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Formulation and evaluation sustained and immediate release bilayer tablet of telmisartan and amlodipine

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***Abstract*---**The study was undertaken with the aim to Formulation and evaluation of bilayer tablet formulation of Telmisartan and Amlodipine. Thus, from the results, it is concluded that the formulation of immediate release layer of Amlodipine using 4-2% concentration of Crospovidone & PVA K30 and 30-20-1.5% concentration of HPMC K 100M-HPMC K4 M-HPMC K15 M are considered as ideal for optimized bilayer tablet formulation. The drug release data of the Telmisartan and Amlodipine was fitted into various kinetic models which as shown in figures 3.8 and 3.11. The order of release of drug was found to be zero order, in which R2 value was close to 1. The n value of Korsmeyer Peppas equation was found to be 0.746. Good correlation coefficients are obtained for Higuchi equation. The results showed that the formulation followed Peppas Model release. Thus, this optimized bilayer tablet formulation can be successfully used in the treatment of hypertension. This modified release bilayer tablets also reduced dosing frequency, increase the bioavailability and provide better patient compliance. From the results it was found that formulation F4 was the best formulation amongst the 5 formulations. Thus formulation F4 was selected for stability studies. Formulation F4 was analyzed for % Friability and % Drug Release (min), Drug Content Uniformity and Hardness at the end of each month up to three months, results are shown in Table.

***Keywords*---**antihypertensive, sustained, immediate release bilayer, bioavailability.

Introduction

Hypertension, or high blood pressure, is a major public health concern around the world because of its large contribution to the global health burden and its function as a major risk factor for a variety of disease processes. In the year 2019, high blood pressure was responsible for 54% of strokes, 47% of ischemic heart disease, 75% of hypertensive disease, and 25% of all cardiovascular disease worldwide. Hypertension has a demonstrable negative influence on health, especially when considering the disability, reduced quality of life, and mortality associated with stroke and cardiovascular disease [1, 2].

Hypertension has a demonstrable negative influence on health, especially when considering the disability, reduced quality of life, and mortality associated with stroke and cardiovascular disease. Systolic blood pressure of more than 115mmHg was responsible for 7.6 million fatalities (13.5 percent of all deaths) and 92 million disability life-years (6% of total) in 2019. It's disheartening to learn that such widespread negative consequences are linked to a preventable cause. For the chronic treatment of many disorders, the oral route has been the most common route of medication delivery. The goal of this study was to use an optimization technique to generate an optimum bilayer tablet for anti-hypertension patients utilizing a hypertensive agent as a model drug candidate. For the treatment of hypertension, combination drug therapy is advised because it allows drugs with distinct mechanisms of action to complement each other and effectively lower blood pressure at lower than maximum dosages of each. Any drug delivery system's purpose is to deliver a therapeutic amount of medicine to the appropriate spot in the body in order to establish and then maintain the correct drug concentration quickly. The spatial placement and temporal distribution of medicine are the two most significant components of drug delivery. Drug targeting to a specific organ or tissue requires spatial positioning. The concept of Bilayer tablet technology is utilized to develop sustained release and immediate formulation for a single drug or combination of drugs. Bilayer tablets are preferred in some cases because they maintain uniform drug levels, reduce dose, side effects, increase the safety margin for high-potency drugs and thus offer better patient compliance. Telmisartan and Amlodipine is anti-hypertensive drug which acts by controlling antagonizing effect on the angiotensin receptor blocker (ARB) and a calcium channel blocker [3, 4].

Materials and Methods

Materials

Material Used

S.N0	Material	Taken by
1	Drug (Telmisartan and Amlodipine)	Hetro Pharma Roorkee U.K
2	Crospovidone	CPS Pharm labs
3	HPMC K4 M	-
4	HPMC K 100M	-
5	HPMC K 15M	Pharma Tech lab

6	PVP K30	-
7	MCC	IIMT University
8	Talc	IIMT University
9	Aerosil	Pharma Tech lab
10	Mannitol	IIMT University

List of Instruments

S. No	Instruments	Suppliers
1	Weight balance	Shimadzu corporation
2	Hardness tester	Monsanto, India
3	pH Meter	Electro lab, India
4	Roche Friablator	Electro lab, India
5	FTIR Spectroscopy	Shimadzu corporation, Japan
6	DSC	Electro lab, India
7	Tray dryer	Electro lab, India
8	Uv- Spectrophotometer	Lab India
9	Disintegrator	Electro lab, India
10	Dissolution apparatus	Electro lab, India

Method

Preformulation Study

Calibration Curve of Telmisartan and Amlodipine

Accurately weighed 100mg Telmisartan and Amlodipine was transferred into 100ml volumetric flask and dissolved in Small quantity of Methanol and the volume was made up with phosphate buffer pH 6.8 to give a stock solution of concentration of 1mg/ml. Further dilutions were made in the range of 2-20mcg/ml with phosphate buffer pH 6.8 and absorbance was measured at 258nm and 235nm [5].

Physicochemical Interaction of Drug & Polymer

Physicochemical Interaction of drug and Excipients for Telmisartan and Amlodipine was done as per IP by the identification test carried out by the Fourier Transform Infra red spectrophotometer (FTIR) and the reports were shown in figures.

Precompressional Parameter

Bulk density

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and the initial volume was noted. This initial volume is

called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It expressed in g/cc and is given by:

$$Db = M/Vo$$

Where,

M = mass of powder.
V0 = the bulk volume of the powder.

Tapped Density

It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume was noted (the difference between these two volumes should be less than 2 %). If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted.
It is expressed in g/cc and is given by:

$$Dt = M/V1$$

Where,

M = mass of powder.
Vt = tapped volume of the powder.

Carr's index (%)

The bulk density is the measurement of weight to the volume of the sample. Tapped density is determined as the measurement of weight of the sample to the volume after tapping the measuring cylinder for 500 times from a height of 2 inches. The percentage compressibility (Carr's index) was calculated as 100 times the ratio of the difference between tapped density and bulk density to the tapped density.

$$\frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

Hausner's ratio

Hausner's ratio is the ratio of tapped density to bulk density. Lower the value of Hausner's ratio better is the flow property.
Hausner's Ratio = Bulk Density

Angle of Repose

The angle of repose of blends was determined by the funnel method. The accurately weighed blend was taken in funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the blend. The blend was allowed to flow from the funnel on the surface. The diameter and height of the heap formed from the blend were measured. The angle of repose was calculated using following formula [6].

$$\text{Tan } \theta = h/r$$

Where,

H = height of the heap.

R = radius of the heap of granules.

Method

The powder mixture was allowed to flow through the funnel with its tip fixed to stand at a definite height (h) from a graph paper placed on a horizontal surface. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. A value for angle of repose 0° to 40° suggests a poorly flowing material.

Preparation of Immediate Release Layer of Amlodipine

The Amlodipine layer was prepared by using direct compression method. All the ingredients except Crospovidone and Aerosil were passed through sieve No: 40, weighed and mixed for 15 mints and finally blended well in ascending order of their weights. Crospovidone and Aerosil were passed through sieve No: 60 and mixed it to the above blend. Finally colorant was added and blended uniformly and compressed in a 16 station automatic punching machine with a punch size of 6mm.

Preparation of Immediate release layer of Amlodipine

Ingredients (mg/tab)	F1	F2	F3	F4	F5
Amlodipine	10	10	10	10	10
Crospovidone	1.5	3	4.5	6	7.5
Mannitol	40	50	55	60	62
Aerosil	1.1	1.1	1.1	1.1	1.1
PVA K30	2	2	2	2	2
Colorant	Q.S	Q.S	Q.S	Q.S	Q.S

Preparation of Sustained Release Layer of Telmisartan

The SR ingredients were accurately weighed and added into the blender in ascending order. The powder mixture was blended for 20 minutes to obtain uniform distribution of the drug in formulation and subjected for pre-formulation studies.

Compression of Bilayer Tablet

In the present study bilayer tablet was prepared manually using single station punching machine (Rimek mini press-1). Accurately weighed amount of SR powder mixture was fed manually into die cavity. SR layer was compressed at mild compression force (2-3 kg/cm2). After that accurately weighed IR powder mixture was manually fed into the die on SR layer and compressed using 9 mm circular punches. Both the layers were identified on the basis of colon since the

immediate release layer had pink color and the sustained release layer has white color.

Compression of Bilayer Tablet

Ingredients (mg/tab)	F1	F2	F3	F4	F5
Telmisartan	25	25	25	25	25
HPMC K4M	20	20	20	25	20
HPMC K100M	30	30	30	30	30
HPMC K15M	1.5	1.5	1.5	1.5	1.5
MMC	4	4	4	4	4
Talc	3	3	3	3	3

Post Compression Parameters

Weight Uniformity

Twenty tablets from each batch at random were taken and weighted. The average weight was calculated, then each tablet was weighed individually and weights of each tablets was noted. The weights of individual tablets were then compared with the average weight that was already calculated. The deviation if any in the weight of individual tablets from the average weight was checked. This test highly describes that all the tablets of a particular batch should be uniform in weight. If any weight variation is there, that should be within IP limits. The test was considered correct if not more than two tablets fall outside the IP limits out of twenty tablets taken for the test.

Hardness

Hardness of the tablets determined by using Monsanto hardness tester (Tab machines, Mumbai). The tablet to be tested held fixed & moving jaw & reading of the indicator adjusted to zero. Then force to the edge of the tablets was gradually increased by moving the screw knob forward until tablets breaks. The reading was noted from scale which indicates the pressure required in kg to break the tablet. The hardness of tablets depends on weight of material used, space between the upper and lower punches at the time of compression and pressure applied during compression.

Friability

Friability test was performed by using Roche friabilator (Remi equipments, Mumbai). Twenty tablets of a batch were weighted and placed in a friabilator chamber and it was allowed to rotate for 100 revolutions. During each revolution these tablets fall from a distance of six inches to undergo shock. After completion of 100 revolutions, tablets were again weighed and the loss in weight indicated the friability. The acceptable limits of weight loss should not be more than 0.8%. This test was performed to evaluate the ability of the tablets to with stand abrasion during packing, handling and transporting.

Content Uniformity Test

Ten immediate and sustained release layers were weighed and powdered, a quantity of powder equivalent to 10mg of Amlodipine and 25mg of Telmisartan was taken. The Amlodipine and Telmisartan content was estimated by HPLC method at 239nm and 297nm respectively after appropriate dilutions. The mean percent drug content was calculated as an average of three determinations.

Drug Release Studies for Bilayer Tablets

The in vitro dissolution of Amlodipine and Telmisartan bilayer tablets were determined using USP XXIII (basket method) dissolution apparatus. The basket was allowed to rotate at a speed of 100rpm & temperature of 37±0.5°C was maintained. The dissolution medium used was 900ml of 0.1N HCl (pH 1.2) for the initial 2hours followed by study in simulated intestinal fluid Phosphate buffer solution (pH 6.8). Aliquots (5ml) of sample were collected at predetermined time intervals (5, 10, 15, 20, 25, 30 and 60min) from the dissolution apparatus and it was replaced with equal volume of fresh dissolution medium. The aliquots withdrawn were filtered through 0.45µm Millipore filters. The concentration of both the drugs in the dissolution media was estimated by HPLC method at 239nm and 297nm for Amlodipine & Telmisartan respectively.

Release Kinetics Studies

To study the release kinetics and mechanism of release in-vitro release data was applied to kinetic models such as zero order (Cumulative % drug release vs. time), first order (Log Mean % drug unreleased vs. time), Higuchi (Mean % cumulative drug release vs. square root of time) and Koresmeyer-Peppas (Log mean % cumulative drug release vs. Log time) using Microsoft Excel-2003 software and the regression values (R2) were calculated [7, 8]

Stability Studies

In the present study, stability studies were carried out for both at room temperature and accelerated stability conditions. The conditions for storing at room temperature were kept as 30±2 °C and 65±5% RH and for accelerated stability conditions were kept at 40±2°C and 75±5% RH in a humidity chamber. At regular intervals of time (0, 2, 4 and 6 months) samples were withdrawn and were evaluated for drug content and in-vitro release profile [9, 10].

Results and Discussion

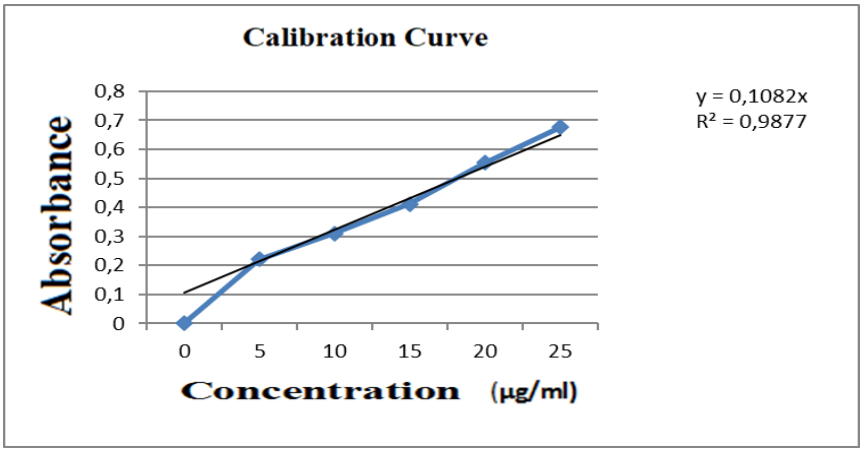
Preformulation Study

Calibration Curve of Telmisartan and Amlodipine

The absorption curve showed characteristic absorption maxima at 258nm and 235nm for Telmisartan & Amlodipine (pure drug). The resulting spectrum (graph between absorbance and wavelength) is shown in Fig 3.1.

Preparation of standard calibration the curve of Telmisartan (λmax258)

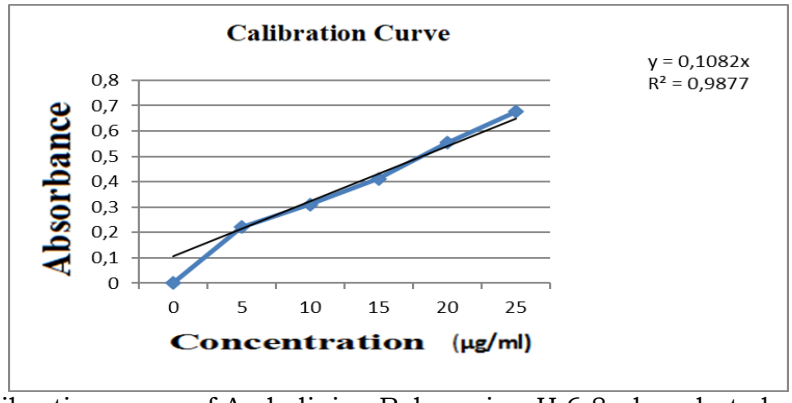
S.No	Conc.	Abs.
1	0	0
2	5	0.220
3	10	0.310
4	15	0.412
5	20	0.554
6	25	0.676



Calibration Curve of Telmisartan Bilayer in pH 6.8 phosphate buffer

Preparation of Standard Calibration Curve of Amlodipine Bilayer (λmax235)

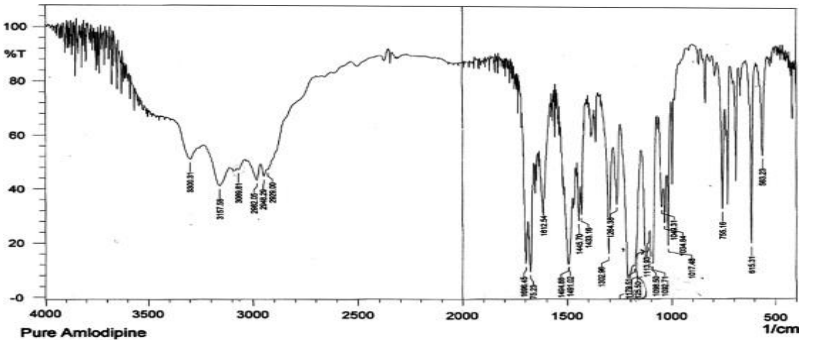
S.No	Conc.	Abs
1	0	0
2	5	0.154
3	10	0.276
4	15	0.352
5	20	0.576
6	25	0.698



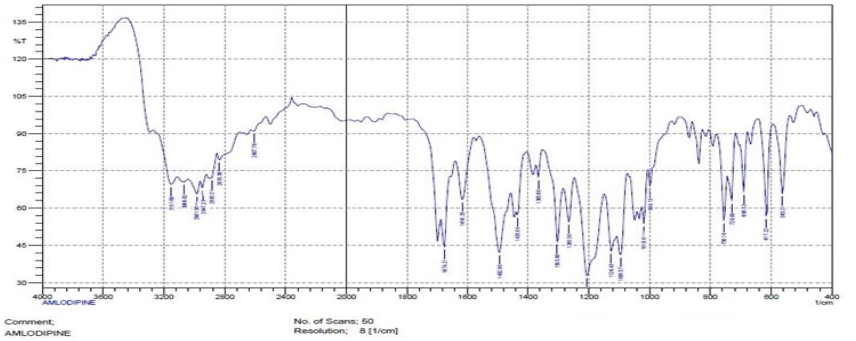
Calibration curve of Amlodipine Bylayer in pH 6.8 phosphate buffer

Drug Excipients Interaction Studies

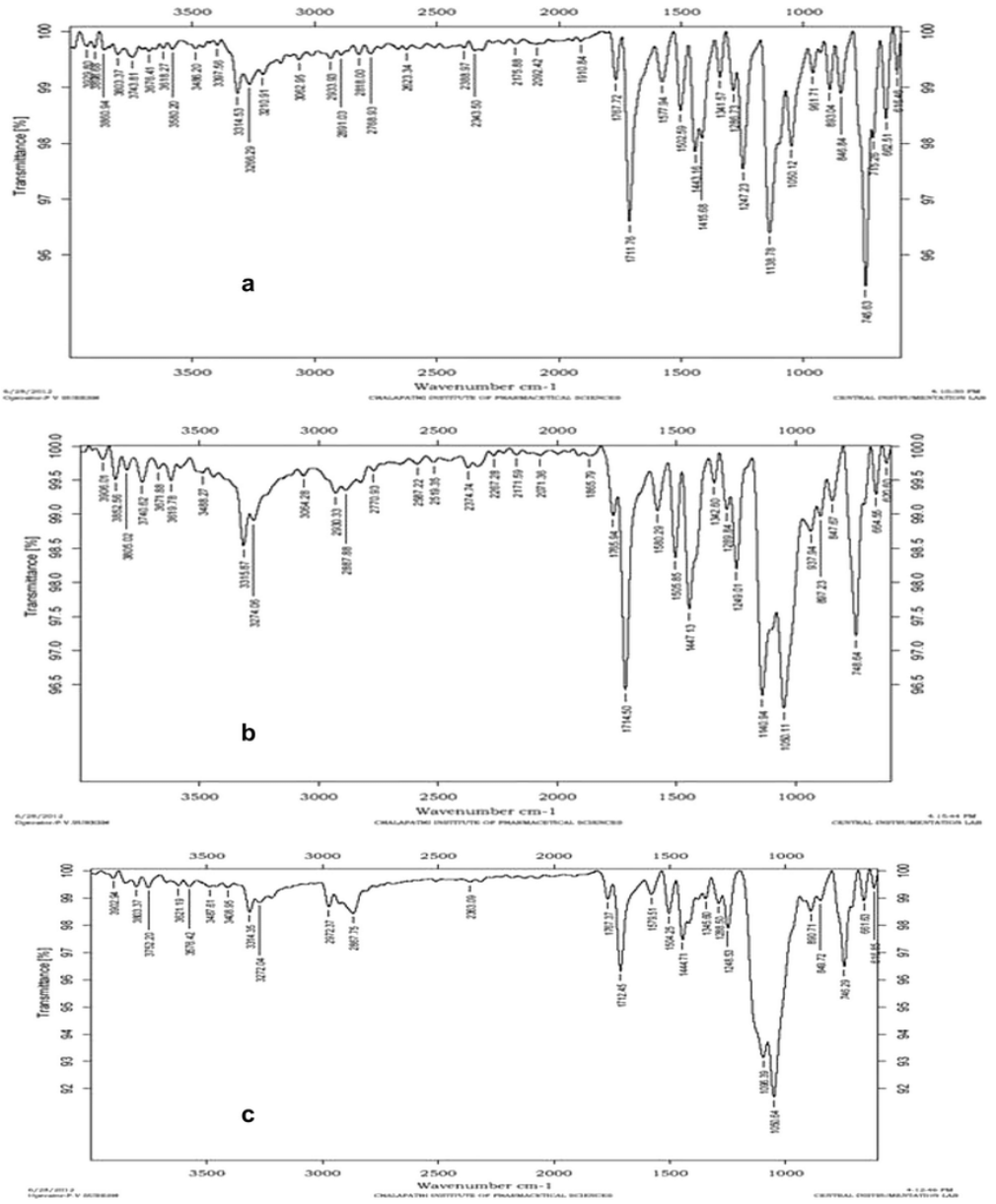
When the spectra's of pure drug and its combination with Excipients were taken as shown in Fig.3.3-3.6 It was found that all the peaks corresponding to the constituents were found to be present in its higher spectra indicating that none of the functional groups of either drug or polymer have undergone any chemical reaction. All functional groups are intact. Hence, it is a confirmation that no chemical reactions have taken place amongst any of the constituents in the bilayer tablet formulation and thus it can be used for its desired purpose.



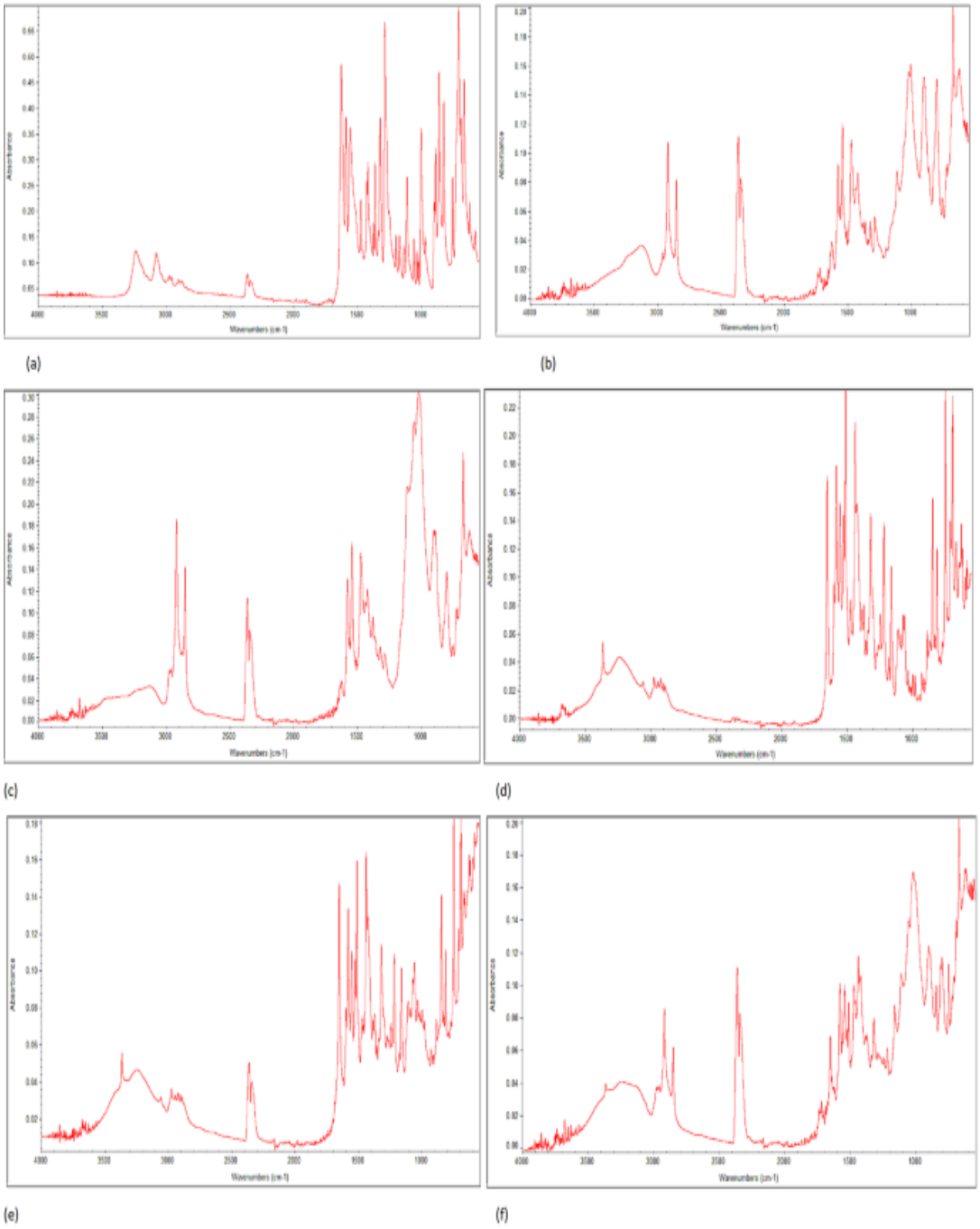
FTIR Spectra of Telmisartan



FTIR Spectra of Amlodipine



FTIR Spectra of Telmisartan, Amlodipine and HPMC



FTIR Spectra of HPMC K 100M, Polyvinyl Pyrollidone, Talc, Areosil 200, Crospovidone and Microcrystalline cellulose

FTIR of Pure Telmisartan and Amlodipine drug

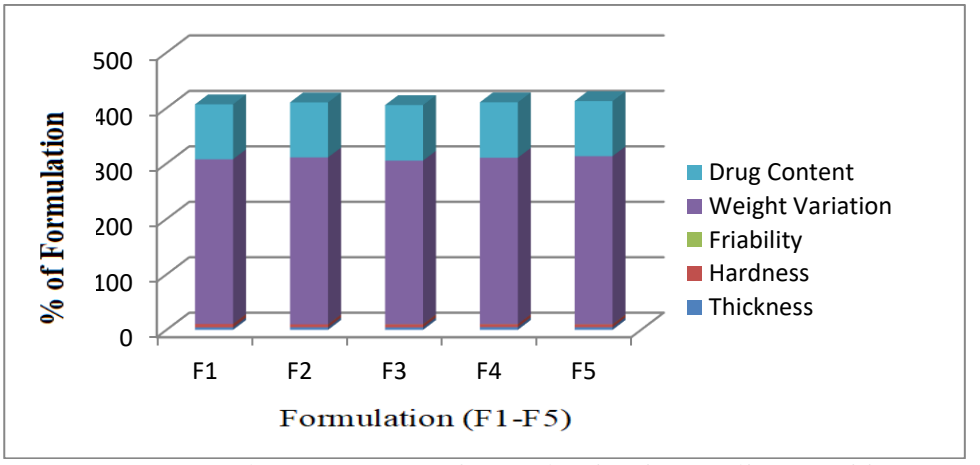
S.No	Functional group	Wavelength (nm)
	Alkanes. a) C – H stretching Methyl group (-CH2) b) C – C stretching c) C – H bending	 3000-2890 1200-1890 1390-1395
	Alkenes. a) C=C unconjugated b) C=C conjugated	1767-1740 1850-1800
	Alkynes. a) C – H	800-710
	Mononuclear aromatic hydrocarbons a) C – H bending b) C – H stretching	1400- 1100 3200-3100
	Aldehydes. a) C=O stretching b) C – H stretching	1840- 1820 2930- 2795
	Amides. a) N – H bending	1550- 1510
	Amines. a) N – H stretching b) C – N stretching	1750- 1680 1530-1330
	Organic halides. a) C – Br	790-615

Precompressional Parameter

Formulation Code	Bulk density (gm/ml)	Tapped density(gm/ml)	Carr's index. (%)	Hausner's ratio	Angle of repose (θ)
F1	0.345	0.410	12.78	1.15	22.98
F2	0.326	0.402	11.76	1.20	21.78
F3	0.376	0.396	13.12	1.16	24.18
F4	0.364	0.388	14.54	1.14	20.44
F5	0.370	0.424	12.90	1.18	18.24

Post-compression Parameter of Sustained Release Bilayer Tablets

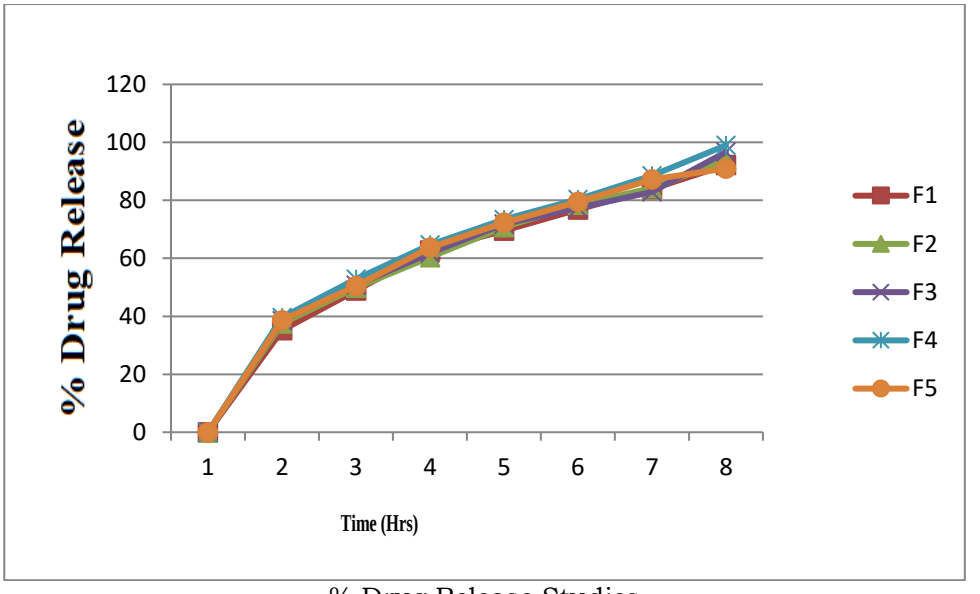
Formulation Code	Thickness (mm)±SD	Hardness (kg/cm2)±SD	Friability (%)±SD	Weight variation (gm)±SD	Drug content (%w/w)±SD
F1	4.44±0.014	6.10±0.053	0.10±0.011	297±1.42	99.1±0.2
F2	4.67±0.020	5.20±0.045	0.14±0.018	301±1.37	99.19±0.3
F3	4.56±0.021	5.44±0.034	0.20±0.023	295±1.43	100.2±0.1
F4	4.98±0.027	5.16±0.033	0.24±0.016	300±1.48	99.98±0.5
F5	4.76±0.015	5.06±0.030	0.28±0.013	303±1.50	99.4±0.7



Post-compression Parameter of Sustained Release Bilayer Tablets

Drug Release Studies for Immediate Release Layer

Time	F1	F2	F3	F4	F5
0	0	0	0	0	0
5	35.21	37.54	38.46	39.60	38.61
10	48.90	49.88	50.76	52.87	50.47
15	62.65	60.32	61.84	64.72	63.72
20	69.56	70.76	71.90	73.36	72.31
25	76.80	78.43	77.42	80.40	79.51
30	83.90	84.24	82.85	88.50	87.21
60	92.20	93.90	96.67	98.97	90.99

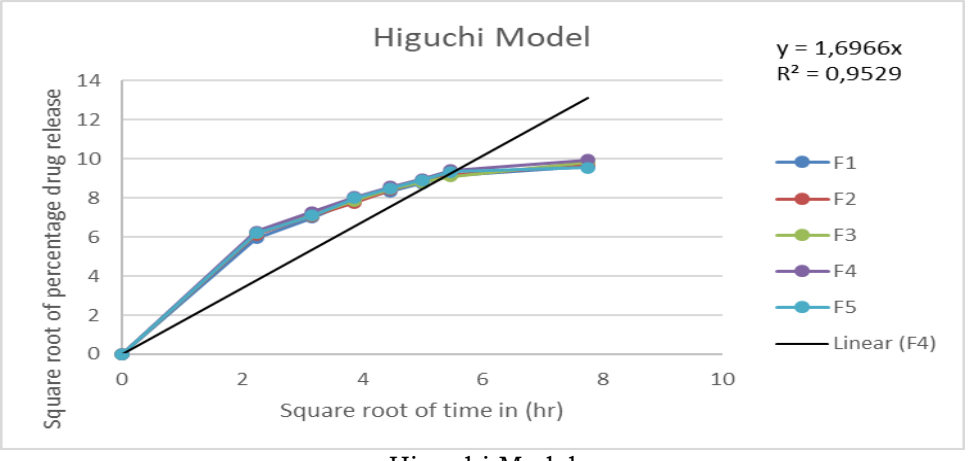


% Drug Release Studies

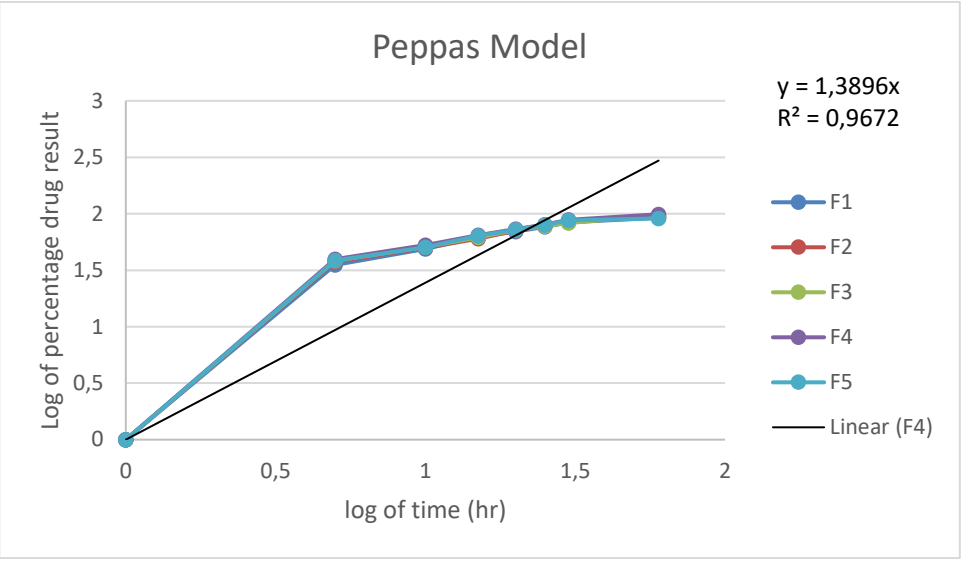
Release Kinetics Studies

Zero Order Release Kinetics Study

1st Order Release Kinetic Study



Higuchi Model



Peppas Model

The order of release of drug was found to be zero order, in which R2 value was close to 1. The n value of Korsmeyer Peppas equation was found to be 0.746. Good correlation coefficients are obtained for Higuchi equation. The results showed that the formulation followed zero order release. The drug release data of the Telmisartan and Amlodipine was fitted into various kinetic models which as shown in figures 3.8 and 3.11. The order of release of drug was found to be zero order, in which R2 value was close to 1. The n value of Korsmeyer Peppas equation was found to be 0.746. Good correlation coefficients are obtained for Higuchi equation. The results showed that the formulation followed Peppas Model release.

Stability Studies

From the results it was found that formulation F4 was the best formulation amongst the 5 formulations. Thus formulation F4 was selected for stability studies. Formulation F4 was analyzed for % Friability and % Drug Release (min), Drug Content Uniformity and Hardness at the end of each month up to three months, results are shown in Table 3.7.

Stability Studies of Selected Formulation F4

Evaluation Parameters	Initial	1st Month	2nd Month	3rd Month
Hardness	5.16±0.033	5.16±0.030	5.15±0.024	5.10±0.019
Drug Content Uniformity	99.98±0.5	99.90±0.4	99.54±0.4	98.86±0.2
% Friability	0.24±0.016	0.24±0.014	0.23±0.010	0.22±0.012
% Drug Release	98.97	98.96	98.80	97.12

Conclusion

The study was undertaken with the aim to Formulation and evaluation of bilayer tablet formulation of Telmisartan and Amlodipine. Thus, from the results, it is concluded that the formulation of immediate release layer of Amlodipine using 4-2% concentration of Crospovidone & PVA K30 and 30-20-1.5% concentration of HPMC K 100M-HPMC K4 M-HPMC K15 M are considered as ideal for optimized bilayer tablet formulation. The drug release data of the Telmisartan and Amlodipine was fitted into various kinetic models which as shown in figures 3.8 and 3.11. The order of release of drug was found to be zero order, in which R2 value was close to 1. The n value of Korsmeyer Peppas equation was found to be 0.746. Good correlation coefficients are obtained for Higuchi equation. The results showed that the formulation followed Peppas Model release. Thus, this optimized bilayer tablet formulation can be successfully used in the treatment of hypertension. This modified release bilayer tablets also reduced dosing frequency, increase the bioavailability and provide better patient compliance. From the results it was found that formulation F4 was the best formulation amongst the 5 formulations. Thus formulation F4 was selected for stability studies. Formulation F4 was analyzed for % Friability and % Drug Release (min), Drug Content Uniformity and Hardness at the end of each month up to three months, results are shown in Table.

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