Study Reports
5.3.2.2	Reports of Hepatic Metabolism and Drug Interaction Studies
5.3.2.3	Reports of Studies Using Other Human Biomaterials
5.3.3	**Reports of Human Pharmacokinetic (PK) Studies**
5.3.3.1	Healthy Subject PK and Initial Tolerability Study Reports
5.3.3.2	Patient PK and Initial Tolerability Study Reports
5.3.3.3	Intrinsic Factor PK Study Reports
5.3.3.4	Extrinsic Factor PK Study Reports
5.3.3.5	Population PK Study Reports
5.3.4	**Reports on Human Pharmacodynamic (PD) Studies**
5.3.4.1	Healthy Subject PD and PK/PD Study Reports
5.3.4.2	Patient PD and PK/PD Study Reports
5.3.5	**Reports on Efficacy and Safety Studies**
5.3.5.1	Study Report of Uncontrolled Clinical Studies
5.3.5.2	Reports of Analysis of Data from More than One Study
5.3.5.3	Other Clinical Study Reports

5.3.6	**Report on Post-Marketing Experience**
5.3.7	**Case Report Forms and Individual Patient Listings**
5.4	**Literature References**

5.3.1 Reports of Biopharmaceutics Studies

Comparative Drug Release Profile

1. **Comparison of drug release of Telmisartan**

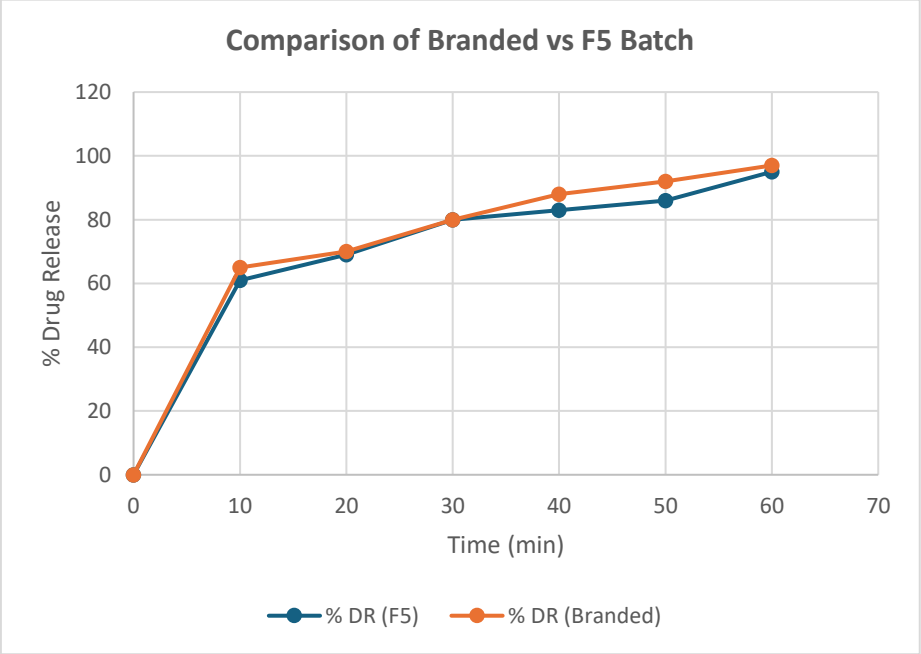


Figure: Comparative dissolution study of Marketed tablet vs Formulated batches (F5) for Telmisartan

Parameter	Batch F5
Similarity Factor (f_2)	72
Difference Factor (f_1)	4

Conclusion:

The above graph shows the comparative drug release of telmisartan from formulation batch F5 and a marketed tablet. From the graph, we can see that batch F5 showed a similar drug release pattern compared to the reference product.

2. Comparison of drug release of Hydrochlorothiazide

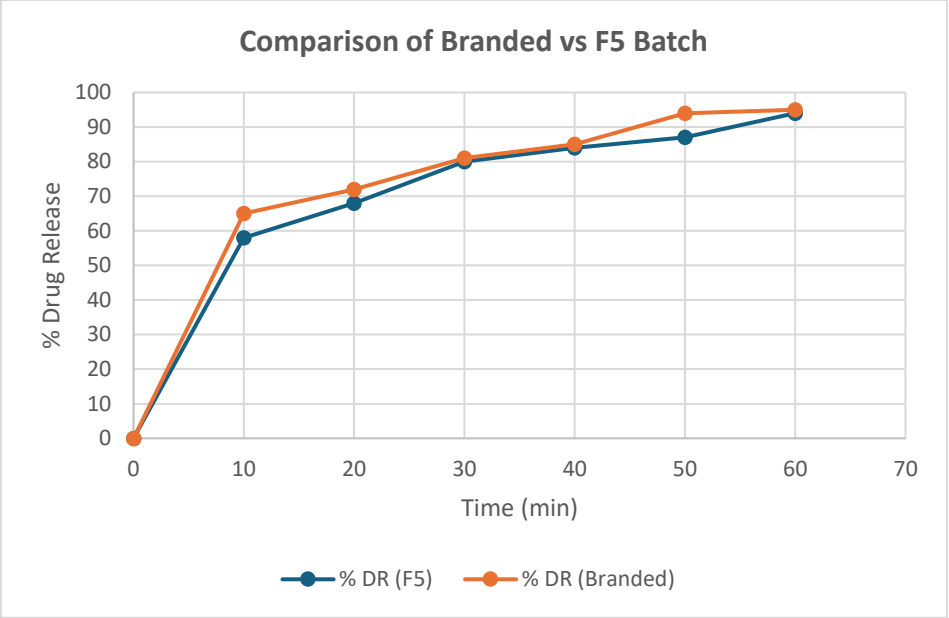


Figure: Comparative dissolution study of Marketed tablet vs Formulated batches (F5) for Hydrochlorothiazide

Parameter	Batch F5
Similarity Factor (f_2)	69
Difference Factor (f_1)	4

Conclusion:

The above graph shows the comparative drug release of hydrochlorothiazide from formulation batch F5 and a marketed tablet. From the graph, we can see that batch F5 showed a similar drug release pattern compared to the reference product.

Clinical Study Reports:

A clinical study of a drug refers to a systematic investigation conducted in human subjects to evaluate the safety, efficacy, and/or pharmacokinetics of the drug. It involves studying the drug's effects, side effects, dosage regimens, and its overall therapeutic benefit in a controlled and monitored environment.

Clinical studies are not typically required for generic drugs because they are intended to be bioequivalent to the reference (innovator) drug that has already undergone extensive clinical testing. Generic drugs are copies of approved reference drugs that have demonstrated safety and efficacy through clinical trials and non-clinical studies during the original drug's development.

Telmisartan and Hydrochlorothiazide Combination Tablet USP is a generic drug application so this part is **NOT APPLICABLE.**