DEVELOPMENT AND CHARACTERIZATION OF TELMISARTAN IMMEDIATE RELEASE TABLETS

A PROJECT SUBMITTED TO

NIRMA UNIVERSITY

In partial fulfillment of the requirements for the degree of

MASTER OF PHARMACY
IN
PHARMACEUTICS

BY

KHUSHBOO MATHUR (20MPH109), B. Pharm

UNDER THE GUIDANCE OF

DR. TEJAL MEHTA
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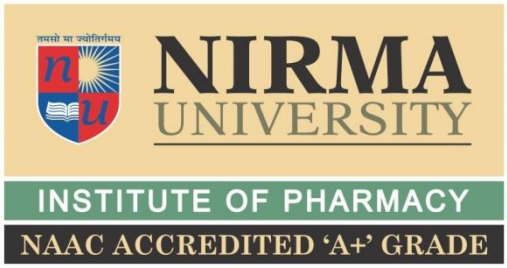

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MAY 2022

CERTIFICATE

This is to certify that the dissertation work entitled "DEVELOPMENT AND CHARACTERIZATION OF TELMISARTAN IMMEDIATE RELEASE TABLETS" submitted by Ms. Khushboo Mathur with Registration No. (20MPH109) in partial fulfillment for the award of Master of Pharmacy in "Pharmaceutics" is a bonafide research work carried out by the candidate at the Department of pharmaceutics, Institute of Pharmacy, Nirma University under my/our guidance. This work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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TO WHOM IT MAY CONCERN

This is to certify that **Ms. Khushboo Mathur** Student of M.Pharm at **Institute of Pharmacy, Nirma University (Ahmedabad)** has undergone on Industrial Project Training w.e.f **05-07-2021** to **04-01-2022** in our **F&D Department**.

During the above period we found her dedicated and regular.

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CERTIFICATE OF SIMILARITY OF WORK

This is to undertake that the dissertation work entitled "*DEVELOPMENT AND CHARACTERIZATION OF TELMISARTAN IMMEDIATE RELEASE TABLETS*" Submitted by Ms. Khushboo Mathur (20MPH109) in partial fulfillment for the award of Master of Pharmacy in "Pharmaceutics" is a bonafide research work carried out by me at the Department Of Pharmaceutics, Institute of Pharmacy, Nirma University under the guidance of "Dr. Tejal Mehta". I am aware about the rules and regulations of Plagiarism policy of Nirma University, Ahmedabad. According to that, this work is original and not reported anywhere as per best of my knowledge.

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DECLARATION

I hereby declare that the dissertation entitled "DEVELOPMENT AND CHARACTERIZATION OF TELMISARTAN IMMEDIATE RELEASE TABLETS is based on the original work carried out by me under the guidance of Dr. Tejal Metha, Head, under the Department of Pharmaceutics, Institute of Pharmacy, Nirma University. I also affirm that this work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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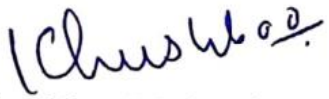

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ABSTRACT

Hypertension is a chronic illness characterized by chronically high arterial blood pressure. It is not a disease in and of itself, but it is a significant risk factor for cardiovascular death and morbidity. Telmisartan is a drug that belongs to the class of AT_1 receptor antagonists, which act on the renin-angiotensin system and lead to the eventual decrease in blood pressure. The candidate is an FDA approved, first line drug in the treatment of hypertension. As the drug is a BCS class II substance, it is practically insoluble in water and shows solubility only in a highly basic media. Thus, the present work aims to prepare immediate release tablets of the drug using wet granulation method, and match all the parameters according to the reference tablets. First of all, the reference tablet was evaluated and the critical processing parameters were identified. The prepared tablets were evaluated for appearance, weight variation, friability, disintegration time and dissolution. Optimization of the formula as well as the processing parameters was also done such a way that it favored similar dissolution, upto 101.5% drug release in 45 minutes, proper disintegration time, 8:30 minute as well as reduction in processing cost. Stability batches were prepared and stability data is being generated according to the ICH guidelines.

Keywords: Hypertension treatment drug, AT_1 Receptor antagonist, Wet granulation using RMG.

CHAPTER 1

INTRODUCTION

1.1 Introduction to Hypertension

- Hypertension is a chronic illness characterised by chronically high arterial blood pressure. (BP). (Dipiro et al., 2017)
- Hypertension is a highly prevalent condition, especially in people who have crossed middle age. It cannot be classified as a disorder in and of itself, although it is a significant risk factor for cardiovascular death or morbidity. (Tripathi, 2013)

Table 1: Classification of blood pressure

BLOOD PRESSURE CATEGORY	SYSTOLIC BLOOD PRESSURE	DIASTOLIC BLOOD PRESSURE
NORMAL	<120 mmHg	<80 mmHg
ELEVATED	120-129 mmHg	<80 mmHg
STAGE 1 HT	130-139 mmHg	80-89 mmHg
STAGE 2 HT	≥140 mmHg	≥90 mmHg

(Tripathi, 2013)

- Blood pressure can be is strongly linked to the risk of cardiovascular disease (CVD) and mortality. (Dipiro et al., 2017)

- Increased systolic blood pressure (>115 mmHg) is considered to be blamed for 62% of strokes also 49% of ischemic heart disease cases globally, resulting in more than 7 million deaths per year.(Dipiro et al., 2017)

- Essentially Hypertension is classified into two types:

- Primary/ Essential Hypertension:

→ Essential hypertension is a rise in blood pressure that has no recognised cause and it raises the risk of cerebral, cardiac, or renal problems.

→ Other cardiovascular risk factors including age, obesity, hyperlipidaemia, insulin resistance, and diabetes frequently coexist with essential hypertension.(Tripathi, 2013)

→ More than 90% of instances of hypertension are caused by unknown factors. (Oparil et al., 2003)

- Secondary Hypertension:

→ Secondary hypertension is the increase in blood pressure caused due to an underlying, distinguishable, and frequently, treatable cause. (Grossman & Messerli, 2012)

→ A wide range of medicinal treatments or chemical compounds can cause a momentary or long-term rise in blood pressure, or interfere with antihypertensive medications' blood pressure-lowering actions. (Onusko, 2003)

→ With increased awareness and emphasis on hypertension, modifiable risk factors such as food, physical activity, body weight, and blood glucose have been identified, as well as nonmodifiable perils such as age, ethnicity, genetics, and gender. (Chiong et al., 2008)

→ Renal parenchymal disease, pheochromocytoma, hyperaldosteronism, and renal artery stenosis, are all well-known forms of secondary hypertension. (Grossman & Messerli, 2012)

- The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) specifies four aims for evaluating patients with increased blood pressure in its 6th report: (Onusko, 2003)
- Hypertension identification and confirmation; detection of target organ disease
- Determination of other cardiovascular risk factors, such as diabetes mellitus, hyperlipidaemia, and so on.
- Secondary causes of hypertension are identified based on the patient's medical history. (Oparil et al., 2003)

❖ Pathogenesis:

➢ Many different pathophysiologic variables have been linked to the development of hypertension. Such as:(et al., 2019)

- Escalation in sympathetic nervous system activity.
- Sodium-binding hormones and vasoconstrictors are produced in excess.
- Leong-term excessive salt consumption and/or potassium and calcium deficiency in the diet.
- Excessive or inappropriate renin secretion, resulting in elevated angiotensin II and aldosterone production
- Vasodilators such prostacyclin, nitric oxide (NO), and natriuretic peptides are insufficient.
    - Changes in the kallikrein–kinin system expression which impacts vascular tone and renal salt handling
    - Resistance vessel irregularities
    - Underlying variables such as genetics, diseases, and the use of blood pressure medications, among others.

1.2 Treatment of Hypertension

- Reduced blood pressure lowers the risk of strokes, heart attacks, and renal disorders.(B.N.a et al., 2016)
- Antihypertensive drug therapy has been shown in clinical studies to bring down the risk of cardiovascular events and death in persons with high blood pressure. (Dipiro et al., 2017)
- Antihypertensive medicines might reconstitute the barostat to work at an inferior Blood pressure by reducing blood pressure over time. (Dipiro et al., 2017)
- Here are the examples of drugs used in the treatment of hypertension along with their class:

Table 2: Classification of drugs used in treatment of hypertension

CLASS		DRUGS
Diuretics	Thiazides	Hydrochlorothiazide, Chlorthalidone, Indapamide
	High- ceiling	Furosemide
	K^+ Sparing	Spironolactone, Amiloride
ACE inhibitors		Captopril, Enalapril, Lisinopril, Perindopril, Ramipril, Fosinopril
Angiotensin (AT1 receptor) blockers		Losartan, Candesartan, Irbesartan, Valsartan, **Telmisartan**
Direct renin inhibitor		Aliskiren
Calcium channel blockers		Verapamil, Diltiazem, Nifedipine, Felodipine, Amlodipine, Nitrendipine, Lacidipine
β Adrenergic blockers		Propranolol, Metoprolol, Atenolol
β + α Adrenergic blockers		Labetalol, Carvedilol
α Adrenergic blockers		Prazosin, Terazosin, Doxazosin Phentolamine, Phenoxybenzamine
Central sympatholytic		Clonidine, Methyldopa
Vasodilators		Arteriolar Hydralazine, Minoxidil, Diazoxide
		Arteriolar + venous Sodium Nitroprusside

Source: (Tripathi, 2013)

1.3 Angiotensin Receptor Blockers (ARBs)

- Angiotensin-II (Ang II) is an octapeptide that is produced in the plasma from a precursor plasma 2 globulin and is found to be important for maintaining

blood volume, electrolyte, and blood pressure equilibrium. (Sekar & Chellan, 2008)

- Although the sympathetic and renin-angiotensin systems (RAS) might be or might not be hyperactive, both of them contribute to blood vessel tone. (Chiong et al., 2008)

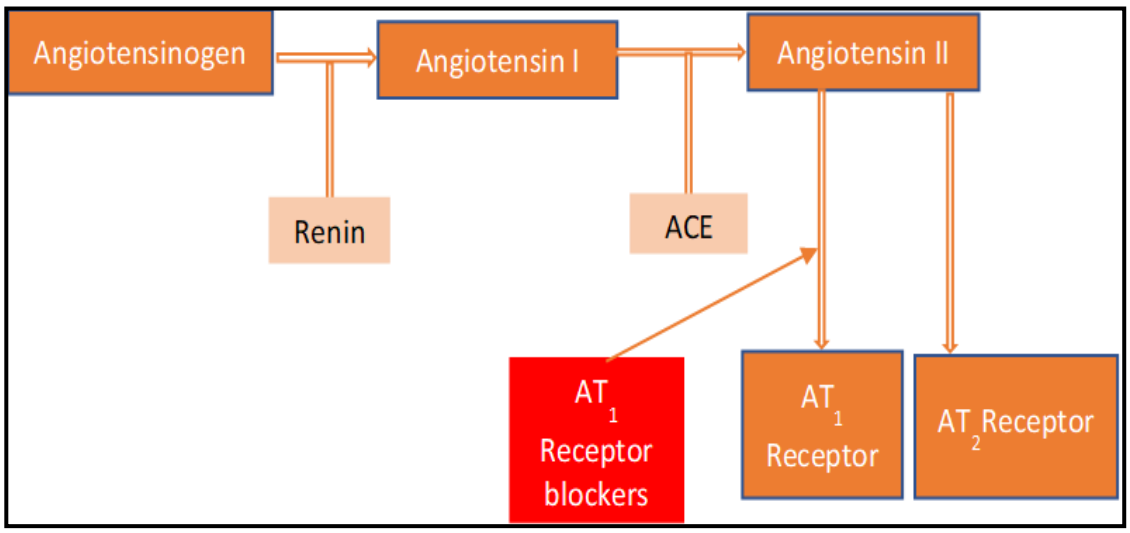

Figure 1: Mechanism of action of AT_1 Receptor antagonists

- As an alternative to ACE inhibitors, many nonpeptide orally active AT1 receptor blockers (ARBs) have been explored. Losartan, Olmesartan, Telmisartan, Candesartan, Valsartan, and Irbesartan are some examples.(Tripathi, 2013)
- These drugs directly act on the angiotensin 1 receptor i.e., AT_1 receptor as they show 10,000 times more affinity to AT_1 receptor as compared to AT_2 receptor and inhibit its effects leading to eventual reduction in the blood volume and vasodialation.(Weber, 2010)
- Selective AT2 receptor antagonists, as well as combination AT1 + AT2 antcagonists, have been developed. (Akhrass & McFarlane, 2011)
- They produce a 24-hour drop in blood pressure in hypertensive individuals, although heart rate is stable and cardiovascular reflexes are unaffected. (Tripathi, 2013)
- There was no discernible effect on plasma lipid profile, glucose tolerance, or insulin (Chiong et al., 2008)

- It is currently considered as first-line treatments for hypertension. (Dipiro et al., 2017)
- It is equivalent to ACE inhibitors in terms of effectiveness and advantageous characteristics, along with the added benefit of not causing cough and a decreased risk of angioedema, rashes, also dysgeusia. (Elliott, 2007)

1.4 Introduction to the Method of Manufacturing for Marketed preparations

- Telmisartan exhibits low water solubility and dissolving rate, which makes developing tablet formulations difficult. (K, Bhargavi, P, Hima Bindu, Dr. K, 2019)
- Numerous researches have been conducted in effort to increase the bioavailability of poorly soluble medicines by altering their dissolution kinetics.(Zhong et al., 2014)
- Amorphous forms, such as solid dispersions/cocrystals, size reduction, polymeric micelles, inclusion complexation, , including nanonization, self-microemulsifying drug delivery systems, solid lipid nanoparticles (SLN)/liposomes, pH-modified form, surfactant/co-solvent systems, and salt forms are used in a variety of pharmaceutical technologies to improve the solubility of insoluble drugs.(Oh et al., 2018)
- The production of a solid dispersion (SD) using a hydrophilic polymer polyvinyl pyrrolidone and other varied carriers is a typical strategy for betterment of the dissolution rate of a poorly water soluble medication. Key processes by which SD improves drug dissolving include changes in the crystallinity of drug to an amorphous state also decreased particle size for greater wettability.(B.N.a et al., 2016)
- In these processes, the granules containing the drug are prepared by using the fluidised bed drying process.(Messerli et al., 2007)
- The rate of dissolution is accelerated in this procedure by depositing the medication in minuscular form on the surface of an adsorbent. The term “minuscular form” refers to a medicine that has been molecularly micronized

and is widely diffused across the vast surface of micro particle adsorbents.(K, Bhargavi, P, Hima Bindu, Dr. K, 2019)

- The minuscular drug mechanism releases only free, absorbable medication into solution after breakdown. The minuscular drug delivery method may be thought of as a drug in micro particle form that has been molecularly disseminated over a large surface area of the carrier. (Sowers & Sowers, 1999)
- The reduction in particle size and associated increase in surface area contribute to boost the drug's thermodynamic activity in the dispersed form, resulting in a significant rise in the drug's rate of solution.(K, Bhargavi, P, Hima Bindu, Dr. K, 2019)
- A solution of pH above 9 is concocted by the addition of meglumine and NaOH.(Chae et al., 2018)
- As the drug is soluble in highly alkaline pH, it is dissolved in the solution.
- This solution is then sprayed onto mannitol and disintegrant particles using a fluidized bed dryer. The use of a 40% isopropanol/water mixture as a granulating binder is used. (Patel et al., 2016)
- The prepared granules are then dried and compressed into tablets of desired size and shape and are evaluated for all the different parameters.(Yamashita et al., 2017)

1.5 Telmisartan Hydrochloride Drug profile

- Telmisartan, an AT_1 receptor antagonist is used to treat hypertension (high blood pressure) by inhibiting the hormone angiotensin, which causes blood vessels to relax and expand.(B.N.a et al., 2016)
- It was created by Boehringer Ingelheim and released as Micardis in 1999. (Oh et al., 2018)
- Telmisartan is used to treat hypertension, but its dual mechanism of action may also protect against vascular and kidney impairment caused by diabetes and cardiovascular disease (CVD).(B.N.a et al., 2016)
- Telmisartan shows an aqueous solubility of 0.078 mg/ml in the physiological pH range. (Patel et al., 2016)

- Telmisartan is easily ionizable due to its chemical structure, and so its solubility is pH dependant.(B.N.a et al., 2016)
- Peak activity occurs three hours after an oral dosage, and action lasts for more than 24 hours. (Tripathi, 2013) It reduces dosage administration frequency, avoids nocturnal attacks, and increases patient compliance.(B.N.a et al., 2016)
- It is mostly unaltered in bile and requires dosage lowering in liver illness. (Tripathi, 2013)
- Angiotensin II binding to the AT1 subtype receptor, which is found in vascular smooth muscle and the adrenal gland, is specifically blocked by telmisartan. The antagonism causes vasodilation and inhibits angiotensin II-mediated aldosterone synthesis, resulting in a decrease in salt and water excretion as well as an increase in potassium excretion, lowering blood pressure. (Nagadivya et al., 2012)

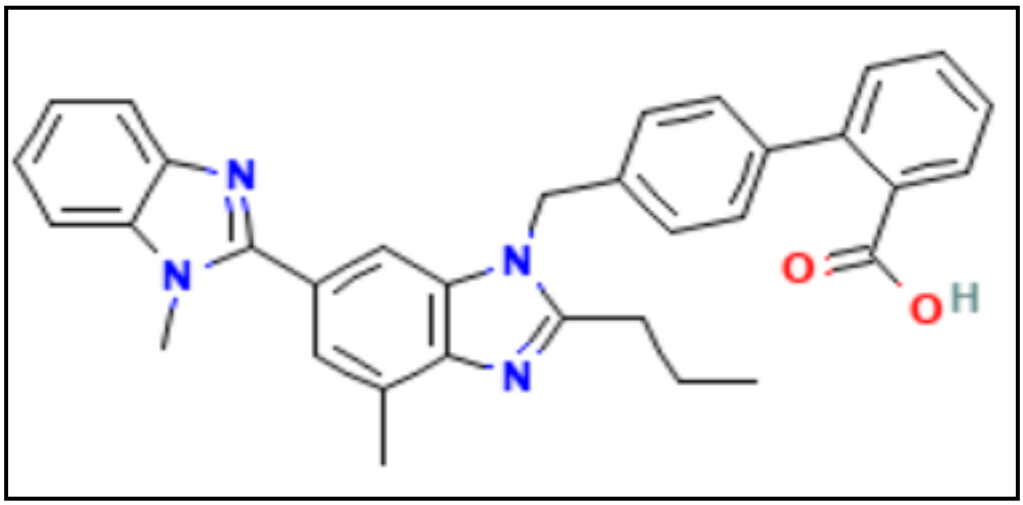

Figure 2: Structure of the drug Telmisartan

Source: (*Telmisartan Drug Profile*, n.d.)

Table 3: Properties of the drug Telmisartan

Name	Telmisartan HCl
IUPAC Name	40 –{[4-Methyl-6-(1-methyl-2-benzimidazolyl)-2-propyl-1-benzimidazolyl] methyl}-2-biphenylcarboxylic acid

Structural formula	$C_{33}H_{30}N_4O_2$
Drug Category	Antihypertensive
Use	Treatment of high blood pressure
Appearance	White colored solid compound
Half life	24 hours
Dose	20,4, 80 mg
BCS Class	II
Distribution	Highly plasma protein bound (>99.5%)
Metabolism/ Elimination	Most of the administered dose (>97%) gets eliminated unchanged in feces through biliary excretion; only minute amounts are found in the urine
Clearance	>800 mL/min
Solubility	Sparingly soluble in strong acids Practically insoluble in water Freely soluble in strong base
Mechanism of action	Antagonism of AT_1 receptors
Contraindications	Renal insufficiency, hepatic insufficiency

Drug details: Telmisartan is a non-peptide angiotensin II receptor antagonist with antihypertensive properties that is derived from benzimidazole ring in the structure.

1.6 Introduction to Excipients

➢ **Diluents:**

- Diluents, often known as fillers, are inert chemicals that are used to enhance the tablet's volume.
- They're also employed to improve tablet qualities including cohesion and flow, among other things.
- Two different diluents were tried in the preparation of these tablets: Microcrystalline cellulose and Avicel PH 102.

→ **Mannitol:**

Table 4: Excipient profile of Mannitol

Name	Mannitol
Nonproprietary Name	Mannitol
Synonym	Pearlitol
Chemical Name	Dextrosemannitol
Molecular formula and Weight	C6H14O6 183.18
Category	Diluent, plasticity inducer, sweetener, therapeutic agent, tonicity agent.
Pharmaceutical application	→ Use as diluent in tablet. → It also inhibits thickening in aqueous suspensions. → Use as a plasticity inducer. → Use as carrier in dry powder inhalers. → Use as fillers. → Use as an osmotic diuretic to diagnose kidney function in the management of acute renal failure.
Description	Mannitol is pale whitish, odor less, crystalline powder or granules and easily flowable. Sweetening index of mannitol is similar to the glucose. It gives a cooling feeling in the mouth upon observation in the

	microscope it shows ortho rhombic needles shape when crystallized from alcohol. Mannitol has various polymorphic forms.
Typical Properties	Appearance: White colored, free flowing powder
Storage and Stability	Stored at cool and dry place in tightly closed container.

→ **Avicel PH 102:**

Table 5: Excipient profile of Avicel pH 102

Name	Avicel PH 102
Nonproprietary Name	Micro crystalline cellulose (MCC)
Synonym	Avicel PH, Cellets, Celphere, crystalline cellulose, Pharmacel
Chemical Name	Cellulose
Molecular formula and Weight	$(C_6H_{10}O_5)_{220}$ 36000
Category	Adsorbent, suspending agent, diluent, disintegrant.
Pharmaceutical application	→ Use as diluent in tablet and in capsule → Used as disintegrating agent as it has adsorbent property.
Description	MCC is a partly depolymerized cellulose. MCC is whitish, odor less, taste less and crystalline powder having of porous particles. There are different grades available of MCC and they can be differentiated by particle size and moisture content.
Typical Properties	→ **Appearance**: white colored free flowing powder or granules → **Melting point**: it burns at 255–265 °C. → **Solubility:** Somewhat in 5% solution of NaOH

	and not soluble in water. → **pH**: 5 – 7.5 True density: 1.5 to 1.6 g/ cm3
Storage and Stability	It is moisture grasping material so store in air tight vessel and keep it in cool and dry place.

➢ **Disintegranting agents:**

- A disintegrating agent is added to a tablet formulation to cause the cohesive forces between the granules to be disrupted. As a result, the tablet begins to break down.
- It works through three different processes:
  - → By swelling by the uptake of water with the help of capillary forces.
  - → Liberation of gas to disintegrate the tablet.
  - → Enzymatic degradation of binders.
- For the preparation of telmisartan tablets, various different kinds of disintegrating agents, such as Sodium starch glycolate, croscarmellose sodium, crosspovidone is used.

→ **<u>Sodium starch Glycolate:</u>**

Table 6: Excipient profile of Sodium starch glycolate

Name	Sodium-starch-glycolate
Nonproprietary Name	Sodium-glycolate-starch
Synonym	Carboxy methyl starch, Na salt
Chemical Name	Sodiumcarboxymethyl starch
Molecular Weight	5×10^5 to 1×10^6
Category	Disintegrating agent
Pharmaceutical application	→ SSG is utilized as a disintegrant for solid oral dosage forms → Also used as a suspending agent.
Description	→ SSG is a whitish easily flowable hygroscopic powder. → SSG is a substituted derivative of potato starch.

	→ Upon microscopy it is seen uneven shape of granules. → It also shows swelling in contact with water
Typical Properties	→ **Appearance**: It is a white, free flowing powder → **Melting point**: Does not melt, however above 200 8C it chars. → **Solubility:** insoluble in water and other organic solvents → **Average particle size**: 38mm to 42 mm → **Swelling capacity**: 300 times its volume → **pH:** 5 to 7.5 → **Heavy metals:** < 20PPM → **Nacl:** < 7 % → **Sodiumglycolate**: < 2 %
Storage and Stability	→ It is hygroscopic in nature but it is stable it remains protected for three years if stored in control temperate and humidity. → SSG is unstable with ascorbic acid.

→ **<u>Crosscarmellose Sodium</u>**

Table 7: Excipient profile of sodium hydroxide

Name	Crosscarmellose Sodium
Non-Proprietary name	Crosscarmellose Sodium
Synonym	Ac-di-sol, crosslinked carboxy methyl cellulose
Chemical name	Cellulose carboxy methyl ether sodium salt
Molecular formula and weight	$C_{28}H_{30}Na_8O_{27}$ 982.44
Category	Disintegrant

Pharmaceutical application	→ Used as disintegrating agent in capsule and tablet. → It enhances bio-availability of the drug by higher drug dissolution.
Description	CCS is a cross linked polymer of carboxy methyl cellulose sodium. It is whitish in color, fibrous in nature and easily flowable powder.
Typical properties	→ **Appearance**: grayish-white powder. → **Solubility:** Isoluble in water and in other organic solvents → **Swelling capacity**: 4-8 times from its original volume → **pH**: 5 to 7 → **Heavy metals**: NMT 10ppm
Storage and stability	Store in an air tight container, cool and dry place

→ **<u>Crosspovidone</u>**

Table 8: Excipient profile of crosspovidone

Name	Crosspovidone
Non-Proprietary name	Crosspovidone
Synonym	Polyplasdone Polyvidonum
Chemical name	1-[1,2-bis(phosphanyl)ethyl]22ydroxide22e-2-one
Molecular formula and weight	$C_6H_{13}NOP_3$ 177.12
Category	Disintegrant
Pharmaceutical application	→ It is used as a superdisintegrant in tablet formulations. → It is used in a very small quantity and hence it

	does not have much effect on the final flowability of the tablet blend.
Description	Crosspovidone is a white-light yellow free-flowing powder which is inert and insoluble. In typical usage as a pharmaceutical excipient, crosspovidone is not frequently linked with toxicity.
Typical properties	→ **Appearance:** White-light yellow free flowing powder. → **Solubility:** Insoluble in water, ethanol and ether → **Swelling capacity**: 2-3 times its original volume → **pH**: 5 to 8
Storage and stability	Store in an air tight container, cool and dry place

- **Binder:**
  - They're also known as pharmaceutical glue since they enable powder particles to stick together and form granules.
  - They are used to create a cohesive link between granules during the compaction process to make a tablet.
  - The binder provides appropriate hardness to the tablet and helps to maintain its integrity even after compression.
  - We have used PVP K30 as a binder in dry from as well as, as a binder solution.

→ **PVP K 30:**

Table 9: Excipient profile of PVP K-30

Name	**PVP K 30**
Non- proprietary name	**Copovidone**
Synonyms	Copolyvidone, copovidonum, Kollidon, Plasdone, polyvinylpyrrolidone-vinyl acetate

Chemical name	Acetic acid ethenyl ester, polymer with 1-ethenyl-2-pyrrolidinone
Molecular weight and formula	$(C_6H_9NO)n * (C_4H_6O_2)_m$ 50000
Category	Film-forming agent, binder
Pharmaceutical application	→ PVP K 30 use as tablet binder for wet as well as dry granulation and also, in direct compression. → Use as a film-forming agent for delayed release formulations. → It provides good 'adhesiveness, firmness, and hardness'
Description	It is a yellowish or creamy, odour less and having faint taste amorphous powder. PVP K 30 is generally manufacture by spraying technology to get smaller particle size
Typical properties	**Appearance:** white coloured easily flowable powder or granules **Melting point**: 140 °C **Solubility:** >10% aqueous solubility and other organic solvents **Flowability:** Relatively easily flowable powder **Hygroscopicity:** At 50% relative humidity, it grasp ≤10% weight. **Clarity in 10% water:** Clear **pH:** 3-5 in 5% water
Storage and stability	Stored in air tight vessel and keep it in cool & dry place

- **Alkalizer:**

- Alkalizers were added to the formulation to increase the pH of the environment during the granulation process as the drug is soluble only in highly alkaline pH, i.e., above 9.
- This leads to the uniform distribution of the drug and proper granules to be formed.
- We added combinations of three different alkalizers such as sodium hydroxide, meglumine and sodium bicarbonate to maintain the alkaline pH during processing.
- **Sodium Hydroxide:**

Table 10: Excipient profile of Sodium 31ydroxide

Name	Sodium hydroxide
Non- proprietary name	Sodium hydroxide
Chemical name	Sodium hydroxide
Molecular weight and formula	NaOH 39.997
Category	Alkalizer
Pharmaceutical application	→ Added to certain pharmaceutical formulation to increase the pH of the surrounding environment. → It helps in enhancing the dissolution.
Description	Pellets, flakes, sticks, fused masses, and various shapes in white or virtually white. When exposed to the air, solutions maybe clear or slightly turbid, or colourless or faintly tinted, extremely caustic, and hygroscopic, absorbing carbon dioxide and producing sodium carbonate.
Typical properties	→ **Appearance:** White or nearly white pellets and flakes → **Melting point:** 318^0C

	→ **Solubility:** Very soluble in water, freely soluble in ethanol. → **pH:** 0.1N solution give 13 pH
Storage and stability	Containers must be tightly closed to prevent conversion to sodium bicarbonate by carbon di oxide off air.

→ **Meglumine:**

Table 11: Excipient profile of Meglumine

Name	Meglumine
Non- proprietary name	Meglumine
Chemical name	N-Methyl-D-glucamine
Molecular weight and formula	$C_7H_{17}NO_5$ 195.21
Category	Alkalizer
Pharmaceutical application	→ Added to certain pharmaceutical formulation to increase the pH of the surrounding environment. → It helps in enhancing the dissolution.
Description	It is a white coloured powder, which is soluble in water, which immediately increases the pH of the solution and helps in creating an alkaline environment.
Typical properties	→ **Appearance:** white coloured powder. → **Melting point:**128.5^{0}C → **Solubility:** Soluble in water → **pH:** 10-11
Storage and	Stored in air tight vessel and keep it in cool & dry

stability	place.

→ **Sodium Bicarbonate:**

Table 12: Excipient profile of Sodium bicarbonate

Name	Sodium Bicarbonate
Chemical name	Sodium Bicarbonate
Synonyms	Baking soda
Molecular weight and formula	$NaHCO_3$ 84.007
Category	Alkalizer
Pharmaceutical application	→ Added to certain pharmaceutical formulation to increase the pH of the surrounding environment. → It helps in enhancing the dissolution.
Description	Sodium bicarbonate, the monosodium salt of carbonic acid, possesses alkalinizing and electrolyte replacement properties. The sodium and bicarbonate ions separate from sodium bicarbonate. By raising plasma bicarbonate and buffering excess hydrogen ion concentration, ion production elevates blood pH.
Typical properties	→ **Appearance:** white in colour, crystalline powder → **Melting point:** 50^o C → **Solubility:** Soluble in water. → **pH:** 8-9
Storage and stability	Stored in air tight vessel and keep it in cool & dry place.

- **Lubricant:**
- They assists in reducing the friction amongst the granules and the tablet press die wall when added to the tablet formulation. Hence, they are also called as anti- frictional agents.
- They are required during tablet compression and ejection.
- Magnesium stearate was used as a lubricating agent for this formulation.

→ **Magnesium stearate:**

Table 13: Excipient profile of Magnesium stearate

Name	Magnesium Stearate
Non- proprietary name	Magnesium Stearate
Synonym	Dibasic magnesium salt
Chemical name	Octadecanoic acid magnesium salt
Molecular weight and formula	$C_{38}H_{72}MgO_4$ 592.26
Category	Lubricating agent
Pharmaceutical application	→ It is used in formulation on of tablet and capsule as lubricant. → Also used in creams.
Description	Magnesium Stearate consists of Mg and stearic acid, and different quantities of Mg. Stearate and Mg. Palmitate. Magnesium stearate is finest buff whitish powder having mild smell of stearic acid. It has low bulk density. The powder is slippery to the touch and have adhesive property to the skin.
Typical properties	→ **Appearance:** Buff white powdery material → **Melting point**: 117 to 155 °C → **True density:** 1.092 g / cm3

	→ **Solubility:** Not soluble → **Flowability:** poorly flowable and cohesive in nature
Storage and stability	Pack it in an air tight vessel and keep it in a cool and dry place.

➢ **Glidant:**

- These ingredients which are incorporated in the tablet formulations to facilitate granule flow.
- These compounds have the ability to increase granule flow properties from the hopper to the die cavity.
- In this project, we've used aerosol as a glidant.

→ **<u>Aerosil</u>:**

Table 14: Excipient profile of Aerosil

Name	**Aerosil**
Non- proprietary name	Colloidal Silicon Dioxide
Synonyms	Colloidalsilica, silicondioxide
Chemical name	Silica
Molecular weight and formula	SiO_2 61.0
Category	Glidant, suspending agent, Disintegrating agent
Pharmaceutical application	→ Used as glidant in tablet manufacturing process. → Used as a stabilizer in emulsions → Used as a suspending agent in semisolid formulation. → In aerosols as a suspending agent to promote particulate suspension

Description	Aerosil is a micron sized fumed silica having particle size of about 15 nm. It is least dense, free, bluish white coloured, odourless, tasteless powder having low bulk density. It is prepared by the flame hydrolysis of $SiCl_4$ at 1800 °C temperature using a flame. Quick cooling of the melted mass during manufacturing leads to amorphous form of powder.
Typical properties	→ **Appearance:** bluish white coloured powder → **Melting point:** 1600 °C → **Solubility:** 150 mg in 1L water at 25 °C
Storage and stability	In an air tight vessel

➢ **Solublizer:**

- The solubilizing agents include surfactants, which are incorporated into the tablet formulations to improve the dissolution for poorly soluble substances.
- Sodium lauryl sulphate was used for the same purpose.

→ **<u>Sodium laureth sulphate:</u>**

Table 15: Excipient profile of Sodium laureth sulphate

Name	Sodium Laureth sulphate
Non- proprietary name	Sodium lauryl sulphate
Chemical name	Sodium 2-(dodecyloxy)ethyl sulphate
Molecular weight and formula	$C_{14}H_{29}NaO_5S$ 332.43
Category	Surfactant
Pharmaceutical application	→ SLS is utilized as an emulsifying agent, penetration enhancer and solubilizing agent for

	pharmaceutical formulations. → It can also used as a lubricant for some tablet and capsule formulations.
Description	→ SLS is a natural anionic surfactant acquired from coconut and/or palm kernel oil. → SLS decreases the surface tension of aqueous solutions and is used in cosmetics, medicines, and toothpastes as a fat emulsifier, wetting agent, and detergent.
Typical properties	→ **Appearance:** White coloured solid compound. → **Melting point:** 206^0 C → **Solubility:** Soluble in water
Storage and stability	In an air tight vessel

➢ **Solvent:**

- Iso propyl alcohol was used as a solvent to dissolve the binder PVP K30 and prepare a binder solution for the granulation process.
- As it is an inorganic solvent, the granules formed were also light and soft that proved to be beneficial for further processing parameters.

→ **<u>Iso propyl alcohol</u>**

Table 16: Excipient profile of Iso propyl alcohol

Name	Iso propyl alcohol
Chemical name	Iso propyl alcohol
Molecular weight and formula	C_3H_8O 60.10
Synonyms	Isopropanol, isopropyl alcohol, 2-Propanol, Propan-2-

	2-ol
Category	Solvent
Pharmaceutical application	→ It is majorly used as a solvent in pharmaceutical industries. → Also used as a disinfectant liquid.
Description	Isopropyl alcohol is a flammable liquid that smells like a combination of ethanol and acetone.
Typical properties	→ **Appearance:** colourless, volatile liquid → **Boiling point:** 83^0C → **Relative density:** 0.79 → **LogP:** 0.05
Storage and stability	To be stored in a tightly closed container in a cool, dry and well-ventilated area.

CHAPTER 2

AIM AND OBJECTIVE

AIM:

- The aim for this research was to "To develop and evaluate an Immediate Release tablets of Telmisartan Hydrocholride to achieve therapy for patients with Hypertension."
- The tablets were developed to match the reference brand. Hence the evaluation of reference brand was carried out first.
- Various process parameters which eventually greatly influence the quality of the dosage form were also identified.
- Dosage forms were evaluated Appearance, Disintegration time and Dissolution etc..

PLAN:

- Preparation of immediate release tablets by:
  - → Screening of suitable Alkalizing agent
  - → Screening of suitable excipients for Immediate release tablet.
- In vitro studies for the developed formulation.
- Perform stability studies for the optimized formulation as per the ICH guidelines.

RATIONALE:

- <u>Rationale for selection of Immediate release as dosage form:</u>

- Easy and fast delivery of the drug by self-medication.
- Tablet dosage forms are unit dosage forms and show high dose precision and very high patient compliance.

- <u>Rationale for selection of Telmisartan Hydrochloride:</u>

- The drug is already approved by the FDA was an anti-hypertensive agent.

- It is now a 1st line drugs in treatment of hypertension.
- Peak activity occurs 3 hours after an oral dosage, and action lasts > 24 hours.

➢ Rationale for the method for preparation of granules:

- Marketed formulations use the fluidized bed process in the preparation of tablets. However, in the present study, focus was to develop a formula and process to prepare granules using the wet granulation method.
- Less expensive method, more feasible for small scale pharmaceutical industries.

CHAPTER 3

LITERATURE SURVEY

3.1 Literature review of Disease and drug:

Sr. no.	Name of book/article	Description
1	Essentials of medical pharmacology. 7th edition. Tripathi KD	Information about the mechanism of action of the class of drug and the pharmacokinetic parameters of the drug.
2	Pharmacotherapy: A pathophysiologic approach. Dipiro, J. T., Talbert, G. C. ., Yee, G. R. ., Matzke, B. G. ., & Wells, L. M. P.	
3	Hypertension and Vascular Disease. Austin E. Doyle	This article describes the basic types of hypertensions and its epidemiology and the types in brief.
4	Systemic Hypertension Elliott, W. J	This article mentions the different definitions of hypertension, the parameters that can be measured, the disease markers and risk factors.
5	Telmisartan and cardioprotection Philippe R Akhrass Samy, McFarlane	The role of telmisartan in reliving the increase in blood pressure and its use in high-risk patients.
6	Telmisartan in High-Risk Cardiovascular Patients Michael A. Weber, MD	
7	Hypertension and Vascular Disease	Information about the vascular increase

	Austin E. Doyle	in blood pressure.
8	Pathogenesis of Hypertension Suzanne Oparil, MD; M. Amin Zaman, MD; and David A. Calhoun, MD	Pathogenesis, also various factors which might lead to the progress of hypertension have been described.

3.2 Literature review on Dosage form:

Sr. no.	Name of article and author	Description
1	Immediate Release Tablets of Telmisartan Using Superdisintegrant Formulation, Evaluation and Stability Studies Vasanthakumar Sekar, Vijaya Raghavan Chellan	The formulation, evaluation of IR tablets of telmisartan also 6 months stability studies have been carried out and the results are mentioned.
2	Quality-by-design approach for development of telmisartan potassium tablets Ga-hui Oh, Jin-Hyun Park, Hye-Won Shin, Joo-Eun Kim & Young-Joon Park	A quality-by-design approach was adopted to develop telmisartan potassium (TP) tablets, which were bioequivalent with the commercially available Micardis..
3	Formulation and evaluation of telmisartan tablets employing solvent deposited systems. K. Bhargavi, P. Hima Bindu and Dr. K. Ravi Shankar	The formulation and methodology for

4	Formulation, optimization and evaluation of immediate release tablet of *telmisartan.* B.N Parikh, D.N. Patel, C.N. Patel, J.B. Dave	the preparation of telmisartan tablets using the fluidized bed process has been described.

3.3 Literature review on Superdisintegrants

Sr. no.	Name of article and author	Description
1	Superdisintegrants – A review Anup Megotia*, Meenu Nagpal, Upendra K Jain, Varun	Basic information provided about the mechanism of action of disintegrants, the various factors affecting and a few examples and details of superdisintegrants.
2	Superdisintegrants: A recent invsestigation and current approach. Deshmkh Himanshu, Chandrashekhara S.*, Nagesh C., Murade Amol, Usgaunkar Shridhar	Comparative study for various disintegrants, to understand which disintegrant gives the better result.
3	An Overview of Factors Affecting Superdisintegrants Functionalities. Jemal Dilebo, Tesfaye Gabriel	Different superdisintegrants are given and the various factors which may affect the disintegration process of the agents are listed and explained.

3.4 Literature review on Alkalizer

Sr. no.	Name of article and author	Description
1	Design of supersaturable formulation of telmisartan with pH modifier: in vitro study on dissolution and precipitation Shinji Yamashita, Arima Fukunishi, Haruki Higashino, Makoto Kataoka, Koichi Wada.	Telmisartan granules are prepared using different concentrations of meglumine and the effect is evaluated by in vitro dissolution.
2	Tablet Formulation of a Polymeric Solid Dispersion Containing Amorphous Alkalinized Telmisartan Jun Soo Chae, Bo Ram Chae, Dong Jun Shin, Yoon Tae Goo, Eun Seok Lee, Ho Yub Yoon, Chang Hyun Kim, and Young Wook Choi	Solid dispersion of the drug is prepared for enhancement of its solubility and sodium hydroxide is added as an alkalizing agent to increase the pH of the solution to above 9.
3	Influence of alkalizers on dissolution properties of telmisartan in solid dispersions prepared by cogrinding. Lin Zhong, Xyngyi Zhu, Bo Yu, weike Su	Five different alkalizers are studied in the present research to check the effect of alkalizers on the dissolution properties of the drug.

3.5 Literature review on Binder

Sr. no.	Name of article and author	Description
1	Effect of various binding agents on tablet hardness and release rate profiles of diclofenac sodium tablets. P. Nagadivya, R. Ramakrishna, G. Shridhar, R. Bhanushashank	
2	Effect of binders on 500mg metformin hydrochloride tablets produced by wet granulation. Block, L.C., Schmeling, L.O., Couto, A.G., Silva, M.A.S., Tagliari, M.P., Bresolin, T.M.B, Mourão, S.C.	Different binding agents we evaluated for the formation of granules and the granules were then evaluated for various parameters such as flow, bluk density, compressibility, etc.

CHAPTER 4

METHODOLOGY

4.1 List of Materials

The active substance along with the various excipients used in the tablet formulation have been mentioned in table 17:

Table 17: List of materials

Ingredients	Category	Company
Telmisartan	API	Verdant
PVP K-30	Binder	Boainky pharma
Sodium Starch Glycolate	Disintegrating agent	Rosswell indust
Crosscarmellose Sodium	Disintegrating agent	Prachin
Crosspovidone	Disintegrating agent	Jhnanhang
Sodium Hydroxide	Alkaliser	Lobachem
Meglumine	Alkaliser	Suzhoutianma
Microcrystalline Cellulose	Diluent	NB enterpreneurs
Mannitol	Diluent	supreme
Aerosil	Lubricant	Cabot
Mg. stearate	Lubricant	Sunshine
Iso-propyl Alcohol	Solvent	--
Purified Water	Solvent	--

4.2 List of Equipment

The equipments used along with the manufacturer have been mentioned in table 18:

Table 18: List of equipment used

Name of Equipment	Make
Weighing Balance	Shimadzu, Japan
Vibratory sifter	Hugopharm, India
Octagonal mixer	Hugopharm, India
Rapid mixer granulator	Hugopharm, India
Unimill	Hugopharm, India
Fluidized bed dryer	Hugopharm, India
LOD	Shimadzu, Japan
Compression Machine	Fluidpack, India
Disintegrating Apparatus	Veego, India

Hardness tester	Electrolab, India
Vernier Calliper	Mitutoyo, India
Friablity tester	Veego, India
Dissolution Apparatus	Electrolab, India
UV spectrophotometer	Shimadzu, Japan

4.3 Pre- formulation studies

4.3.1 Calibration curve of telmisartan in 7.5 pH buffer:

Preparation of 7.5 pH phosphate buffer:

The buffer solution was prepared according to IP. .Two solutions are prepared:

Solution I: 119.31 g of disodium hydrogen phosphate is dissolved in sufficient water to produce 1000ml. And **solution II:** 45.36 g of potassium dihydrogen phosphate is dissolved in sufficient water to product 1000ml. Mix 85ml of solution I to 15ml of solution II and adjust the pH if necessary.

Preparation of stock solution:

100mg of drug is taken in a 100ml volumetric flask and 15ml methanol is added to it. The flask is then kept on a sonicator until the drug completely dissolves. Then the volume of the solution is made up to the mark by addition of the buffer solution. 2.5 ml of the above solution is taken in a 25ml volumetric flask and buffer is added up to the mark. From this solution, solutions of varying strengths are prepared and absorbance is checked using a UV spectrophotometer. An absorbance v/s concentration graph is prepared.

Table 19: Standard curve of Telmisartan in 7.5 pH buffer

Concentration	Absorbance	Wavelength
10 µg/ml	0.145	253 nm
20 µg/ml	0.260	252.8 nm
30 µg/ml	0.381	252.8 nm
40 µg/ml	0.505	253nm
50 µg/ml	0.631	252.8 nm

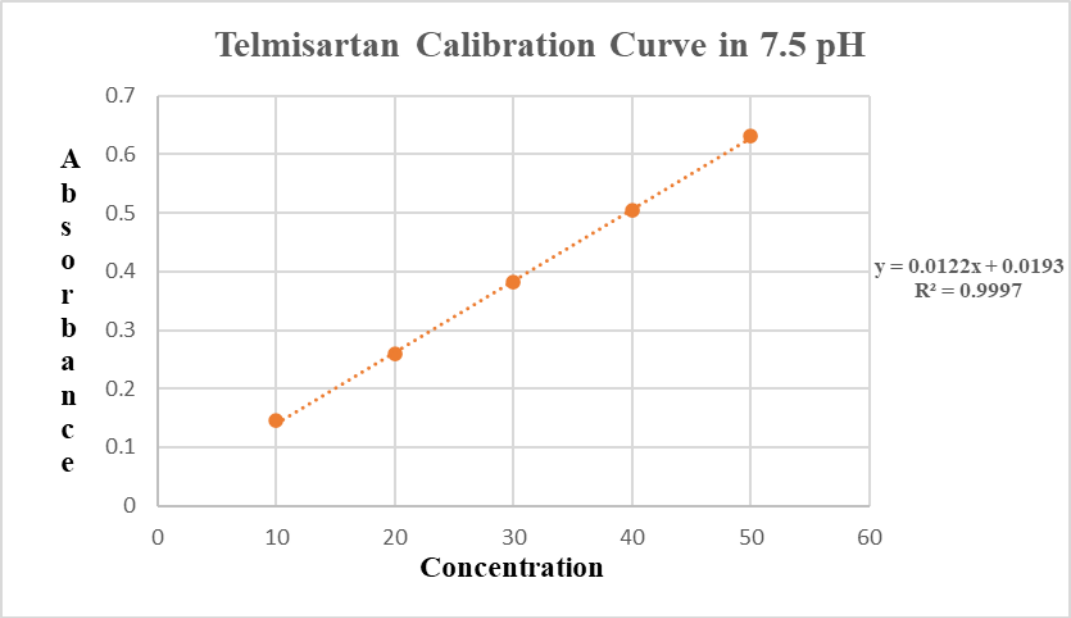

Figure 3: Calibration curve of Telmisartan HCl in 7.5 pH

4.3.2 Solubility studies

- Because to its weak dissolving properties, it has inconsistent absorption and bioavailability. (Patel et al., 2016)
- Drug solubility in various solvents and aqueous solubility in various pH buffers.
- The solubility criteria for API as per USP and BP is given in table

Table 20: Solubility criteria as per USP and BP

Type of solubility	Part of solvent required per part of solute
Very soluble	**Less than 1**
Freely soluble	**From 1 to 10**
Soluble	**From 10 to 30**
Sparingly soluble	**From 30 to 100**
Slightly soluble	**From 100 to 1000**
Very slightly soluble	**From 1000 to 10,000**
Practically insoluble	**10,000 and over**

Table 21: Solubility of drug in different solvents

Solvent	Solubility
Methanol	Slightly soluble
Ethanol	Practically insoluble
2 – propanol	Practically insoluble
Acetonitrile	Practically insoluble

Table 22: Solubility of drug in aqueous media

Aqueous buffer solution	Inference
water	Practically insoluble
1.2 pH buffer	Sparingly soluble
2.0 pH buffer	Sparingly soluble
3.0 pH buffer	Sparingly soluble
4.0 pH buffer	Slightly soluble
4.5 pH buffer	Slightly soluble
5.0 pH buffer	Slightly soluble
6.0 pH buffer	Very slightly soluble
6.8 pH buffer	Practically insoluble
7.0 pH buffer	Practically insoluble
9.0 pH buffer	Freely soluble
11.0 pH buffer	Freely soluble

4.3.3 Pre- Compression evaluation parameters

Before compression of tablets, the tablet blend is subjected to the following test to determine its flow.

4.3.3.1 Angle of repose

It is the greatest angle formed by a pile of powder's surface and the horizontal plane.

It's commonly determined using a fixed funnel approach and a measurement of powder/granule flowability.

$$\Phi = \tan^{-1}(h/r)$$

Where,

h = height of heap of pile

r = radius of base

The powder flow can be determined by:

Table 23: Standard table to determine flow property from angle of repose

Angle of repose	Flow Property
25-30	**Excellent**
31-35	**Good**
36-40	**Fair**
41-45	**Passable**
46-55	**Poor**
56-65	**Very poor**
>66	**Very very poor**

4.3.3.2 Bulk density

- The notion of powder packed in space without tapping is conveyed by bulk density. Every powder has various particle properties; a few particles pack loosely in space, resulting in a powder with a soft, light density.
- Bulk density is helpful for determining the capacity of instruments such as granulators and blenders used in subsequent processes.
- The height is measured after a weighed quantity of powder is put into a 100 ml measuring cylinder.

It can be calculated by:

$$\text{Bulk density} = M/Vb$$

Where,

M= weight of sample (gm)

Vb= Volume of powder (ml)

4.3.3.3 Tapped density

- It's a blend-to-tapped-volume ratio in which a certain amount of blend is weighed and poured into a cylinder, and the height is measured. That cylinder was physically tapped and put on a bulk density instrument.
- Blend is tapped for 500 times for the first time, and volume was recorded; following that, the apparatus tapped for 750 and 1500 times, and the final tapped volume was tallied and the Tapped density was calculated.

Tapped density= M/Vt

Where,

M= weight of sample (gm)

Vt= Volume of powder (ml)

4.3.3.4 Carr's index

Compressibility can be described as the capacity of the powder to decrease in volume under pressure. It is a measure obtained from density determinations.

% Compressibility = [(Tapped density- Bulk density)/ Tapped density] * 100

4.3.3.5 Hausner's ratio

It is also parameter measured to understand the flow of the powder or granules. It is also determined after the calculation of bulk density and tapped density.

$$\textbf{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Table 24: Standard table to determine flow property from Carr's Index and Hausner's ratio

Flow property	Carr's Index	Hausner's ratio
Excellent	**<10**	**1.00-1.11**
Good	**11-15**	**1.12-1.18**
Fair	**16-20**	**1.19-1.25**
Passable	**21-25**	**1.26-1.34**
Poor	**26-31**	**1.35-1.45**
Very poor	**32-37**	**1.46-1.59**
Very very poor	**>38**	**>1.60**

4.4 Formulation of Immediate release tablets

4.4.1 Method of preparation

- Wet granulation method was employed for the preparation of granules. In this method, addition of granulating fluid is used in this approach to prepare the mix.
- pH manipulation in dosage forms has been highlighted as an encouraging technique to change the release rate of numerous pH-dependent and ionizable drugs. The incorporation of water soluble or insoluble pH modifying chemicals into micro tablets, for example, was discovered that retainss high pH values within the tablets, resulting in better release.(B.N.a et al., 2016)
- By lowering the microenvironmental pH, the incorporation of weak acids as pH modifiers in hydrophilic matrix tablets also improves the release rate of weakly basic medicines (pHM). The pHM, which is defined as the pH of the saturated solution in the immediate proximity of the drug particles, has been utilised to control the predictable dissolution of ionizable pharmaceuticals from pharmaceutical formulations.(B.N.a et al., 2016)
- The low solubilization capacity of the SD technique and pHM modulation, especially with a high drug-loaded system, is one downside. Moreover, little effort has also been made to fully comprehend the modifying mechanisms of pH modifiers in solid dispersion systems, and how these putative changes in drug crystallinity and pHM control are linked to improved dissolution of poorly water-soluble medicines. (B.N.a et al., 2016)

- NaOH is a strong base in this formulation, which can aid in the dissolution of the medication because it is soluble in strong bases. Meglumine is a basic ingredient that aids in the dissolution of the medicine, allowing the formulation to attain the appropriate solubility.(B.N.a et al., 2016)
- The liberation of the drug substance from the drug product/dosage form determines the bioavailability/rate of dissolution of a poorly soluble medication from a solid oral dosage form i.e., Disintegration of the solid oral dosage form, which increases the surface area of the drug particles and hence increases wettability.
- This emphasises the necessity of selecting the right disintegrant/superdisintegrant and ensuring its consistency of performance in order to maximise the rate of dissolution and thereby bioavailability. (Sekar & Chellan, 2008)

Table 25: Process steps for preparation of tablets

Sr. No.	**Process step**		**Process**
1	**Sifting**		The drug is sifted through sieve 20# MCC PH101 and Crosspovidone are co-sifted through sieve 40#
2	**Dry mixing**		Carried out in Rapid mixer granulator for 20 minutes. Impeller speed: 70 RPM Chopper: off LOD of the dry mix is checked after mixing.
3	**Granulation**	**Binder solution 1**	Binder addition time: 8 minutes Impeller: 70 rpm Chopper: off After the complete addition of solution- Kneading time: 1 minute Impeller: 140 rpm Chopper: 1200 rpm
		Binder	Binder addition time: 2:30 minute

		solution 2	Impeller: 70 Chopper: off After the complete addition of solution- Kneading time: 30 seconds Impeller: 150 rpm Chopper: 1200 rpm
4	**Wet milling**		Milling is done through screen 4.00 mm at 2000 rpm for 10 mins
5	**Drying**		Air drying is carried out of the screened granules for 20 minutes. Then, semi-drying is done at 60^0 C for 7 minutes.
6	**Milling**		The semi-dried granules are milled through screen 2.0mm at 2000 rpm for 10 minutes.
7	**Drying**		Drying of the milled granules is done at 60^0C for 40 minutes till the desired LOD of the granules is achieved.
8	**Blending and Lubrication**		Remaining crosspovidone is shifted through sieve 40#. Blending is done using an octagonal blender for 20 minutes at 16 rpm. Magnesium stearate is sifted through sieve 60#. Lubrication is again carried out in an octagonal blender for 5 minutes at 16 rpm.
9	**Compression**		Tablets are compressed using a rotary compression machine using 10.5mm FFBE punch and the prepared tablets are then submitted for evaluation.

4.4.2 Post compression evaluation parameters:

4.4.2.1 Weight variation:

20 tablets are weighed individually, selected at random form each batch and then the

average weight is calculated. Individual tablet weight is compared with average weight. Criteria is met if not more than 2 tablets are outside percentage limit.

Weight variation tolerances for uncoated, film coated and other than film coated tablets:

As per Indian Pharmacopoeia:

Table 26: Weight variation criteria as per IP

Avg wt of tablet (mg)	Maximum % variation allowed
80	10
80-250	7.5
>250	5

4.4.2.2 Hardness:

- It can be defined as the force necessary to break the tablet in a compression test. It is also known as the tablet crushing strength.
- It can be measured in the units: Kilogram(kg), Newton(N), Pound(lb)

Method-

- The standard method used for tablet hardness testing is compression testing.
- The tablet is placed between two jaws that crush the tablet.
- The machine measures the force applied to the tablet and detects when it fractures.
- Various devices used to test hardness are: Monsanto tester, Pfizer ester, Strong–Cobb tester, Erweka tester, Schleuniger tester.

4.4.2.3 Friability:

- It is another measure for the tablet's strength.
- Roche friablilator as used for measurement.

Method-

- Number of tablets equivalent to the weight 6.5 gm are taken and placed itno the drum of the assembly.
- The drum is rotated at the speed of 25±1 rpm.
- Upto 100 rotations are done and then the tablets are removed and weighed again.
- Percentage friability is calculated from the formula:

$$\%\textbf{Friability} = \frac{\text{Initial weight of tablets- Final weight of tablets}}{\text{Initial weight of tablets}} * 100$$

- Loss in weight of tablets should not be more than 1%.

4.4.2.4 Thickness:

- It can be measured by the use of a vernier caliper.
- The tablet thickness should be limited within ±5% variation of a standard value.

4.4.2.5 Disintegration:

- This test provides the information, whether the tablets disintegrate within a prescribed time when place in a liquid medium at experimental conditions.
- Basket rack assembly is used for the test.
- Two beakers of 1000ml capacity contain a basket each, with a 10# (2mm) screen at the bottom of the basket. 6 open ended tubes are present in the basket.
- The assembly has an attached standard motor drive device to move the basket at the frequency of 28-32 cycles/min through the distance of 53-57mm.
- Volume of fluid contained in the beaker is such that at the highest point of upward stoke wire mesh remains at least 25mm from the bottom of the vessel on downward stroke.
- Thermostatic arrangements are also present in the assembly for heating liquid and maintaining temperature at 35 ± 2^0C.
- For uncoated tablets, the medium taken is water and the maximum time for the tablet to get completely disintegrated is 15 minutes.

4.4.2.6 Dissolution:

- The dissolution test is performed according to B.P.
- 6 tablets from each batch were submitted for dissolution testing.
- A U.S.P type II, paddle apparatus was used for the testing.
- The test was carried out in 900ml, 7.5 pH phosphate buffer. The speed was maintained at 75 rpm.
- Sampling was done at time points 5,10,15,20, 30 and 45 minutes.

- The samples were then evaluated by UV spectroscopy and the percentage drug release at each time point was calculated.

CHAPTER 5

EXPERIMENTAL WORK

5.1 Preliminary Trials

5.1.1 Evaluation of reference tablet

The reference brand tablets were evaluated for various criteria, and the results are as such:

Table 27: Evaluation of Reference tablets

Parameter	Value
Type of tablet	Immediate release tablet without coating.
Breakline	Yes
Average weight	335mg
Hardness	130-150N
Thickness	3.63 mm
Diameter	10.18 mm
Disintigration time	6.45 mins
% Drug release in 45 minutes	101%

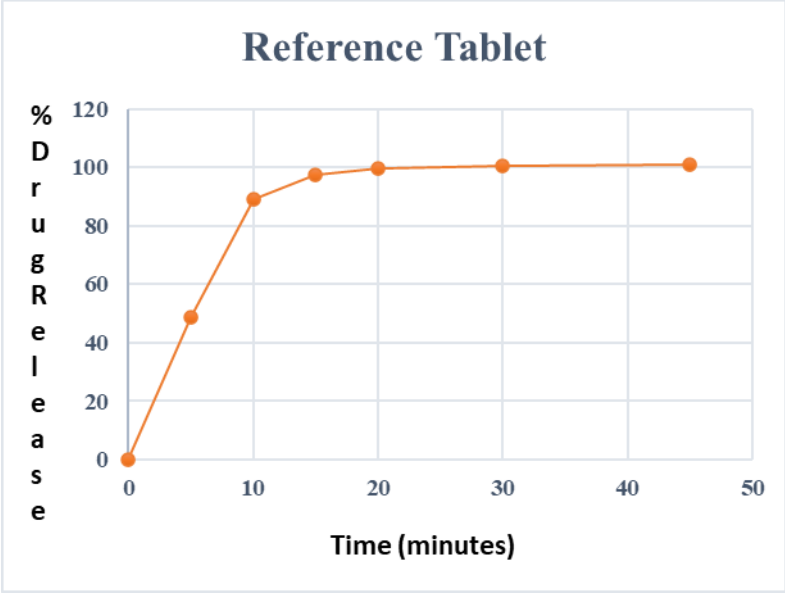

Figure 4: Dissolution of Reference tablet

5.1.2 Binder Solubility

- Preliminary trials were taken to determine the solubility of the binder in the highly basic solution which is to be used as the binder solution for the granules formulation.
- Several different trials were taken with varying amounts of sodium hydroxide and meglumine in water along with PVP K30, and it solubility was to be determined.

Table 28: Trials to check solubility of binder in alkaline environment

Excipient	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5
Sodium Hydroxide	-	3.35g	3.35g	4g	2g
Meglumine	12	-	12g	10g	14g
PVP K-30	5 g	5g	5g	5g	5g
Water	20ml	20ml	20ml	20ml	20ml

- The observations of these trials exhibited that PVP K30 will precipitate when added in the same solution as sodium hydroxide and meglumine.
- So, it was decided that PVP K30 needs to be added separately into the formulation.

5.2 Optimization of formulation and process parameters

Trial No.: T/001

Formulation:

Optimization of Binder.

In this trial, manual granulation of the drug was carried out.

Table 29: Formula for trial T/001

Ingredient	Quantity	%w/w

INTRAGRANULAR		
Telmisartan	80	23.880
MCC PH 102	122.55	36.581
Mannitol	90	26.865
Sodium starch gycolate	3	0.895
Crosscarmellose sodium	3	0.895
BINDER		
NaOH	7	2.089
PVP K30	16.75	5.000
Purified water	q.s.	--
EXTRAGRANULAR		
Sodium starch glycolate	3	0.895
Croscarmellose sodium	3	0.895
Colloidal silicon dioxide	3.35	1.000
Mg. stearate	3.35	1.000

The drug was sifted through mesh #20 and the diluents through mesh #40. The binder solution was prepared in aqueous media. Granulation was carried out and the extra granular excipients were then added.

Results:

Observation:

Granules were not formed and hence they could not be subjected to check the IPQC parameters, and compression was also not done.

Discussion:

The binder solution is needed to be optimized, and the quantity of alkalizing agent needs to be optimized. Trial to be taken by using meglumine as an alkalizing agent in addition to NaOH.

Trial No.: T/002

Formulation:

Optimization of Binder.

For this trial, half quantity of the drug was added to the binder solution containing alkalizing agents, as the drug is soluble in highly alkaline environments.

Table 30: Formula for trial T/002

Ingredient	Quantity	%w/w
INTRAGRANULAR		
Telmisartan	40	11.940
MCC PH 102	130.59	38.982
Mannitol	90	26.865
Sodium starch gycolate	3	0.895
Crosscarmellose sodium	3	0.895
BINDER		
Telmisartan	40	11.940
Meglumine	8.71	2.600
NaOH	7	2.089
Purified water	q.s.	--
EXTRAGRANULAR		
Sodium starch glycolate	3	0.895
Croscarmellose sodium	3	0.895

Colloidal silicon dioxide	3.35	1.000
Mg. stearate	3.35	1.000

The drug was sifted through mesh #20 and the diluents through mesh #40. Manual granulation was to be carried out.

Results:

Observation:

The drug started precipitating upon standing. Proper binder solution could not be prepared. Hence granulation not carried out.

Discussion:

It was concluded that the drug needed to be added in the dry mix and wet granulation to be done.

Trial No.: T/003

Formulation:

Optimization of Binder.

In this trial the water-soluble diluent, Mannitol was only used. Along with that only one disintegrating agent, i.e., crosscramellose sodium was added, completely extragranularly. The binder used was added to the dry mix and an aqueous solution of the alkalizers was prepared.

Table 31: Formula for trial T/003

Ingredient	Quantity	%w/w
INTRAGRANULAR		
Telmisartan	80	23.880
Mannitol	190	56.716
PVP K-30	21.50	6.417

BINDER		
Meglumine	24.00	7.164
NaOH	6.70	2.000
Purified water	q.s.	--
EXTRAGRANULAR		
Croscarmellose sodium	12.00	3.582
Mg. stearate	3.35	0.238

The drug was sifted through mesh #20 and the diluents through mesh #40. Manual granulation was carried out.

Results:

Observation:

The granules formed were very hard and incompressible. Hence tablets were not compressed.

Discussion:

It was observed that by addition of the binder, i.e., PVP K-30, to the dry mix, the granules become incompressible. Hence next trial was to be taken without PVP as a binder.

Trial No.: T/004

Formulation:

Optimization of Binder, Disintegrating agent and Alkalizer.

For this trial, PVP K30 was not added in the dry mix as well as in the binder solution. The binder solution was an aqueous solution of the alkalizers and the disintegrating agent used was crosspovidone and it was completely added extragranularly along with the lubricating agent.

Table 32: Formula for trial T/004

Ingredient	Quantity	%w/w
INTRAGRANULAR		
Telmisartan	80	23.880
Mannitol	211.50	63.134
BINDER		
Meglumine	24.00	7.164
NaOH	6.70	2.000
Purified water	q.s.	--
EXTRAGRANULAR		
Crosspovidone	12.00	3.582
Mg. stearate	0.80	0.238

Again, the drug was sifted through mesh #20 and the diluents through mesh #40 and after preparation of the binder solution, manual granulation was carried out. Then the extra granular excipients were added to the prepared granules and tablets were compressed.

Result:

Observation:

The granules obtained exhibited a waxy appearance. Upon compression, sticking was observed.

Evaluation of tablets:

Table 33: Evaluation of T/004 tablets

Parameter	Value
Thickness	4.01mm

Diameter	10.18mm
Hardness	120-130N
Friability	0.1%
Disintegrating time	03:40 mins

Dissolution-

Dissolution was carried out in 900ml 7.5 pH phosphate buffer using USP paddle II apparatus.

Table 34: Dissolution of T/004 tablets

Time	**% Cumulative Drug release**
0	0
5	46.7
10	55.4
15	70.7
20	71.7
30	75.4
45	77.4

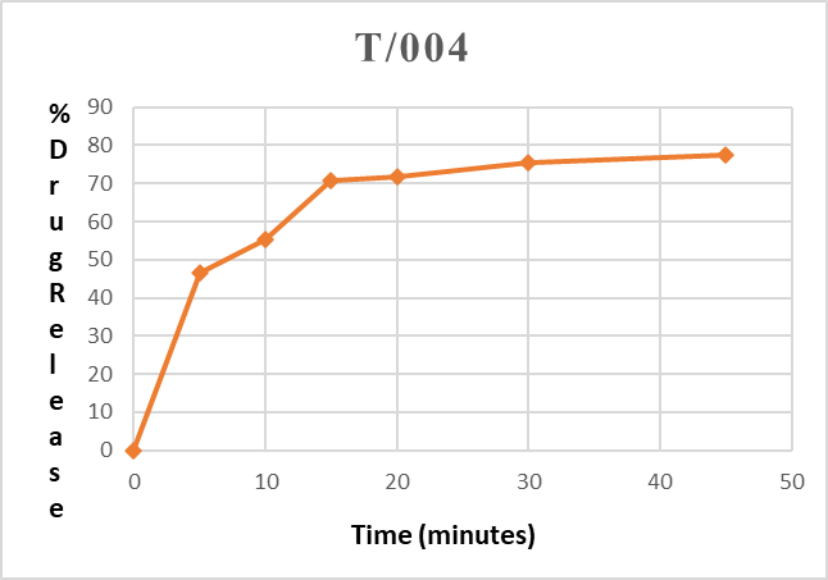

Figure 5: Dissolution of T/004 tablets

Discussion:

Optimal disintegrating time was observed for this trial and hence crosspovidone was confirmed to be used as the disintegrating agent. However, the dissolution showed less than 80% drug release, therefore it was decided to check the effect of increase in the quantity of alkalyzing agent on the drug release. Also addition of another alkalizer, i.e., sodium bicarbonate and of a surfactant such as sodium lauryl sulphate to be done toh help with dissolution.

Trial No.: T/005

Formulation:

In this trial, the quantity of alkalizing agent, meglumine was increased and was added as both, in the intragranular dry mix as well as in the binder solution. Also, to help with dissolution sodium bicarbonate, another alkalizer, and sodium lauryl sulphate, a surfactant were added extra granularly, to help with the drug release process and the drug is soluble in highly alkaline media and the surfactant will help in maintain the sink conditions for the dissolution media. The diluent was also divided intra and extragranularly.

Table 35: Formula for trial T/005

Ingredient	Quantity	%w/w
INTRAGRANULAR		
Telmisartan	80	23.880
Mannitol	149.26	44.555
Meglumine	6.00	1.791
BINDER		
Meglumine	24.00	7.164
NaOH	6.20	1.850
Purified water	q.s.	--
EXTRAGRANULAR		
Mannitol	50.00	14.925
$NaHCO_3$	3.35	1.000
SLS	0.34	0.100
Crosspovidone	12.00	3.582
Mg. stearate	3.35	1.000

Results:

Observation:

Sticking was again observed during compression.

Evaluation of tablets:

Table 36: Evaluation of T/005 tablets

Parameter	Value

Thickness	4.04mm
Diameter	10.18mm
Hardness	120-130N
Friability	0.2%
Disintegrating time	05:30 mins

Dissolution-

Dissolution was carried out in 900ml 7.5 pH phosphate buffer using USP paddle II apparatus.

Table 37: Dissolution of T/005 tablets

Time	**% Cumulative Drug release**
0	0
5	37.8
10	49.0
15	69.6
20	70.3
30	71.9
45	73.9

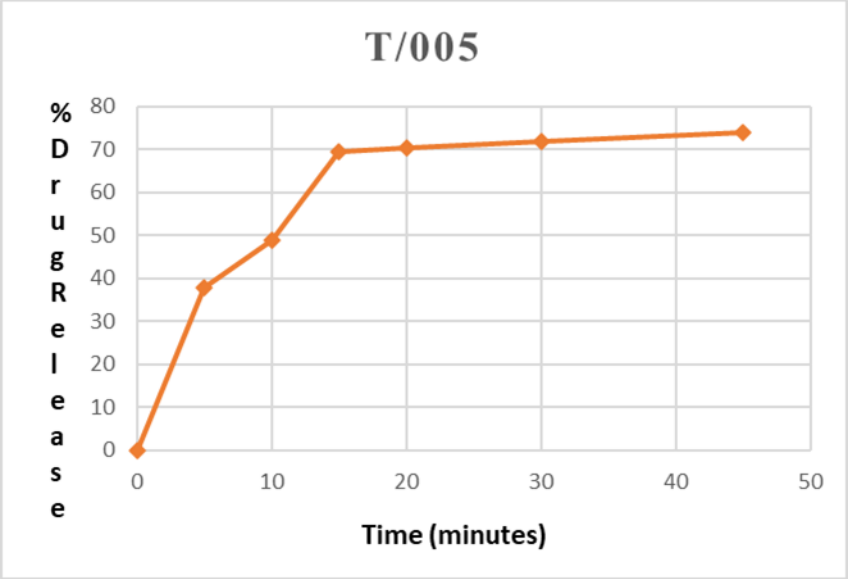

Figure 6: Dissolution of T/005 tablets

Disscussion:

Dissolution observed was still less than 80% drug release in 45 minutes. So to improve dissolution, it was planned to check the effect of increase in the concentration of sodium hydroxide.

Trial No.: T/006

Formulation:

The diluent, which is Mannitol was again divided and 30% was added extragranularly while rest was added in the dry mix. Batch similar to the one before was taken, the only difference being the increase in quantity of sodium hydroxide, which might affect the drug release.

Table 38: Formula for trial T/006

Ingredient	Quantity	%w/w
INTRAGRANULAR		
Telmisartan	80	23.880
Mannitol	155.26	46.346

Meglumine	4.00	1.194
BINDER		
Meglumine	20.00	5.970
NaOH	6.700	2.00
Purified water	q.s.	--
EXTRAGRANULAR		
Mannitol	50.00	14.925
$NaHCO_3$	3.35	1.000
SLS	0.34	0.100
Crosspovidone	12.00	3.582
Mg. stearate	3.35	1.000

Results:

Observation:

Sticking defect was not resolved with this batch also.

Evaluation of tablets:

Table 39: Evaluation of T/006 Tablets

Parameter	Value
Thickness	4.00mm
Diameter	10.18mm
Hardness	120-130N
Friability	0.1%
Disintegrating time	05:30 mins

Dissolution-

Dissolution was carried out in 900ml 7.5 pH phosphate buffer using USP paddle II apparatus.

Table 40: Dissolution of T/006 tablets

Time	% Cumulative Drug release
0	0
5	35.6
10	47.8
15	68.3
20	69.9
30	71.7
45	72.5

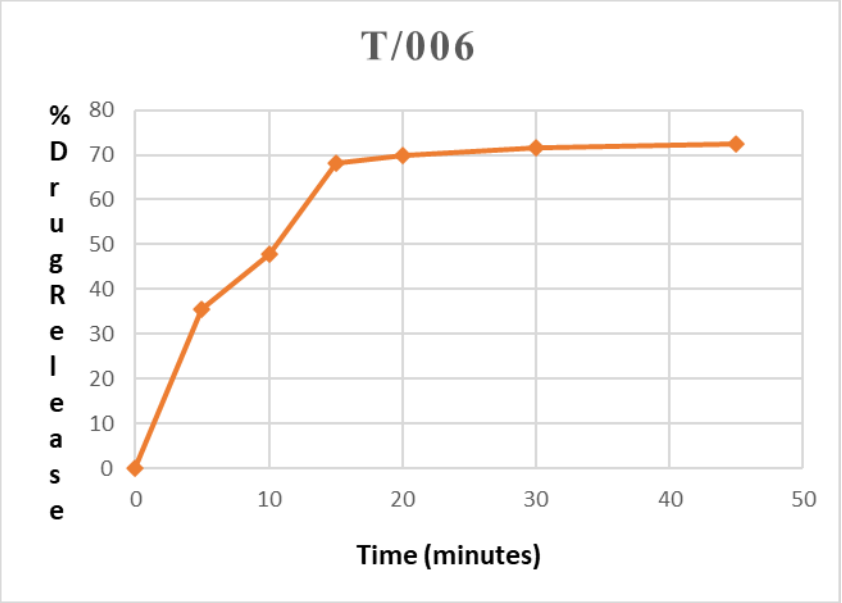

Figure 7: Dissolution of T/006 tablets

Discussion:

Dissolution observed was still less than 80% drug release in 45 minutes. So to improve dissolution, it was planned to evaluate the outcome of increase in the concentration of Meglumine. And it was concluded that, to resolve sticking, we need to add a binder into the formulation.

Trial No.: T/007

Formulation:

The diluent, which is Mannitol was now completely added intra-granularly. Also, PVP K-30 was to be used as a binder. As the preliminary trials showed that PVP starts precipitating when added to an alkaline environment, it was incorporated into the dry mix. The concentration of Meglumine was also increased intra-granularly as well as in the binder solution. To improve the flow of the blend, glidant was also added, and to resolve sticking, the quantity of lubricant was doubled.

Table 41: Formula for trial T/007

Ingredient	Quantity	%w/w
INTRAGRANULAR		
Telmisartan	80.00	23.880
Mannitol	188.00	56.119
Meglumine	6.00	1.791
PVP K-30	10.00	2.985
BINDER		
Meglumine	24.00	7.164
NaOH	6.700	2.00
Purified water	q.s.	--
EXTRAGRANULAR		
Crosspovidone	12.00	3.582

Collodial Silicon Dioxide	1.60	0.477
Mg. stearate	6.70	2.000

Results:

Observation:

Sticking was yet observed. The granules formed were hard and difficult to compress.

Evaluation of tablets:

Table 42: Evaluation of T/007 tablets

Parameter	Value
Thickness	4.08mm
Diameter	10.18mm
Hardness	120-130N
Friability	0.1%
Disintegrating time	>15 mins

Dissolution-

Dissolution was carried out in 900ml 7.5 pH phosphate buffer using USP paddle II apparatus.

Table 43: Dissolution of T/007 tablets

Time	% Cumulative Drug release
0	0
5	34.9

10	43.2
15	58.8
20	61.3
30	62.6
45	63.8

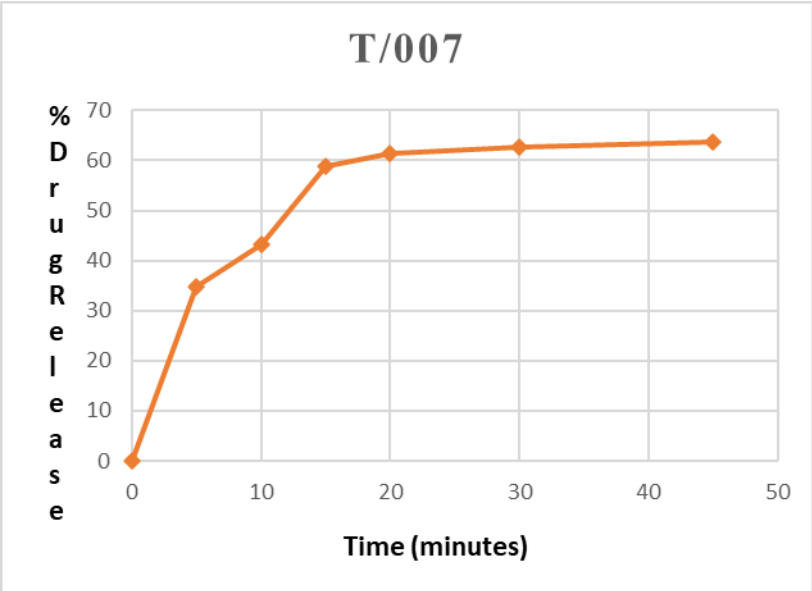

Figure 8: Dissolution of T/007 Tablets

Discussion:

Very little drug release was achieved at 45minutes. So to improve dissolution, it was planned to check the effect of further increase in the concentration of Meglumine and the addition of sodium bicarbonate. The disintergration time was observed to be more than 15 minutes. Hence to settle that it was discussed to increase the concentration of disintegrating agent.

Trial No.: T/008

Formulation:

Concentration of the disintegrating agent was increased for this formulation, and 30% of it was added along with the extra-granular excipients, while remaining was blended into the intra-granular dry mix. Meglumine concentration was also increased and sodium bicarbonate was added to the dry mix to aid in dissolution. Surfactant was again added along with the extra-granular excipients and the quantity of lubricant was reduced.

Table 44: Formula for trial T/008

Ingredient	Quantity	%w/w
INTRAGRANULAR		
Telmisartan	80.00	23.880
Mannitol	135.27	40.379
Crosspovidone	11.90	3.552
Meglumine	10.00	2.985
$NaHCO_3$	10.00	2.985
PVP K-30	6.70	2.000
BINDER		
Meglumine	30.00	8.955
NaOH	5.00	1.492
Purified water	q.s.	--
EXTRAGRANULAR		
Crosspovidone	5.10	1.522
SLS	1.67	0.498
Collodial Silicon Dioxide	1.67	0.498
Mg. stearate	5.03	1.500

Results:

Observation:

Sticking was yet observed. The granules formed were very hard and compression was difficult.

Evaluation of tablets:

Table 45: Evaluation of T/008 tablets

Parameter	Value
Thickness	4.05mm
Diameter	10.18mm
Hardness	100-130N
Friability	0.1%
Disintegrating time	07:22 mins

Dissolution-

Dissolution was carried out in 900ml 7.5 pH phosphate buffer using USP paddle II apparatus.

Table 46: Dissolution of T/008 tablets

Time	% Cumulative Drug release
0	0
5	33.3
10	41.2
15	49.6
20	52.2

30	53.2
45	54.6

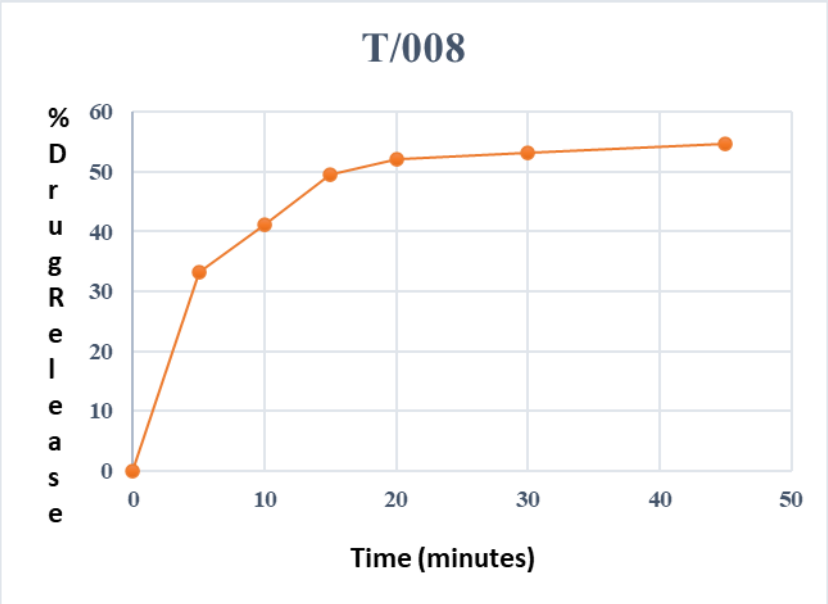

Figure 9: Dissolution of T/008 Tablets

Discussion:

Close to half of the drug was only released at 45minutes. It was observed that due to the resistant nature of the granules, compression as well as drug release were greatly affected. So to form lighter and softer granules was the first priority. After literature review it was decided that the use of water soluble diluent might be the cause of it. Hence for the next trial, a water insoluble diluent was to be taken in place of mannitol. Also, optimization of the binder solution was of great improtance. As PVP could not be added to the solution containing the alkalizers, two different binder solutions were decided to be prepared.

Trial No.: T/009

Formulation:

For this trial, mannitol was replaced with Microcrystalline cellulose, a water insoluble diluent. The drug along with the diluent and 33% of the disintegrating agent were

added to the intra-granular dry mix. And most importantly, in this trial, two different binder solutions were prepared:

Binder solution 1: Meglumine+ NaOH+ water

This solution served to provide an alkaline environment to the drug during the granulation process.

Binder solution 2: PVP K-30+ water

As adding PVP directly into the dry mix led to higher disintegration time, here and aqueous solution was prepared and added to the formulation. This formed a coating around the dissolved drug particles and helped to form granules.

Extra-granular excipients just included rest of the disintegrating agent and the lubricant.

Table 47: Formula for trial T/009

Ingredient	Quantity	%w/w
INTRAGRANULAR		
Telmisartan	80.00	23.880
MCC PH 101	184.27	55.006
Crosspovidone	4.00	1.194
BINDER		
Meglumine	40.00	11.940
NaOH	7.00	2.089
PVP K-30	10.05	3.000
Purified water	q.s.	--
EXTRAGRANULAR		
Crosspovidone	8.00	2.388

Mg. stearate	1.68	0.507

Results:

Observation:

The granules formed were hard, but not as rigid as with mannitol. Tablets were not compressed.

Discussion:

For the next trial it was planed to prepare the inder solution 2 using Iso-propyl alcohol instead of water, which might further help in making of lighter, easily compressible granules.

Trial No.: T/010

Formulation:

A batch similar to the former one was taken with the only difference being in the binder solution 2. Here water was replaced with an inorganic solvent, which is Iso-propyl alcohol and the granulation was done.

Table 48: Formula for trial T/010

Ingredient	Quantity	%w/w
INTRAGRANULAR		
Telmisartan	80.00	23.880
MCC PH 101	184.27	55.006
Crosspovidone	4.00	1.194
BINDER		
Meglumine	40.00	11.940
NaOH	6.50	1.940

PVP K-30	10.06	3.002
IPA	q.s.	--
Purified water	q.s.	--
EXTRAGRANULAR		
Crosspovidone	8.00	2.388
Mg. stearate	1.68	0.507

Results:

Observation:

Sticking issue was completely resolved. The granules formed were very soft and light and easily compressible.

Evaluation of tablets:

Table 49: Evaluation of T/010 tablets

Parameter	Value
Thickness	4.05mm
Diameter	10.18mm
Hardness	100-130N
Friability	0.1%
Disintegrating time	>30 mins

Dissolution studies were not done for this particular batch as the disintegration time was more than 30 minutes.

Discussion:

As the disintegration time was high, it was planned to increase the concentration of disintegrating agent in the next batch.

Trial No.: T/011

Formulation:

The quantity of disintegrating agent was increased, essentially doubled for this trial both intra and extra granularly to reduce the disintegration time.

Table 50: Formula for T/011

Ingredient	Quantity	%w/w
INTRAGRANULAR		
Telmisartan	80.00	23.880
MCC PH 101	163.27	48.737
Crosspovidone	16.75	5.000
BINDER		
Meglumine	40.00	11.940
NaOH	6.50	1.940
PVP K-30	10.05	3.000
IPA	q.s.	--
Purified water	q.s.	--
EXTRAGRANULAR		
Crosspovidone	16.75	5.000
Mg. stearate	1.68	0.507

Results:

Observation:

Soft, light and porous granules formed. Compression was done without the presence of any defects.

Evaluation of tablets:

Table 51: Evaluation of T/011 tablets

Parameter	Value
Thickness	4.01mm
Diameter	10.18mm
Hardness	100-120N
Friability	0.1%
Disintegrating time	>15 mins

Tablets were again not submitted to dissolution testing as the disintegration time was more than 15 minutes.

Discussion:

For next batch, the disintegrating agent concentration was to be further increased to achieve disintegration time within limit.

Trial No.: T/012

Formulation:

The quantity of disintegrating agent was increased, doubled again, both intra and extra granularly to and check if the disintegration time is within limits.

Table 52: Formula for trial T/012

Ingredient	Quantity	%w/w
INTRAGRANULAR		
Telmisartan	80.00	23.880

MCC PH 101	129.77	38.737
Crosspovidone	33.50	10.000
BINDER		
Meglumine	40.00	11.940
NaOH	6.50	1.940
PVP K-30	10.05	3.000
IPA	q.s.	--
Purified water	q.s.	--
EXTRAGRANULAR		
Crosspovidone	33.50	10.000
Mg. stearate	1.68	0.507

Results:

Observation:

Soft, light and porous granules formed. Compression was done without the presence of any defects.

Evaluation of tablets:

Table 53: Evaluation of T/012 tablets

Parameter	Value
Thickness	3.97mm
Diameter	10.18mm
Hardness	130-140N
Friability	0.1%

Disintegrating time	08:00 mins

Dissolution-

Dissolution was carried out in 900ml 7.5 pH phosphate buffer using USP paddle II apparatus.

Table 54: Dissolution of T/012 tablets

Time	% Cumulative Drug release
0	0
5	46.9
10	76.2
15	89.8
20	90.5
30	90.6
45	90.7

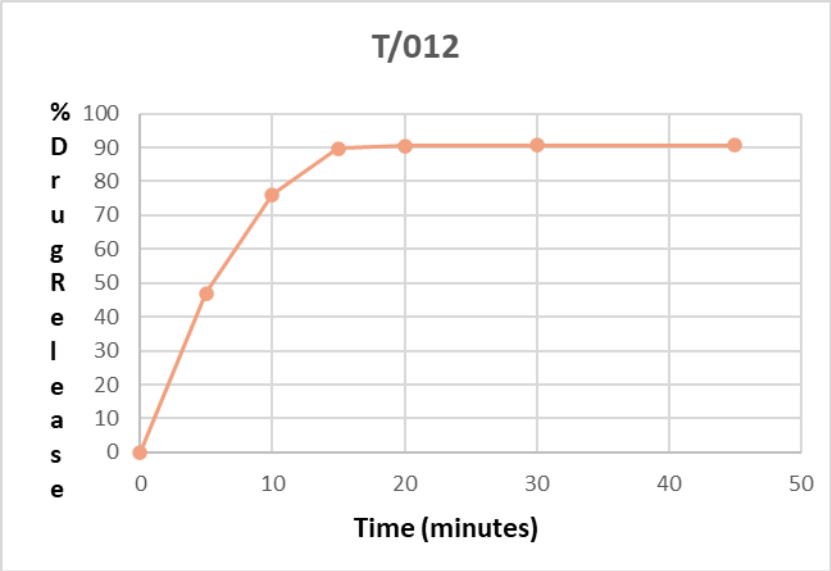

Figure 10: Dissolution of T/012 Tablets

Discussion:

The current batch showed very promising results with all the parameters within limit. The drug release was also found to be 90.7% at the 45 minute mark. So for the next batch, the quantity of disintegrating agent was decided to be reduced a little bit to make the formulation more cost effective.

Trial No.: T/013

Formulation:

In this trial, the concentration of crosspovidone was reduced in the dry mix, and rest of the formula was same as the previous trial and the disintegration time was evaluated.

Table 55: Formula for trial T/013

Ingredient	Quantity	%w/w
INTRAGRANULAR		
Telmisartan	80.00	23.880
MCC PH 101	146.52	43.737

Crosspovidone	16.75	5.000
BINDER		
Meglumine	40.00	11.940
NaOH	6.50	1.940
PVP K-30	10.05	3.000
IPA	q.s.	--
Purified water	q.s.	--
EXTRAGRANULAR		
Crosspovidone	33.50	10.000
Mg. stearate	1.68	0.507

Results:

Observation:

Soft, light and porous granules formed. Compression was done without the presence of any defects.

Evaluation of tablets:

Table 56: Evaluation of T/013 tablets

Parameter	Value
Thickness	3.97mm
Diameter	10.18mm
Hardness	120-130N
Friability	0.1%
Disintegrating time	10:30 mins

Dissolution-

Dissolution was carried out in 900ml 7.5 pH phosphate buffer using USP paddle II apparatus.

Table 57: Dissolution of T/013 tablets

Time	% Cumulative Drug release
0	0
5	67.8
10	85.7
15	97.7
20	97.7
30	97.8
45	97.8

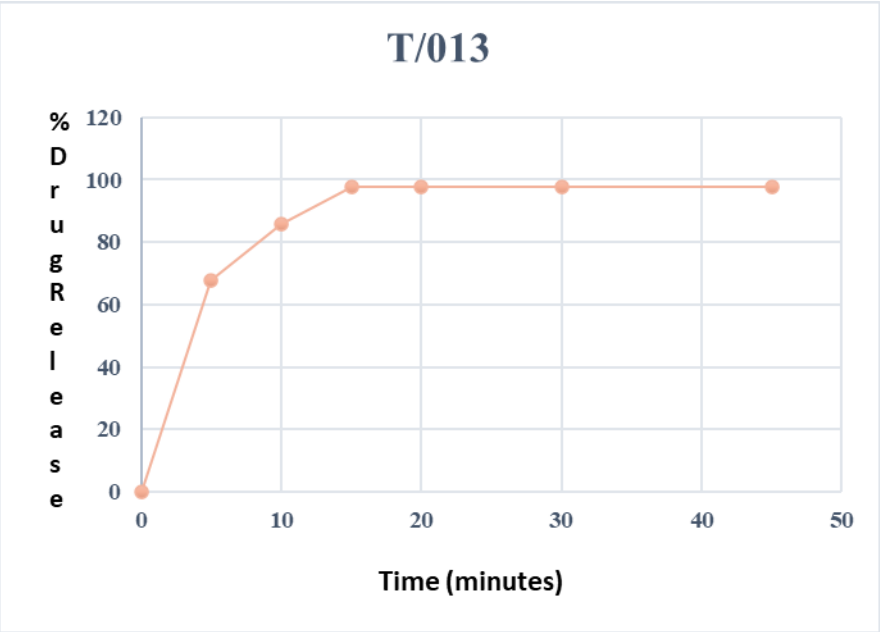

Figure 11: Dissolution of T/013 Tablets

Discussion:

Satisfactory disintegration time as well as dissolution was observed. So to make the formulatiom even more cost effective, further trial was to be taken with a reduced concentration of meglumine.

Trial No.: T/014

Formulation:

In this trial, the concentration of Meglumine was reduced in binder solution 1, and rest of the formula was same as the previous trial, with a slight change that the extra-granular crosspovidone was increased a little bit to aid in formation of smaller particles. And percentage drug release was evaluated.

Table 58: Formula for trial T/015

Ingredient	Quantity	%w/w
INTRAGRANULAR		
Telmisartan	80.00	23.880
MCC PH 101	149.82	44.722
Crosspovidone	16.75	5.000
BINDER		
Meglumine	30.00	8.955
NaOH	6.50	1.940
PVP K-30	10.05	3.000
IPA	q.s.	--
Purified water	q.s.	--
EXTRAGRANULAR		
Crosspovidone	40.20	12.000
Mg. stearate	1.68	0.507

Results:

Observation:

Soft, light and porous granules formed. Compression was done without the presence of any defects.

Evaluation of tablets:

Table 59: Evaluation of T/014 tablets

Parameter	Value
Thickness	3.7mm
Diameter	10.18mm
Hardness	120-130N
Friability	0.1%
Disintegrating time	10:30 mins

Dissolution-

Dissolution was carried out in 900ml 7.5 pH phosphate buffer using USP paddle II apparatus.

Table 60: Dissolution of T/014 tablets

Time	% Cumulative Drug release
0	0
5	45.5
10	74.9
15	92.4

20	92.8
30	93
45	93.1

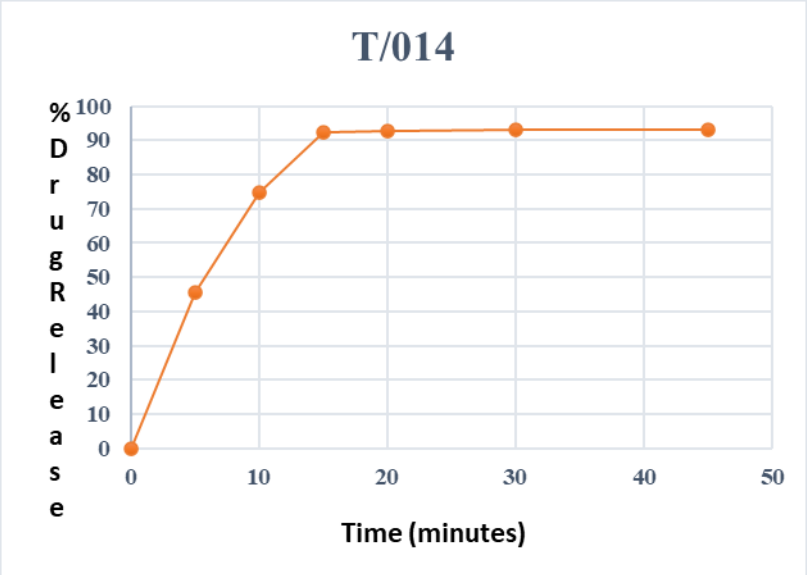

Figure 12: Dissolution of T/014 Tablets

Discussion:

Satisfactory disintegration time as well as dissolution was observed. Now trial to be taken in Rapid Mixer Granulator.

<u>Trial No.: T/015</u>

Formulation:

Same formula as above was taken, but this time, instead of manual granulation, the batch was taken in the Rapid mixer granulator.

Table 61: Formula for trial T/015

Ingredient	Quantity	%w/w

INTRAGRANULAR		
Telmisartan	80.00	23.880
MCC PH 101	149.82	44.722
Crosspovidone	16.75	5.000
BINDER		
Meglumine	30.00	8.955
NaOH	6.50	1.940
PVP K-30	10.05	3.000
IPA	q.s.	--
Purified water	q.s.	--
EXTRAGRANULAR		
Crosspovidone	40.20	12.000
Mg. stearate	1.68	0.507

Observation:

Soft, light and porous granules formed. Compression was done without the presence of any defects.

Evaluation of tablets:

Table 62: Evaluation of T/015 tablets

Parameter	Value
Thickness	3.7mm
Diameter	10.18mm
Hardness	120-130N

Friability	0.1%
Disintegrating time	13:30 mins

Results:

A spike was observed in the disintegration time and the prepared tablets were not submitted for dissolution studies.

Discussion:

To increase the concentration of disintegrating agent to achieve better disintegration. Aalong with that the kneading time was optimized to achive better granulation.

Trial No.: T/016

Formulation:

A formula similar to the one in the former trial was taken with a slight difference in the concentration of the disintegrating agent. It was increased in the intra-granular dry mix.

Table 63: Formula for trial T/016

Ingredient	Quantity	%w/w
INTRAGRANULAR		
Telmisartan	80.00	23.880
MCC PH 101	129.55	38.671
Crosspovidone	33.50	10.000
BINDER		
Meglumine	40.00	11.940
NaOH	6.70	2.000
PVP K-30	10.05	3.000

IPA	q.s.	--
Purified water	q.s.	--
EXTRAGRANULAR		
Crosspovidone	33.50	10.000
Mg. stearate	1.70	0.507

Results:

Observation:

Soft, light and porous granules formed. Compression was done without the presence of any defects.

Evaluation of tablets:

Table 64: Evaluation of T/016 tablets

Parameter	Value
Thickness	3.7mm
Diameter	10.18mm
Hardness	120-130N
Friability	0.1%
Disintegrating time	08:30 mins

Dissolution-

Dissolution was carried out in 900ml 7.5 pH phosphate buffer using USP paddle II apparatus.

Table 65: Dissolution of T/016 tablets

Time	% Cumulative Drug release
0	0
5	46.7
10	86.7
15	98.9
20	99.7
30	101.5
45	101.5

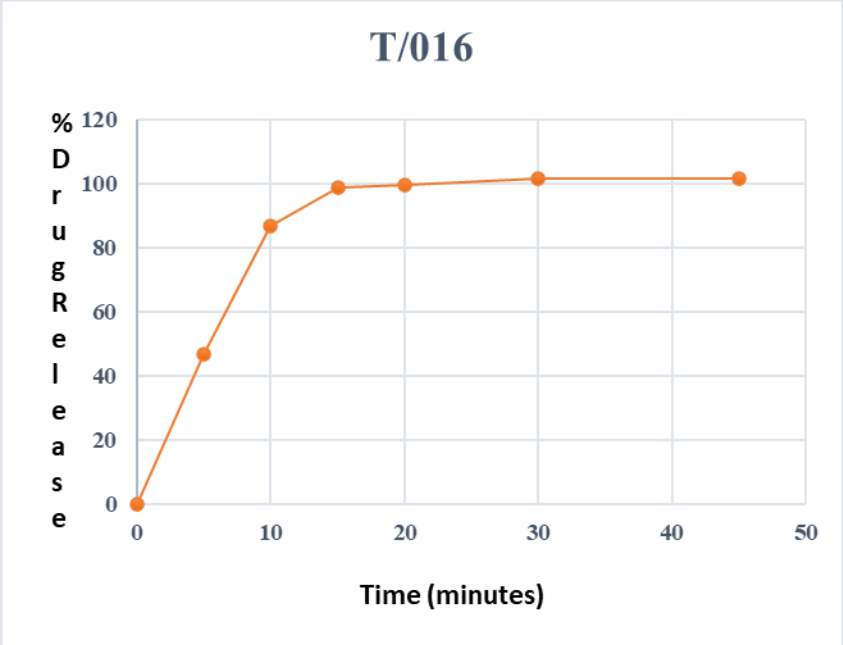

Figure 13: Dissolution of T/016 Tablets

Discussion:

Tablets with parameters matching the reference tablets were obtained. This formula and process was reproduced and finally stability batches were taken for the same.

5.3 Comparison of Reference and Test Tablets

The formula for the optimized batch i.e., T/016 was reproduced and tablets were prepared. The prepared tablets were then compared with the reference tablets for various parameters. The comparison is described in table 66:

Table 66: Comparison of parameters of Reference and Test Tablets

Parameter	Reference product	Prepared tablets
Type of tablet	IR tablet without coating	IR tablet without coating
Break line	Present	Present
Average weight	335mg	335mg
Hardness	130-150 N	120-130 N
Thickness	3.63 mm	3.7 mm
Diameter	10.18 mm	10.18 mm
Disintegration Time	6:45 mins	8:30 mins
% Drug release in 45 minutes	101 %	101.5 %

The dissolution profiles for both the tablets are as follows:

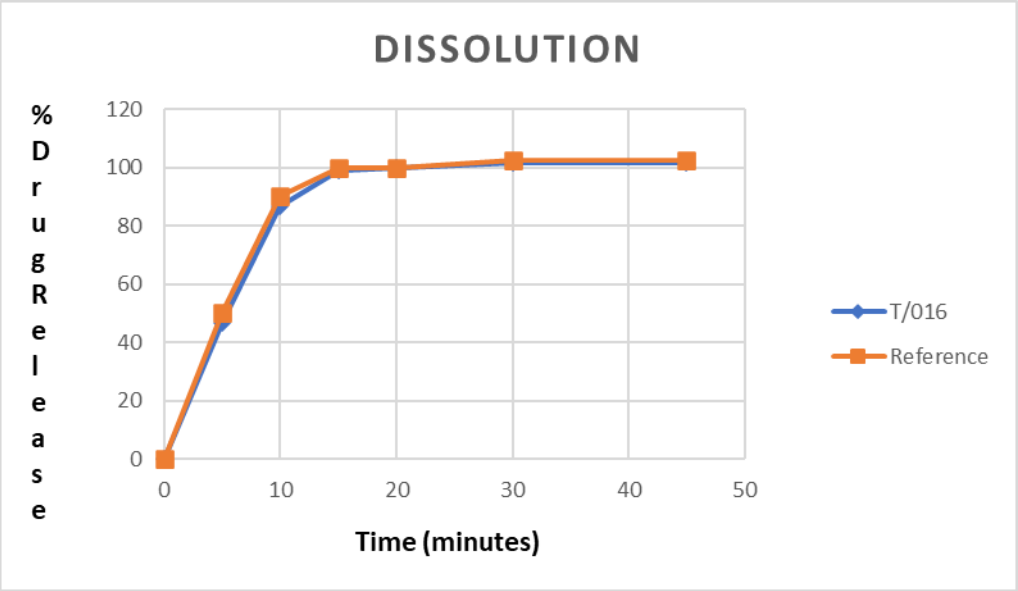

Figure 14: Comparison of dissolution profiles of Reference and Test tablet

CHAPTER 6

CONCLUSION

Conclusion:

Almost half of the population for a country like India suffers from high blood pressure. Hence the requirement for a less expensive and highly patient compliant medication is in high demand. Telmisartan is a drug that shows poor solubility and a very long half-life. Hence it is possible to be formulated as an immediate release tablet, as the immediate release tablet formulation, though conventional, shows very high patient compliance, cost effectiveness and is mechanically strong and therefore very compatible for shipment. Hence the requirement for such a product is very high.

Here the project was carried out to formulate immediate release tablets of the drug Telmisartan using simple wet granulation method and compare all the parameters with the reference product. As the drug is a BCS class II drug, formulation proved to be challenge because it is practically insoluble in water, sparingly soluble in strong acids and freely soluble only in alkaline environments. Hence an alkaline micro-environment was mandatory to be maintained for the drug during the granulation process to obtain soft, light and easily compressible granules and even during the drug release trials such that the drug can dissolve easily into the surrounding environment, the physiological solution.

Total 16 trials were taken to finally obtain the optimum formula containing appropriate quantities of the alkalizer, disintegrating agent, binder, lubricant etc. Samples from each batch were taken and subjected to evaluation parameters such as weight variation, hardness, thickness, friability, disintegration time and dissolution and the results were compared with the values obtained from the evaluation of the reference product.

A paired T-test for two sample means was carried out using Microsoft excel software and the values were found to be:

t Stat = 2.380
t Critical = 2.570

Hence, form the test it can be concluded that no significant variance is observed in the two dissolution profiles and it can be said that the two formulations are Bioequivalent.

The final formula was reproduced. Then stability batches were taken for the same and stability studies are being carried out according to the ICH guidelines.

At the end it can be summarized that formulation Telmisartan tablets by wet granulation method using alkalizers and superdisintegrants prove to be less expensive, and more feasible method for the small-scale industries. The prepare tablets are also highly patient compliant and can be widely used in the treatment of Hypertension.

CHAPTER 7

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ABSTRACT

Development and Characterization of Telmisartan Immediate Release Tablets.

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ABSTRACT

Hypertension is a chronic illness characterized by chronically high arterial blood pressure. It is not a disease in and of itself, but it is a significant risk factor for cardiovascular death and morbidity. Telmisartan is a drug that belongs to the class of AT_1 receptor antagonists, which act on the renin-angiotensin system and lead to the eventual decrease in blood pressure. It is an FDA approved, first line drug in the treatment of hypertension. As the drug is a BCS class II drug, it is practically insoluble in water and shows soluble behavior only in a highly basic media. Thus, in the present study immediate release tablets of telmisartan were prepared using wet granulation. The objective of the study was to prepare the tablets such that they match all the parameters with the reference tablet. First of all, the reference tablets were evaluated and the critical processing parameters were identified. The prepared tablets were evaluated for appearance, weight variation, friability, disintegration time and dissolution. Optimization of the formula as well as the processing parameters was also done such that it favoured better dissolution, reduced disintegration time and reduction of processing cost. Stability batches were prepared and stability data is being generated according to the ICH guidelines. IN conclusion, the final formula obtained showed all the parameters equivalent to the reference formulation.


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