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FORMULATION AND EVALUATION OF TRIPLE DRUG COMBINATION OF TELMISARTAN, AMLODIPINE BESYLATE, AND HYDROCHLOROTHIAZIDE TABLETS BY DIRECT COMPRESSION METHOD

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ABSTRACT

To enhance patient compliance, this research assesses a triple-drug combination that includes Telmisartan, Amlodipine Besylate and Hydrochlorothiazide, all of which are anti- hypertensive drugs. The drug-drug and drug-excipient compatibility was verified using FTIR analysis, which was used to investigate the interaction between drugs and excipients. Using a variety of diluents and binders, nine formulations of tablets (F-1 to F-9) were formulated by using the direct compression method. Tablets were subjected to three tests: hardness, friability, and disintegration time. An in-vitro drug dissolution test was conducted on tablets using 0.1N HCl and pH 6.8 phosphate buffer solution as dissolving media. It was found that the tablet's DT, hardness, and friability were, respectively, 4.4 to 7.5 kg/cm², 0.17 to 0.91%, and 5 to 11 minutes. Around 90% of drugs are released within 30 minutes, according to in-vitro testing. Formulation F-6, with 3.5% croscarmellose, demonstrated superior performance as a disintegrant compared to 3.5% SSG and 3.5% crospovidone. It was found that croscarmellose was a better disintegrant than the other two, as disintegration time and dissolution properties were better with the croscarmellose. Hence, the study concluded that these formulations are promising for hypertension treatment. They can be considered as one of the promising fixed-drug dosage forms.

KEYWORDS: Telmisartan, Amlodipine besylate, Hydrochlorothiazide, Fixed dose combination form, Anti-hypertensive.

INTRODUCTION

Tablet

Tablets are a unit dosage form where a single standard dose of the medication is precisely measured and deposited.[1] Tablets are solid pharmaceutical dosage forms that can contain pharmacological substances with or without appropriate diluents. They are often made by molding or compression techniques.

Tables are produced by the use of punches and dies to compress regular amounts of powders or grains under high pressure. The particles that need to be compressed are made up of one or more medications, either with or without auxiliary ingredients like glide ants, lubricants, binders, disintegration agents, and compounds that can alter how the medications behave in the digestive systems.[2] These compounds have to be safe and therapeutically inactive at the concentrations that are present.

Advantages of the tablet dosage form[3]

1. They come in single units.
2. They offer the greatest capabilities of all oral dosage forms for the best dose precision.
3. Cost is the lowest.
4. Lighter and compact.
5. Easiest and cheapest to be packed as strips.
6. Easy to swallow.
7. Best chemical and microbial stability overall oral dosage form.

Disadvantages of tablet dosage form[3]

1. Children and unconscious patients feel it is hard to take.
2. Drugs with poor wetting, slow dissolution properties, and optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
3. Some drugs resist compression into dense compacts, owing to amorphous nature, and low-density character.
4. Bitter and objectionable odour tablets are hard to intake which may require coating

techniques which in turn reflect in the cost of the tablets make it costly.

Hypertension[4,5]

Hypertension, often known as high blood pressure or arterial hypertension, is a long-term medical disease characterized by elevated blood pressure in the arteries, necessitating greater cardiac effort than usual. This helps the blood flow through the blood vessels. Systolic blood pressure is determined when the heart is contracting, and diastolic blood pressure is determined when the heart is relaxing in between beats.

The peak reading of the systolic range at normal blood pressure is 100–140 mmHg, while the bottom reading is 60–90 mmHg. If blood pressure consistently hovers at 140/90 mmHg or above, it is considered high.

Hypertension is a major risk factor for aneurysms, heart failure, coronary artery disease, myocardial infarction, and stroke. A further consequence is chronic renal dysfunction. Even a slight increase in arterial blood pressure shortens life.

Dietary and lifestyle changes also improve blood pressure regulation and reduce the risk of health problems. Drug treatment is necessary for people for whom the aforementioned accommodations are insufficient.

Antihypertensive drug[5]

Antihypertensive drugs are medications used to manage hypertension (high blood pressure) and prevent its associated complications, such as stroke, heart failure, and kidney failure. These medications work through various mechanisms to lower blood pressure and are categorized into several classes:

Classes of medicines for hypertension

1. **Diuretics:** These medications lower blood volume by assisting the body in getting rid of extra salt and water. Common varieties include loop diuretics like furosemide and thiazide diuretics like hydrochlorothiazide.[6]

2. **ACE Inhibitors:** Angiotensin I is not converted to angiotensin II, a strong vasoconstrictor, by angiotensin-converting enzyme (ACE) inhibitors like lisinopril and enalapril.[6,7]

3. **Angiotensin II Receptor Blockers (ARBs):** These drugs, which include losartan and

valsartan, prevent angiotensin II from acting at its receptor sites, resulting in blood pressure reduction and vasodilation.[7,10]

4. **Calcium channel blockers**: Medicines such as nifedipine and amlodipine prevent calcium from entering the heart and blood vessel cells, causing the vessels to relax and enlarge.[9,11]

5. **Beta-blockers:** These medications, which include atenolol and metoprolol, lower blood pressure by lowering heart rate and contraction force.[8,9]

6. **Renin Inhibitors Directly**: One such medication is Aliskiren, which lowers blood pressure by blocking renin, an enzyme that is needed to produce angiotensin.[7,8]

7. **Vasodilators**: These drugs cause blood vessels to relax directly, lowering blood pressure. Examples are minoxidil and hydralazine.[8,9]

Drug profile[5]

FEATURES	TELMISARTAN	AMLODIPINE	HYDROCHLOROTHIAZIDE
DRUG CLASS	Angiotensin Receptor Blocker	Calcium Channel Blocker	Thiazide Diuretics (Na-Cl co-transport blocker)
ABSORPTION / (TIME)	well-absorbed after oral administration, peak plasma concentrations achieved within about 1 to 2 hours	oral administration, with peak plasma concentrations achieved within 6 to 12 hours.	plasma half-life of between about 5 and 15 hours
DISTRIBUTION	binds extensively to albumin. It distributes into various tissues, including the liver	high protein binding (approximately 97%).	appears to be preferentially bound to red blood cells
METABOLISM	extensive hepatic metabolism via the cytochrome P450 (CYP) enzyme system,	minimal hepatic metabolism via cytochrome P450 enzymes	minimal metabolism in the liver
ELIMINATION	eliminated via the faeces, with minimal renal excretion elimination half-life is 24 to 25 hours	Elimination is via urine, with 60-80% of the administered dose excreted unchanged.	excreted mainly unchanged in the urine And excreted in the urine within 6 hours

Fixed-dose combinations[12,13]

Pharmaceuticals known as fixed-dose combinations (FDCs) are formulations that include two

or more active ingredients in a single dosage form, like a tablet or capsule. By lowering the number of pills, a patient must take daily, they are intended to increase therapeutic efficacy, improve patient compliance, and streamline treatment regimens.

In the case of hypertension, Fixed-dose combinations (FDCs) of antihypertensive medications are increasingly recognized for their effectiveness in managing hypertension. These combinations typically include two or more active agents in a single pill, which contrasts with free-equivalent combinations (FECs) where the drugs are taken separately.

Combination antihypertensive agents are made up of pharmacologic classes such as angiotensin-converting enzyme (ACE) inhibitors and diuretics, beta-blockers and diuretics, angiotensin-II antagonists and diuretics, and calcium channel blockers and ACE inhibitors.

By combining two or more medications that typically act at different sites to block multiple effector pathways, fixed-dose combination therapy effectively lowers blood pressure.

Moreover, when two medications are taken together, the second one might prevent the first one from activating the counter-regulatory system.

Advantages of fixed-dose combinations

FDCs have various advantages, such as

1. Increased Compliance: FDCs assist patients in following their treatment plans by lowering the pill burden.
2. Synergistic Effects: Drug combinations that function through various pathways can increase overall efficacy.
3. Cost-Effectiveness: FDCs may lower distribution and packaging expenses, lowering patient costs.

Rationale for fixed drug combinations[13,19]

The goal of fixed-dose combination therapy is to improve compliance by using a single tablet taken once or twice daily and to achieve improved blood pressure control by utilizing two or more antihypertensive agents with distinct modes of action.

The clinical and metabolic effects of using the maximum dosages of each component of the combined tablet can also be reduced by using low doses of the two separate agents.

Because of these possible benefits, some researchers have suggested starting combination antihypertensive therapy as the first line of treatment, especially for patients who have more severe initial levels of hypertension or damage to target organs.

It has been established that the use of agents with complementary mechanisms of action—such as diuretics, calcium channel blockers, and renin-angiotensin-aldosterone system blockers—in combination for patients needing three medications is sensible and efficient.

Triple medication combinations have been demonstrated in recent research to be extremely safe, effective, and well-tolerated by patients. Lately, the FDA approved three distinct fixed-dose triple-drug combinations to treat hypertension: hydrochlorothiazide, amlodipine besylate, and olmesartan medoxomil. Comparing triple-combination regimens to dual combination regimens, a higher percentage of patients were able to achieve BP control, with noticeably lower BP levels.

AIM OF STUDY

The current study's goal is to create a stable triple medication combination consisting of telmisartan, amlodipine besylate, and hydrochlorothiazide that will be easy to use and effective for treating hypertension in patients who need multiple anti-hypertensive dosages.

MATERIALS AND METHODS

Materials

Deurali-Janata Pharmaceuticals Private Limited and Lomus Pharmaceuticals Private Limited, located in Kathmandu, Nepal, provided hydrochlorothiazide, telmisartan, and amlodipine besylate. The remaining ingredients, which included pregelatinized starch, Mcc ph 102, colloidal silicon dioxide, sodium starch glycolate, croscarmellose sodium, crospovidone, and magnesium stearate, were purchased straight from the vendor.

Drug and Excipients Interaction Study by FT-IR Analysis

Using FTIR, an infrared spectrum was obtained at AMRIT CAMPUS (ASCOL), Lainchaur, Kathmandu, to rule out the possibility that excipients would affect the drug's analysis.

Method of formulation of tablet

Each tablet was made using the Direct Compression method and contained about 200 mg of the triple medication combination. Following precise weighing, the ingredients were added to pregelatinized starch, MCC PH 102, SSG, crospovidone, and croscarmellose sodium.

Everything was well mixed and sieved through #30 meshes before being geometrically mixed for 15 minutes and then lubricated for 3 minutes with magnesium stearate by passing through #60 meshes. Using an eight-station rotary tablet machine with standard circular concave punches measuring 8 mm, the lubricated granules were compressed into tablets using the direct compression method.

Table 1: Formulation composition of triple drug combination tablets.

Material	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Telmisartan	20	20	20	20	20	20	20	20	20
Amlodipine	5	5	5	5	5	5	5	5	5
Hydrochlorothiazide de	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Pregelatinized starch	50	55	60	65	70	75	80	85	90
MCC PH 102	100.5	95.5	90.5	85.5	80.5	75.5	70.5	65.5	60.5
Sodium starch glycolate	7	7	7	-	-	-	-	-	-
Cross carmellose sodium	-	-	-	7	7	7	-	-	-
Cross povidone	-	-	-	-	-	-	7	7	7
Colloidal silicon dioxide	2	2	2	2	2	2	2	2	2
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Total	200	200	200	200	200	200	200	200	200

Evaluation parameters

a. Pre-compression parameters of blend

1. **Angle of repose:** The term "angle of repose" refers to the greatest angle that can be formed between a horizontal plane and a powder pile that is floating freely.[14] Utilizing the equation below angle of repose was ascertained,

$$\text{Angle of repose} = \tan^{-1}\left(\frac{h}{r}\right)$$

The parameters, in this case, are θ (angle of repose), h (powder pile), and r (powder cone radius).

2. **Bulk density:** The mass of a powder divided by the bulk volume is known as bulk density. Particle shape, particle size distribution, and particle adhesion tendency are the main factors influencing a powder's bulk density. A certain amount of precisely weighed bulk powder from every formula was transferred into a 25 ml measuring cylinder, shaken to break up any agglomerates, and the initial volume was noted.[15,16] The equation calculates it as,

$$\text{Bulk density} = \frac{\textit{Mass of the powder}}{\textit{bulk volume of the powder}}$$

3. **Tapped density:** A weighed quantity of tablet blend was transferred into a graduated cylinder. The volume occupied by the powder mixture was noted down. Then measuring cylinder was subjected to 100, 200 and 300 taps in a tap density apparatus.[15,16]

According to USP, tapped density was calculated by the formula as,

$$\text{Tapped density} = \frac{\textit{Mass of the powder}}{\textit{Tapped volume of the powder}}$$

4. **Carr's index:** Another name for Carr's index is compressibility. It is connected to cohesiveness, particle size, and relative flow rate indirectly. This method of predicting the characteristics of powder flow is easy to use, quick, and well- liked.[15,16]

$$\text{Car's index} = \frac{\textit{Tapped density} - \textit{Bulk density}}{\textit{Tapped density}} \text{ x } 100\%$$

5. **Hausner ratio:** The Hausner ratio, which is determined by dividing the bulk density by the tapped density, shows the powder's flow characteristics.[15,16]

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

b. Post compression parameters of tablets[16]

1. **General appearance:** The general appearance of the tablets from each formulation batch was observed. The general appearance parameters are shape, colour, presence or absence of odour and taste were evaluated visually

2. **Uniformity of Weight:** Each formulation's twenty tablets were weighed separately, and the average weight was determined. Subsequently, the weight of each tablet was compared to the weight of tablets on average.[15]

Table no. 2: % deviation for the average weight of the tablet according to IP.

S.No	Average weight of atablets	% deviation
1	80 mg or less	±10
2	80 to 250 mg	±7.5
3	above 250 mg	±5

3. **Thickness:** The uniformity of size and shape was assessed by measuring the thickness. We used a vernier calliper to measure the tablets' thickness.[16]

4. **Hardness:** Hardness is defined as the force required for breaking a tablet at a diametric compression test and it is termed as tablet crushing strength. It was determined by using a Monsanto hardness tester. Five tablets from each batch are taken for the hardness test and results are expressed in kg/cm^2.[16]

5. **Friability:** The tablets' Friability will be determined using the Rochi Friabilator. Ten tablets were weighed and placed in the rotating disc of the Roche friabilator, which was then operated for 25rpm for 4mins or 100 revolutions, dedusted and weighed again.[16]
   The percentage of friability was calculated based on weight loss after the test, using the formula mentioned below,

$$\% \text{ Friability} = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \text{ x } 100\%$$

6. **Disintegration time:** A disintegration apparatus is used specifically for this test. A six-tube basket with a metal sieve base is used by the apparatus. In every tube, a tablet is inserted and secured. A hanger is used to suspend the six-tube assembly, which has six tablets arranged inside. A fixed speed of 28–32 cycles per minute is used to move the six-tube assembly vertically in water or a buffer solution while it is hanging on the hanger. The duration taken by each tablet to dissolve is noted.[15,16]

Table 3: Disintegration time required for tablets.

Tablet	DT (as per IP)
Standard compressed tablet	15 min
Sugar-coated tablet	30 min
Film-coated tablet	30 min
Enteric-coated tablet	1-2 hour
Effervescent tablet	Less than 5 min

7. **Assay**

a. Assay of Telmisartan and Amlodipine[17]

Preparation of standard solution: 25mg of equivalent standard amlodipine besylate and 100mg of standard Telmisartan powder were made up to 200ml with methanol (in separate VF). Further, dilute 10ml of this solution to 50ml with methanol.

Preparation of test solution: Crushed 20 tablets and 25mg of equivalent amlodipine besylate and 100mg of Telmisartan are made up to 200ml with methanol. Further, dilute 10ml of this solution to 50ml with methanol.

Procedure: Measure the absorbance of standard preparation and test preparation into the UV-Vis spectrophotometer at wavelength **236nm** for Amlodipine and **296nm** for Telmisartan then calculate the ASSAY by comparing it with the standard as a reference.

$$\% \text{ Assay} = \frac{\textit{Absortance of Standard solution}}{\textit{Absorbance of test solution}} \text{ x } 100\%$$

b. Assay of hydrochlorothiazide: 20mg of equivalent hydrochlorothiazide is taken in a 100ml VF then 50ml of 0.1N NaOH is added to it and was shaken for 20 min. then the solution is diluted up to the mark. Further, dilute 5ml of this solution to 100ml with solvent and again dilute 5ml of this solution to 100ml with solvent. Test preparation into the UV-Vis spectrophotometer, and record the absorbance at wavelength 273nm.[17]

8. In-vitro dissolution studies[17,18]

a. In vitro dissolution studies of telmisartan: In vitro dissolution studies for all tablet formulations were performed by using USP dissolution test apparatus (Apparatus II, Paddle type, 37ºC) at 75 rpm for 30 minutes. The dissolution medium was 900 ml of freshly prepared pH 6.8 phosphate buffer solution. At different time intervals 5 ml of the sample was taken and analyzed for drug content at 296 nm by using UV-Vis spectrophotometer. A 5 ml fresh dissolution medium was added to make the volume after each sample withdrawal.

b. In vitro dissolution studies of amlodipine: In vitro dissolution studies for all tablet formulations were performed by using USP dissolution test apparatus (Apparatus II, Paddle type, 37ºC) at 75 rpm for 30 minutes. The dissolution medium was used 900 ml of freshly prepared 0.1N HCl solution. At different time intervals 5 ml of the sample was taken and analyzed for drug content at 236 nm by using UV-Vis spectrophotometer. A 5 ml fresh dissolution medium was added to make the volume after each sample withdrawal.

c. In vitro dissolution studies of hydrochlorothiazide: In vitro dissolution studies for all tablet formulations were performed by using USP dissolution test apparatus (Apparatus II,

Paddle type, 37ºC) at 100 rpm for 30 minutes. 900 ml of recently made 0.1N HCl solution was used as the dissolution media. A 5ml sample was obtained at various times, and its drug concentration was measured using a UV-Vis spectrophotometer at 273 nm. Following each 5ml sample removal, 5 ml of new dissolution media was added to maintain the volume in the dissolution apparatus.

RESULTS AND DISCUSSION

UV Spectrophotometer performed analytical method. Standard curves of Telmisartan, Amlodipine and Hydrochlorothiazide in methanol were analyzed in the range of 2-30µg/ml at wavelength 296nm, 236nm and 276nm respectively. The selected range of all drugs was found to be linear. Standard curve data are given in Table 5 to Table 7 below and the Standard curve for all drugs in Figure 1 to Figure 3.

The FT-IR spectra of the pure drugs and their combination with excipients are shown in the Figure no. 4 to Figure no. 6. The spectra of the pure drugs Telmisartan, Amlodipine besylate, Hydrochlorothiazide showed sharp characteristic peaks at 2888.6cm^{-1}, 1694.77cm^{-1}, 1128.69cm^{-1}, 758.34cm^{-1}, 740.61cm^{-1} (Telmisartan), 3298.91cm^{-1}, 1697.51cm^{-1}, 2991.9cm^{-1}, 1672.96cm^{-1}, 1091.13cm^{-1} (Amlodipine), 3360.42cm^{-1}, 1598.67cm^{-1}, 3165.41cm^{-1}, 1598.67cm^{-1}, 1149.09cm^{-1} (Hydrochlorothiazide). The spectra of the physical mixture containing the medication and excipients also showed these peaks. This confirms that the drug and excipients did not interact.

The pre-compression parameters of the blend were evaluated. The results of pre-compression evaluation parameters are shown in Table 12. All these results indicate that the powder blend of all the formulations possessed satisfactory flow properties. In all subsequent formulations (F-1 to F-9) the diluent ratio with MCC PH 102 and pregelatinized starch was changed to improve the flow property and also the disintegration time.

The results of post-compression parameters weight variation, thickness, hardness, and friability of all the prepared tablets are shown in Table 13. These results show that all the prepared tablet formulations agree with the requirements of IP.

Results of all the parameters revealed that prepared Tablets had sufficient mechanical strength. Post-compression parameters like weight variation and friability were in the range of Indian pharmacopoeia. The weight of all the nine batches of Tablets ranges from 197 to

202mg. It revealed that the method selected for the preparation of the tablet is suitable and reproducible.

The disintegration time of all nine batches of tablets ranges from 5 minutes 31 seconds to 11 minutes 55 seconds. In vitro dissolution studies of tablets were conducted for 30 minutes.

Samples were analysed by UV method. The comparative dissolution profile of the formulations is presented in Figure 02. The dissolution profile of the tablet revealed that all three drugs were released up to 90% within 30 minutes.

The formulation F-6 showed acceptable results and complied with the internal specifications of hardness, friability, DT, and In vitro drug release.

The formulation F-6 containing croscarmellose at its optimum concentration of 3.5% is compared with 3.5% SSG and 3.5% crospovidone and it was found that croscarmellose was a better disintegrant than the other two, as disintegration time and dissolution properties are better with the croscarmellose. Compared to all formulations, F-6 showed enhanced disintegration power and drug release rate and possessed good flow properties and hardness.

Table 4: Identification of raw material.

	Telmisartan	Amlodipine	Hydrochlorothiazide
Description	white to off-white crystalline powder	White to off white crystalline powder	White to almost White crystalline powder
Solubility	sparingly soluble in water, (soluble in strong acid, soluble in strong base), Soluble in methanol.	Slightly soluble in water, freely soluble in methanol; Sparingly Soluble in anhydrous ethanol.	Freely soluble in water, soluble in methanol, sparingly soluble in methanol.
Melting point	261-263^{0}C	195 – 204 ^{0}C	274-275 ^{0}C
Loss On Drying	0.5%	0.5%	1.0%
λ max	296 nm	236 nm	273 nm (as per IP)

Table 5: Standard curve data of telmisartan.

Concentration (µg/ml)	Absorbance
0	0
2	0.11
4	0.21
6	0.31
8	0.42
10	0.52
15	0.8

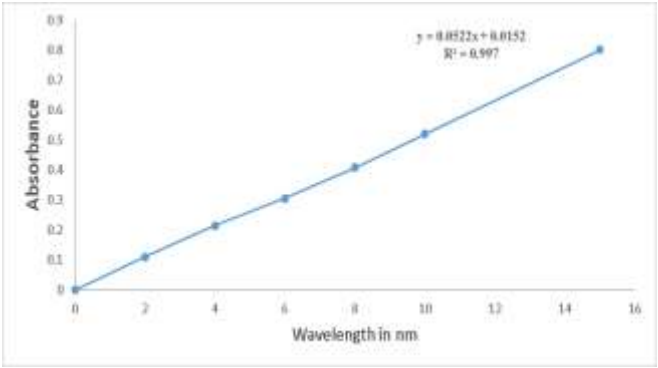

Figure 1: Standard curve of telmisartan.

Table 6: Standard curve data of amlodipine besylate.

Concentration (µg/ml)	Absorbance
10	0.324
20	0.646
30	0.975
40	1.231
50	1.487

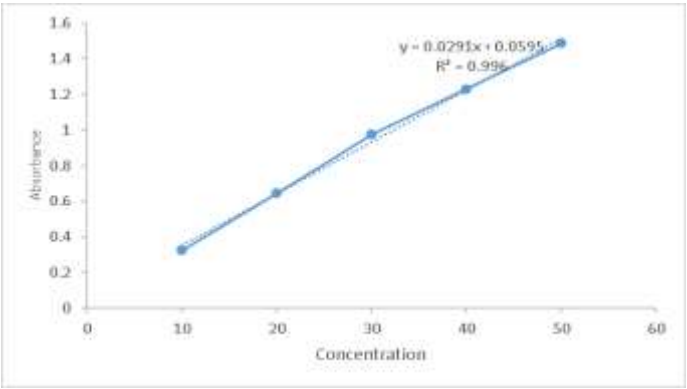

Figure 2: Standard curve of amlodipine besylate.

Table 7: Standard curve data of hydrochlorothiazide.

Concentration (µg/ml)	Absorbance
0	0
10	0.156
20	0.211
30	0.362
40	0.487
50	0.639

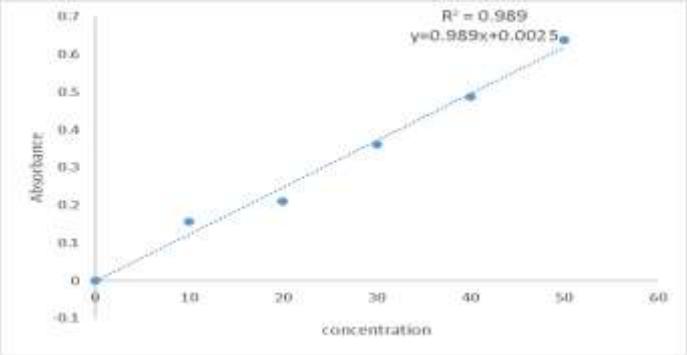

Figure 3: Standard curve of hydrochlorothiazide.

Analytical method validation

a. **Test for Precision of the method of analysis for Telmisartan and Amlodipine:** In the intraday variation (repeatability) study, 6 different solutions of the same concentration 10ppm were analyzed and absorbance was noted.

Note: The lower the value of %RSD, the higher the precision.

Table 8: Precision of the method of analysis for telmisartan.

Absorbance / Concentration	Abs-1	Abs-2	Abs-3	Average	SD	%RSD (<2%)
10ppm	0.521	0.520	0.521	0.520	0.00057	0.11
10ppm	0.520	0.522	0.520	0.520	0.00081	0.15
10ppm	0.523	0.522	0.520	0.521	0.00121	0.23
10ppm	0.521	0.520	0.522	0.521	0.00102	0.19
10ppm	0.522	0.521	0.523	0.522	0.00075	0.14
10ppm	0.521	0.521	0.522	0.521	0.00054	0.10

Table 9: Test for precision of the method of analysis for amlodipine.

Absorbance / Concentration	Abs-1	Abs-2	Abs-3	Average	SD	%RSD (<2%)
10ppm	0.323	0.323	0.325	0.323	0.000115	0.356
10ppm	0.324	0.323	0.324	0.323	0.000816	0.252
10ppm	0.324	0.322	0.321	0.322	0.00126	0.392
10ppm	0.321	0.321	0.323	0.322	0.00126	0.393
10ppm	0.324	0.323	0.322	0.322	0.00121	0.374
10ppm	0.323	0.324	0.324	0.323	0.00075	0.232

b. Test for Accuracy of the method of analysis for Telmisartan and Amlodipine: Solutions were prepared in triplicate form at levels 80%, 100% and 120% of the test concentration using Telmisartan and amlodipine working standards as per method. The absorbance of each solution in its triplicates was measured. The % recovery was calculated. SD and %RSD were calculated.

The limit of %RSD is less than 2% (<2%).

Table 10: Accuracy of the method of analysis for telmisartan.

Level	No. of Preparations	Volume of solutions added and made up to 25 ml		% recovery	Statistical result		
		Of Sample	Of Standard		Mean of % recovery	SD	%RSD (limit <2%)
80%	S1	1.5	1.2	98.89	99.12	0.501	0.505
	S2	1.5	1.2	99.12			
	S3	1.5	1.2	99.35			
100%	S4	1.5	1.5	100.66	100.66	0.812	0.806
	S5	1.5	1.5	100.16			
	S6	1.5	1.5	101.18			
120%	S7	1.5	1.8	101.09	100.90	0.840	0.832
	S8	1.5	1.8	101.17			
	S9	1.5	1.8	100.37			

Table 11: Accuracy of the method of analysis for amlodipine.

Level	No. of Preparations	Volume of solution added and make up to 25ml		% recovery	Statistical result		
		Of Sample	Of Standard		Mean of % recovery	SD	%RSD (limit <2%)
80%	S1	1.5	1.2	100.06	100.08	0.791	0.790
	S2	1.5	1.2	100.12			
	S3	1.5	1.2	101.09			
100%	S4	1.5	1.5	99.4	99.75	0.504	0.505
	S5	1.5	1.5	99.69			
	S6	1.5	1.5	100.18			
120%	S7	1.5	1.8	101.09	101.15	0.813	0.803
	S8	1.5	1.8	101.15			
	S9	1.5	1.8	101.21			

Figure no. 4: FTIR Spectra of Telmisartan.

Figure no. 5: FTIR Spectra of amlodipine besylate.

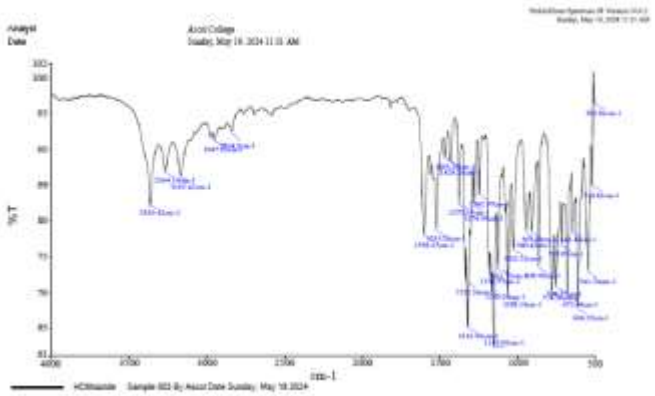

Figure no. 6: FTIR Spectra of Hydrochlorothiazide.

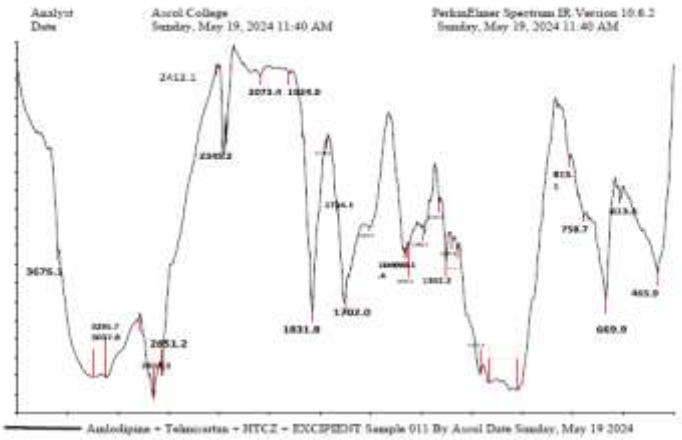

Figure no. 7: FTIR Spectra of Three Drugs and Excipients.

Table 12: Pre-compressional evaluation data for powder blend.

Formulations	Average Weight (N=20)	weight variation	Thickness (mm) (N=5)	Hardness (kg/cm²) (N=5)	Friability (%)	DT
F1	202.561mg	202 ± 4.16	3.01± 0.045	7.5 kg/cm²	0.91%	8m 45s
F2	198.408mg	198 ±4.26	3.05± 0.053	6.0 kg/cm²	0.48%	7m22s
F3	198.714mg	198 ± 3.09	3.15± 0.052	5.5 kg/cm²	0.37%	8m 55s
F4	200.364mg	200 ± 5.01	3.09± 0.030	5.0 kg/cm²	0.22%	8m 30s
F5	201.210mg	201 ± 4.22	3.10± 0.044	5.5 kg/cm²	0.17%	11m 55s
F6	201.581mg	201 ± 4.20	2.98± 0.033	6.0 kg/cm²	0.22%	5m 31s
F7	197.694mg	197 ± 4.56	3.03± 0.044	5.0 kg/cm²	0.13%	10m 45s
F8	199.719mg	199 ± 3.69	3.06± 0.045	4.7 kg/cm²	0.19%	11m 20s
F9	198.269mg	198 ± 4.02	3.11± 0.043	5.5 kg/cm²	0.51%	9m33s

Table 13: Post-compressional evaluation data of tablets.

Formulations	Average Weight (N=20)	weight variation	Thickness (mm) (N=5)	Hardness (kg/cm²) (N=5)	Friability (%)	DT
F1	202.561mg	202 ± 4.16	3.01± 0.045	7.5 kg/cm²	0.91%	8m 45s
F2	198.408mg	198 ±4.26	3.05± 0.053	6.0 kg/cm²	0.48%	7m22s
F3	198.714mg	198 ± 3.09	3.15± 0.052	5.5 kg/cm²	0.37%	8m 55s
F4	200.364mg	200 ± 5.01	3.09± 0.030	5.0 kg/cm²	0.22%	8m 30s
F5	201.210mg	201 ± 4.22	3.10± 0.044	5.5 kg/cm²	0.17%	11m 55s
F6	201.581mg	201 ± 4.20	2.98± 0.033	6.0 kg/cm²	0.22%	5m 31s
F7	197.694mg	197 ± 4.56	3.03± 0.044	5.0 kg/cm²	0.13%	10m 45s
F8	199.719mg	199 ± 3.69	3.06± 0.045	4.7 kg/cm²	0.19%	11m 20s
F9	198.269mg	198 ± 4.02	3.11± 0.043	5.5 kg/cm²	0.51%	9m33s

Table 14: Drug content- Telmisartan, Amlodipine besylate & Hydrochlorothiazide.

S.no.	Formulations	Telmisartan (%)	Amlodipine besylate (%)	Hydrochlorothiazide (%)
1	F-1	94.34%	99.56%	98.23%
2	F-2	98.81%	98.23%	98.24%
3	F-3	86.23%	89.12%	97.17%
4	F-4	95.87%	92.12%	87.47%
5	F-5	91.12%	87.34%	88.19%
6	F-6	102.86%	98.22%	101.76%
7	F-7	98.95%	101.78%	89.80%
8	F-8	88.02%	98.54%	98.98%
9	F-9	96.68%	89.55%	93.68%

Table 15: % of In-vitro Dissolution profile of Telmisartan.

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	23.65	28.21	27.89	29.71	28.09	26.02	25.66	27.09	29.26
10	32.36	37.36	35.89	41.38	36.03	33.29	31.58	36.91	40.01
15	41.51	46.65	44.65	50.56	44.26	41.90	43.07	43.69	51.39
20	51.52	54.40	56.68	58.54	56.10	50.74	56.09	52.57	65.66
25	69.04	66.34	63.36	69.06	65.40	62.36	68.61	65.59	71.49
30	81.09	85.22	87.12	86.11	88.15	93.23	84.28	91.07	90.08

Table 16: % of In-vitro dissolution profile of amlodipine besylate.

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	25.71	29.91	26.67	30.02	29.15	30.99	26.89	29.08	30.69
10	34.13	41.19	38.75	39.31	36.44	39.64	34.79	38.96	37.28
15	42.46	49.23	48.55	48.66	43.59	48.11	42.82	46.78	45.06
20	49.46	57.66	56.41	60.98	56.28	56.09	56.96	52.89	58.49
25	62.91	67.59	61.28	69.55	63.50	64.68	64.08	60.09	66.90
30	70.39	84.18	87.91	88.65	89.66	91.01	86.69	89.59	83.59

Table 17: % of In-vitro dissolution profile of hydrochlorothiazide.

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	26.71	29.22	27.85	25.07	27.28	26.98	24.64	26.05	27.55
10	33.75	37.09	35.77	34.91	36.66	33.69	30.56	34.66	38.65
15	46.13	44.37	42.09	45.33	43.04	40.50	39.34	42.25	46.26
20	52.92	51.26	50.07	53.01	49.09	50.06	47.41	51.53	52.69
25	60.16	59.25	58.69	60.37	58.11	64.55	56.06	59.16	60.16
30	68.12	63.89	65.25	69.50	70.66	**79.71**	73.25	64.36	68.67

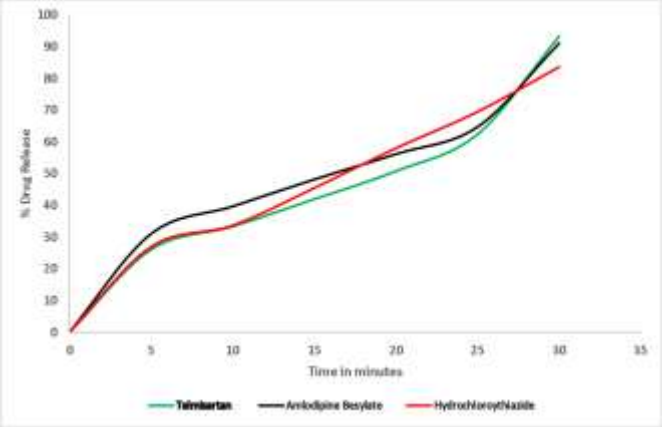

Figure no. 8: In vitro release profile of triple drug combination tablets in F6.

CONCLUSION

The present research was carried out to develop a novel triple-drug combination of amlodipine besylate, Telmisartan and hydrochlorothiazide. A combination of Amlodipine Besylate, Telmisartan and hydrochlorothiazide is indicated for the successful treatment of hypertension.

Tablets were formulated by direct compression methods using Telmisartan, amlodipine besylate, hydrochlorothiazide and various excipients which include pregelatinized starch, MCC PH102, croscarmellose sodium, sodium starch glycolate, crospovidone, colloidal silicon dioxide and magnesium stearate.

The optimized formulation is found by using various evaluation properties. Formulation characteristics such as content drug uniformity, hardness, and % friability was evaluated and found to be satisfactory.

The optimized formulation (F-6) shows enhanced disintegration power and drug release rate. Hence, it is finally concluded that triple-drug combination therapy for hypertension can be considered one of the promising pharmaceutical formulations.

RECOMMENDATION AND LIMITATION

The fixed-dose combination of antihypertensive drugs is a promising future for the effective treatment of hypertension. Real-time and accelerated stability testing can be carried out. HPLC analysis could be performed. A real-time and accelerated stability study can also be done according to ICH Guidelines to know about the stability of tablets over time.

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