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Research Article

Pharmacokinetic of Telmisartan and Cilnidipine Tablet

Pharmacokinetic Evaluation of Telmisartan and Cilnidipine Bilayer Tablet in A Rabbit Model

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Abstract: Hypertension is a chronic medical condition affecting a significant proportion of the global population. It is a major risk factor for cardiovascular diseases, stroke, and kidney failure. Telmisartan and cilnidipine combination are commonly used in managing hypertension due to their complementary mechanism of action. Therefore, a bilayer tablet design that enhances the pharmacokinetic profile of cilnidipine as a sustained-release drug while telmisartan act as an immediate-release drug may provide a better therapeutic option for hypertension management. We aim to evaluate the pharmacokinetic parameters of the bilayer tablet of Telmisartan and Cilnidipine. Our objective is to observe the bioavailability of the bilayer tablet in rabbit plasma. The formulation aims to achieve an immediate release effect for Telmisartan and a sustained release effect for Cilnidipine. The solubility and bioavailability of Telmisartan were enhanced by complexation with beta-cyclodextrin. To achieve our aim, we observe the drug concentration in rabbit plasma. Telmisartan is an angiotensin receptor blocker, while Cilnidipine is a calcium channel blocker. The pharmacokinetics of the drugs were evaluated in New Zealand rabbits following oral administration. Systemic drug bioavailability was assessed, and an HPLC method was developed to estimate Telmisartan and Cilnidipine's plasma concentration simultaneously. A Gemini C-18 column (250 mm X 4.6 mm X 5 microns) Phenomenex was used for peak separation. The mobile phase consisted of acetonitrile with phosphate buffer pH 3.5 v/v, with a flow rate of 1.5 ml per minute. The calibration curve analysis indicated a correlation coefficient of 0.9996 and 0.9997 for Telmisartan and Cilnidipine, respectively. The pharmacokinetics of the optimized batch, including Cmax, Tmax, and AUC values, were compared to those of the pure drug. Drug concentration was detected using a DAD detector with an excitation wavelength of 241nm. No interaction was observed between the drugs and excipients. The in-vivo study of the formulation showed higher bioavailability, indicating that the developed bilayer tablet formulation could be an effective means of delivering Telmisartan and Cilnidipine.

Keywords: Pharmacokinetics, HPLC-UV, Telmisartan, Cilnidipine, Rabbit plasma.

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1. INTRODUCTION

Hypertension indicates high blood pressure. The systolic blood pressure shows a reading of heart contract/beats, whereas diastolic blood pressure indicates blood pressure when the heart rests between beats. Systolic blood pressure is the pressure in the arteries when the heart contracts and pumps blood into the circulatory system. It is the top number in a blood pressure reading measured in millimeters of mercury. On the other hand, diastolic blood pressure is the pressure in the arteries when the heart is resting and filling up with blood. It is the bottom number in a blood pressure reading measured in mmHg. As per WHO report, every year, 17 million people die of cardiovascular disease, heart attack, and stroke [1]. The categories of antihypertensive drugs include Diuretics, Renin-angiotensin system inhibitors, sympathetic inhibitors, Calcium channel blockers, and vasodilators [2]. Telmisartan is an antihypertensive drug with angiotensin II receptor antagonist activity [3]. It is a (Biopharmaceutical classification system) BCS class II drug of low solubility and high permeability, and it can be freely soluble in highly alkalized solution [4]. Telmisartan inhibits binding angiotensin II AT_1 Receptor [5]. It shows a good effect on blood pressure [6-7]. Telmisartan shows oral absorption at 50%. The half-life of Telmisartan is 24 hrs. The telmisartan 160mg dose was given to young males once daily for 7 days in a previous pharmacokinetics study. In that, no clinical accumulation was observed [8]. They improve the solubility of Telmisartan using spray drying and freeze-drying[9]. Cyclodextrin is a good stabilizer. In the food manufacturing process, it is used as a food additive[18]. As per literature, numerous HPLC methods have been reported to determine Telmisartan pharmacokinetic study [10-12]. Cilnidipine is also an antihypertensive drug with calcium channel blocker activity. It blocks the L type of calcium channel of the blood vessel. Cilnidipine also acts on the N-type calcium channel at the end of the sympathetic nerve, thereby inhibiting norepinephrine emission, which causes a decrease in blood pressure [13]. Cilnidipine shows low oral bioavailability and dissolution rate. To improve the solubility of Cilnidipine using in the form of Hydroxypropyl Beta-cyclodextrin [14]. The maximum absorption concentration in blood is seen after 2 hrs. Cilnidipine shows a higher distribution in the liver and kidney. The bioavailability of Cilnidipine is 13% in systemic circulation. According to the literature survey, previous animal studies on diet-induced obese(DIO) mice checked glucose metabolism and adipocytokine effect. DIO mice give Cilnidipine to observe insulin tolerance, and adiponectin level has been increased[15]. Antihypertensive drugs affected facets of metabolic disorder, not only hypertension [16]. According to the literature survey, Cilnidipine treats hypertension and diabetes mellitus patients based on glucose metabolism[17]. The combination of Telmisartan and Cilnidipine was used to control blood pressure and decrease the risk of heart attack and stroke. Greater compliance, synergy, increased efficacy, and decreased adverse effects and costs are all benefits of fixed combination treatments. Telmisartan gives an immediate release effect, and Cilnidipine gives a sustained release effect in systemic circulation. The bioavailability enhancement was confirmed in the pharmacokinetic study. According to the literature survey, the mobile phase of phosphate buffer pH4.8: acetonitrile was used. It gives better peak separation of felodipine. The retention time was observed below 3min[23]. The HPLC method was standardized using different ratios of mobile phase and columns. The chemical structure of Telmisartan and cilnidipine is shown in (fig 1 and Fig 2). The study aimed to observe the bioavailability of the bilayer tablet in rabbit plasma and compare the pharmacokinetics of the optimized batch of the bilayer tablet with those of the pure drug. To develop an HPLC method for simultaneous estimation of the plasma concentration of Telmisartan and cilnidipine and assess the solubility and bioavailability of Telmisartan by complexation with beta-cyclodextrin. To observe the drug concentration of the bilayer tablet in rabbit plasma.

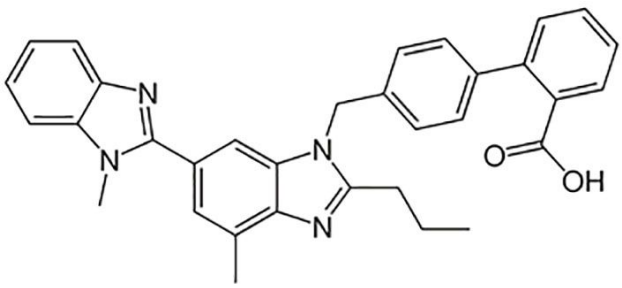

Fig 1: Structure of Telmisartan

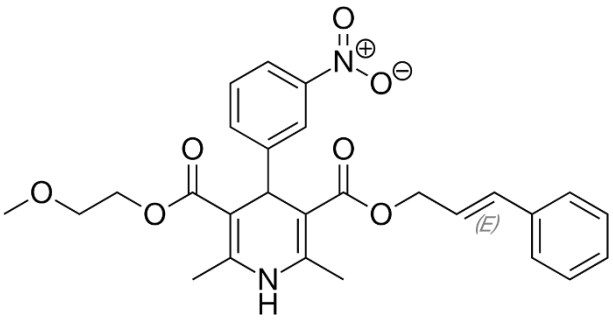

Fig 2: Structure of Cilnidipine

2. EXPERIMENTAL

2.1. Materials and Reagent

Telmisartan (purity 99.9%) was purchased from Manvicare Trade(Ahmedabad) and co., whereas Cilnidipine (purity 98%) was purchased from Dhamtec Pharma and a consultant(MIDC Navi Mumbai). The HPLC grade solvent methanol, water, and acetonitrile were purchased from the Vendant supplier (Navi Mumbai) for HPLC analysis.

2.2. Instrumentation

The Agilent technology 1290 infinity HPLC with binary pump and autosampler was used. The diode array detector (DAD) detector was used to measure concentration. The flow rate of the mobile phase, 1.5 ml/min, was chosen for a particular retention time. The solvent system acetonitrile: phosphate buffer 65:35 v/v as mobile phase was used. The 241nm wavelength was selected for better peak separation. The HPLC data was analyzed by open lab EZchrome software. The P.K. solver was used to analyze various pharmacokinetics parameters.

2.3. Safety analysis

The animal experiment was performed in the Kusum Life science laboratory. Before the start of the animal study and after the end of the study, all Rabbits were observed for their movement, body temperature, and pulse rate. The rectal temperature was checked using a digital thermometer. The pulse rate was checked by placing a finger in the groin area of the rabbit.

2.4. Linearity[21]

For Telmisartan and cilnidipine, solutions of five different concentrations varying from 1-15 micrograms/ml and 50-800 ng/ml, respectively, were made to test the linearity of the developed method. In addition, peak areas on the chromatograms were recorded, and a calibration curve plotting peak area against drug concentration was created.

2.5. Chromatographic conditions[10]

For the peak separation of Telmisartan and Cilnidipine Gemini C-18 column (250 mm X 4.6.mm X 5 microns), Phenomenex was used. As a mobile phase acetonitrile-phosphate buffer, the solvent adjusted the pH to 3.5 with acetic acid. The acetonitrile to phosphate buffer in a ratio of 65: 35 v/v was used for better sensitivity. The flow rate of the mobile phase was 1.5 ml/ min.

2.6. Preparation of Standard solutions[21]

Telmisartan and Cilnidipine stock solutions were prepared by dissolving 5mg of each compound in 50 ml of methanol (100 µg/ml concentration). Telmisartan and Cilnidipine have a concentration range of 1µg/ml to 15 µg /ml for Telmisartan and 50 to 800 ng/ml for Cilnidipine prepared. (Sentence may be rearranged as "Further dilutions were prepared in concentration range of1µg/ml to 15 µg /ml for Telmisartan and 50 to 800 ng/ml for Cilnidipine") The calibration curve shows the correlation and linearity of concentration versus the peak area. The R^2 value and equation for the line were obtained.

2.7. Sample extraction[4]

The 150 µl plasma sample was mixed with 600 µl of methanol, vortexed for 5 min, and then incubated at room temperature for 10 min. Then it was centrifuged (make and model of the centrifuge may be added) at 14000 rpm for 20 min. The supernatant was collected. The 400µl sample was taken in an HPLC autosampler vial.

2.8. Recovery[11]

The telmisartan recovery at 1 µg/ml, 5 µg/ml, and 15 µg/ml were studied, and the recovery percentage was found to be 72.43%, 98.90%, and 99.43%. For Cilnidipine, recovery was studied with plasma samples spiked with 50ng, 100ng, and 800ng cilnidipine, and the recovery percentage was 99.67 %, 86.49%, and 98.09%.

2.9. Statistical analysis[20]

Statistically analyzed C_{max}, T_{max}, the area under the curve (AUC), and the concentration of Telmisartan and cilnidipine. In addition, plasma concentration data were analyzed using non-compartmental analysis. P.K. solver excel was used.

2.10. Pharmacokinetics study[19,25]

The healthy New Zealand male rabbits weighing 2.5 to 3 kg were purchased from the animal house, Kusum Laboratory Vasmat. The pharmacokinetic study was carried out after obtaining the approval of the animal ethics committee according to the protocol number KLS/IAEC -2022-1/031. Before oral administration, rabbits fasted overnight. Then, oral administration was given to each rabbit. The dosage for both medications was equal to 20 mg of Telmisartan and 10 mg of Cilnidipine in humans. The human dose was converted to the rabbit dose. The rabbits were divided into four groups, with four rabbits in each group. Group I was given a telmisartan dose. Group II was given Cilnidipine. Group III was given a formulation tablet of Telmisartan and Cilnidipine. Group IV was kept as the control group. After drug administration, the blood samples were collected from marginal ear veins at different time points as 0 min, 5min,10min,15min,20min, 30 min, 1 hr, 3 hr, 4 hr, 8 hr, 20 hr, and 24 hr. In addition, a blood sample was collected anticoagulant tube containing EDTA. The centrifugation was done at 3000rpm for 15 min. The plasma was collected in a clean tube and stored at -20°C till analysis.

3. RESULTS

Safety analysis

All the rabbit moments were normal. Before and after the study, the body temperature of all animals was in the normal range of 38^0C -39^0C. The pulse rate of all animals was 190-230 from the start to the end of the study.

3.1. Method optimization

For HPLC analysis, two HPLC columns were used for better peak separation of Telmisartan and Cilnidipine. The C8 column provided a shorter run time, and peak separation was not distinct. In contrast, the C18 column also provided good separation with reasonable run time as we used different mobile phases. Methanol: acetonitrile 30:70 v/v, methanol:

water (80:20 v/v). Acetonitrile: Phosphate butter (65:35 v/v). Acetonitrile: Phosphate buffer provided better separation efficiency.

3.2. *Statistical analysis*

The calculations for Cmax, Tmax, t1/2, the area under the curve (AUC), Telmisartan concentration, and cilnidipine were done. These are pharmacokinetics parameters.

3.3. *HPLC system*

The Gemini C-18 column (250 mm X 4.6 mm X 5 micron) Phenomenex was used for the HPLC system. It provides good separation efficiency at a particular run time. The solvent system acetonitrile: phosphate buffer 65:35 v/v as mobile phase was used. The pH was adjusted to 3.5 using acetic acid and measured with a pH meter. The HPLC system comprises a diode array detector (DAD) and an autosampler injector. The flow rate of the mobile phase, 1.5 ml/min, was chosen for a particular retention time. The acetonitrile concentration was chosen below 70% to avoid precipitation of phosphate buffer. The detector's wavelength was selected, and both drugs were scanned separately using a U.V. spectrophotometer. Both spectra were analyzed and showed different wavelengths, 240 and 297nm. The overlay of both spectra was done, and a better peak shape was selected at 241 nm. The column temperature range was kept at 25 to 35 C. Telmisartan and Cilnidipine's internal standard was selected based on recovery, compatibility, and sensitivity. Telmisartan and Cilnidipine showed good recovery and peak separation. Carrying out a plasma recovery study of both drugs showed better recovery. For HPLC, chromatograms were observed analysis after oral administration of Telmisartan and Cilnidipine. The pharmacokinetics parameters of Cmax, Tmax, and AUC were estimated by the non-compartmental analysis using pk solver software (Table 1). Telmisartan and Cilnidipine's average plasma concentration-time curve was shown in (Fig 5,7). Telmisartan and Cilnidipine's percent cumulative drug release was shown in (Fig 4,6). No drug interaction was observed in the drug combination. Telmisartan- beta-cyclodextrin complex has improved the bioavailability of Telmisartan; it gives rapid onset of action.

Table 1: Pharmacokinetic parameters after administration of Telmisartan and cilnidipin

Parameter	Telmisartan	Cilnidipine
Cmax(ng/mL)	119.866	219.182
tmax(h)	3	1
AUC0-t(ng*h/mL)	1337.16	4043.12
AUC0-t∞(ng*h/mL)	2035.89	2510.71
Half-life (hr)	24	2

3.4. *Standerd Graph of Telmisartan and Cilnidipine*

The retention time of Telmisartan was found to be 2.8, and cilnidipine was 5.8 have been detected.

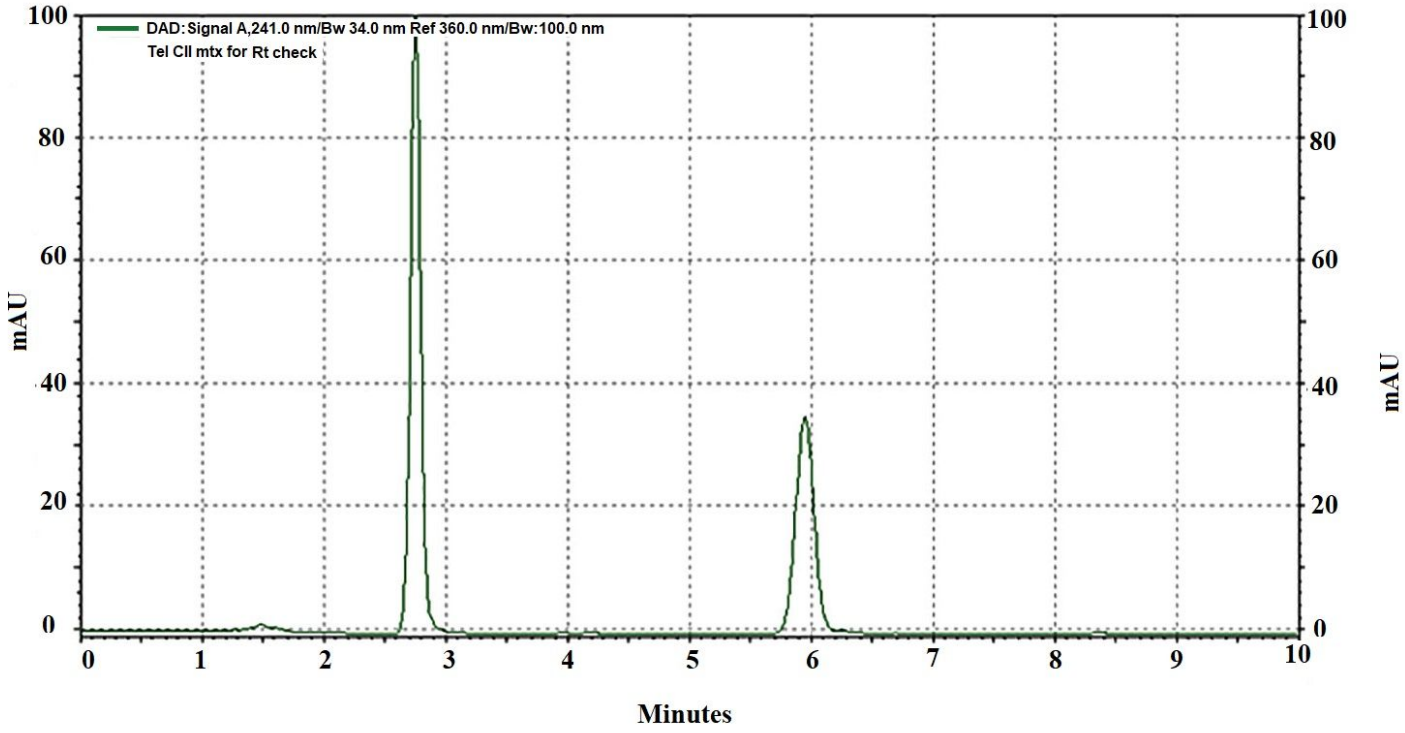

Fig 3: Chromatogram of Telmisartan and Cilnidipine in combination

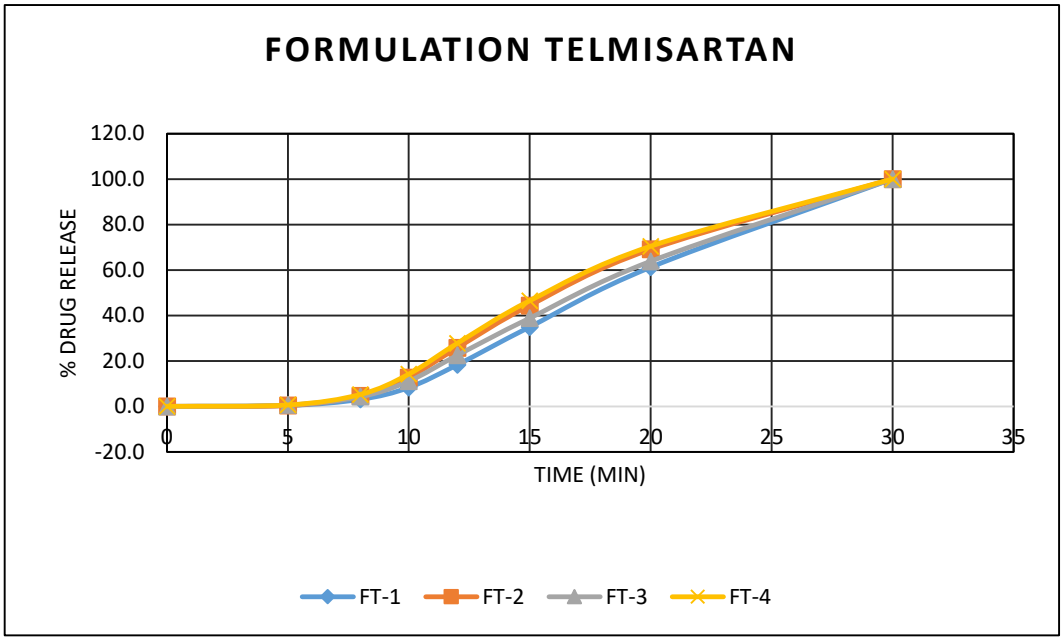

Fig 4: % cumulative of telmiartan (Immediate release)

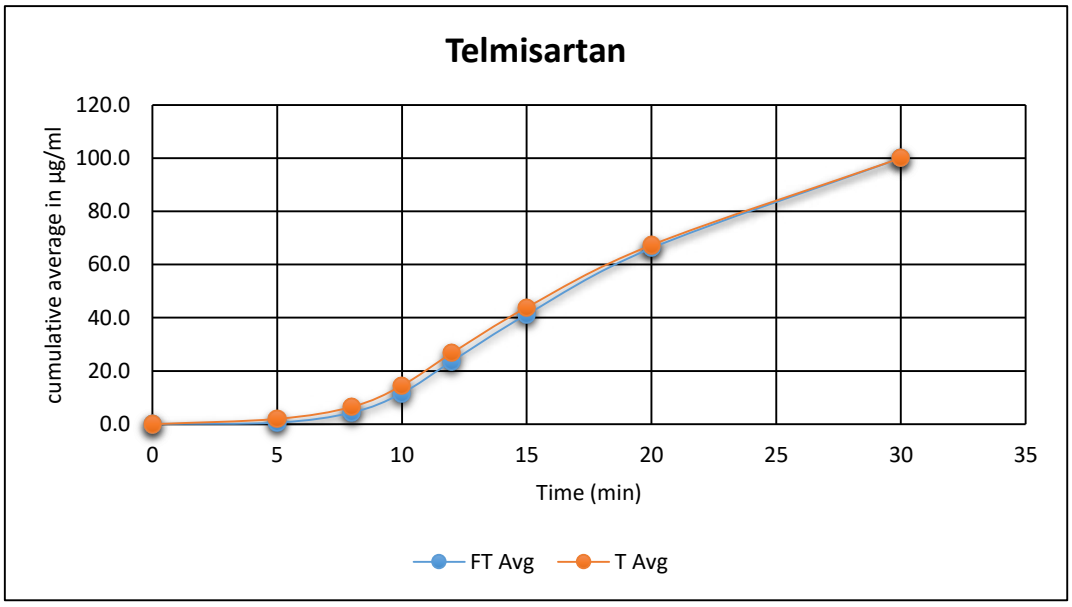

Fig 5: Cumulative average plasma concentration-time profiles of Telmisartan after oral Administrations (FT- Telmisartan)

Telmisartan shows the cumulative average plasma concentration in µg/ml. Telmisartan shows a good % drug release within 15min. The telmisartan formulation group demonstrated good overall drug release (Fig. 4), and a time-dependent cumulative average plasma concentration profile was displayed (Fig 5).

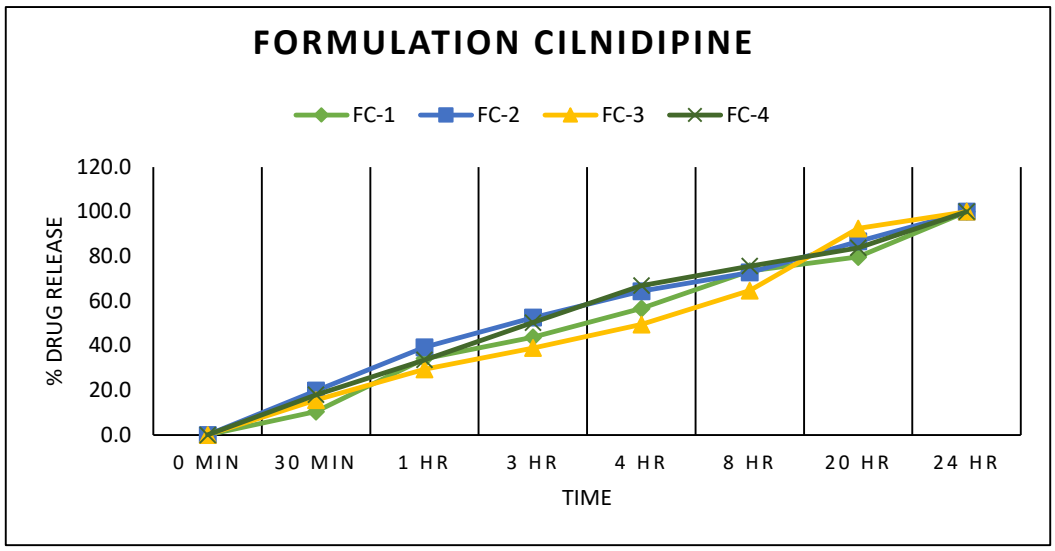

Fig 6: % cumulative of Sustained release

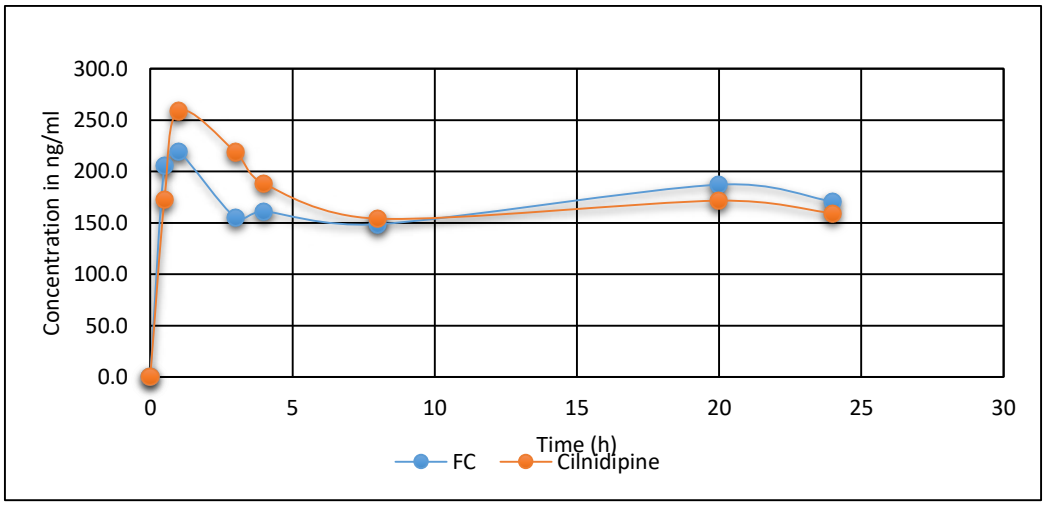

Fig 7: Cumulative average plasma concentration-time profiles of Cilnidipine and Formulation(F.C.) after oral administrations (FC- Formulation tablet)

The cilnidipine shows the drug release up to 24hr. The cumulative average plasma concentration was observed in ng/ml. (Figure 6) The cilnidipine depicts the cumulative drug release percentage and the time-profiled cumulative average plasma concentration (Fig 7).

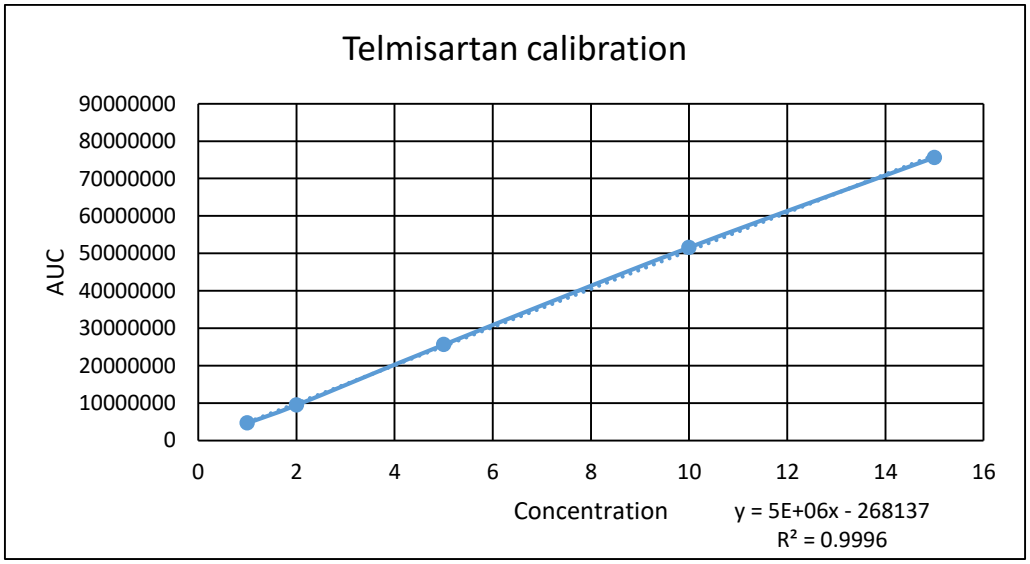

Fig 8: Calibration curve of Telmisartan

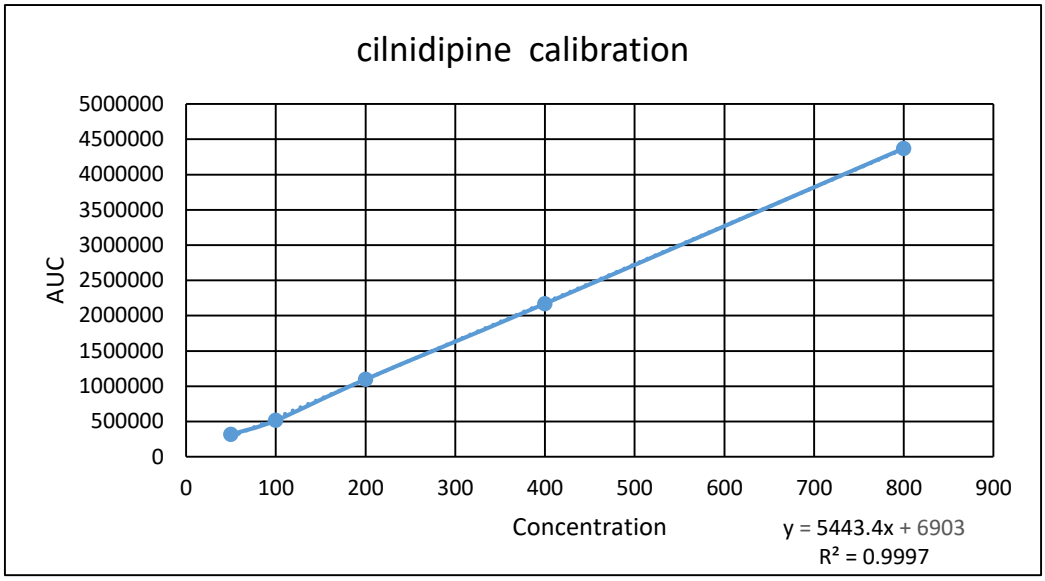

Fig 9: Calibration curve of cilnidipine

The calibration curve of the telmisartan correlation coefficient of R^2 was observed at 0.9996 and cilnidipine at 0.9997, shown in Fig (8,9)

4. CONCLUSION

In this pharmacokinetics study, the HPLC method was used to estimate Telmisartan and Cilnidipine in rabbit plasma simultaneously. The combination of Telmisartan and cilnidipine can provide an effective treatment option for hypertension due to their complementary mechanism of action. The combination bilayer tablet was formulated using HPMC K100m as a polymer for sustained release. The optimized formulation pharmacokinetics study was carried out using rabbit plasma. The HPLC method developed for simultaneous estimation of the plasma concentration of both drugs showed good correlation coefficients of 0.9996 and 0.9997 for Telmisartan and cilnidipine, respectively. The Gemini C-18 column with a DAD detector was investigated to determine Cilnidipine and accurate telmisartan concentration in plasma. The statistically analyzed Cmax. Tmax and AUC values of drug plasma. Developing a bilayer tablet formulation with higher bioavailability than the pure drug can improve hypertension management and patient outcomes. It was found higher bioavailability of tablet formulation.

5. ACKNOWLEDGEMENTS

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6. ABBREVIATIONS

HPMC- Hydroxypropyl methylcellulose, %- Percentage, % CDR- Percent Cumulative Drug Release, DSC- Differential Scanning Calorimetry, Hr-Hours, Min- minute, AUC- Area under the curve, HPLC- High perfumes liquid chromatography, DAD- diode array detector.

7. AUTHORS CONTRIBUTION STATEMENT

Dr. Amar Zalte helped design the experiment and monitored the project's progress. Pooja Kadu conceptualized, performed laboratory work, and gathered and analyzed the data about this work. Dr. Vishal Gulecha gave necessary inputs towards the design of the manuscript. Finally, Pooja Kadu wrote the manuscript, and Dr. Amar Zalte and Dr. Vishal Gulecha proofread the manuscript.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

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