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FORMULATION AND INVITRO EVALUATION OF BILAYERED TABLETS OF CANDESARTAN AND HYDROCHLOTHIAZIDE

Kahira Tasneem*[1] and Mahammad Shahidullah Shaik[1]

[1*]Department of Pharmaceutics, Deccan School of Pharmacy, Dar-Us-Salam, Aghapura, Hyderabad, India.

ABSTRACT

The current work focuses on the formulation and evaluation of bilayer tablet of Candesartan and Hydrochlorthiazide in the treatment of hypertension. The release of Candesartan and Hydrochlorthiazide was controlled by formulating it into a sustained and immediate release layer respectively. The formulae was developed using various individual concentrations of Crospovidone, Sodium Starch Glycolate, Cros Carmellose Sodium, and various individual concentrations and viscosity grades of HPMC K4 M and HPMC K15 M polymers for both immediate and sustained release layers respectively. The compatibility of polymers and excipients along with pure drugs was evaluated using FTIR studies. Both the layers were formulated individually in nine different batches and further Pre- and Post-compression parameters, In-vitro dissolution testing, release rate kinetics and stability studies were evaluated. The FTIR spectra's confirms the absence of chemical interaction between drug and polymers. All the Pre and post-compression parameters were found to be in limits. From the results of dissolution testing it was found that the batch F3 and batch F5 of sustained and immediate layer respectively was found to be best when compared with the marketed product. The data for stability studies revealed that no considerable differences in drug content and dissolution rates for a period of 3 months as per ICH guidelines. Thus, a novel bilayer tablet formulation of Candesartan and Hydrochlorthiazide were successfully developed by combining both immediate and sustained release layers.

KEYWORDS

Candesartan, Hydrochlorthiazide, Crospoidone, Croscarmellose, HPMC K4 M and HPMC K15 M.

Author for Correspondence:

Mahammad Shahidullah Shaik,
Department of pharmaceutics,
Deccan School of Pharmacy, Dar-Us-Salam,
Aghapura, Hyderabad, India.

Email: s.shahidulla@gmail.com

INTRODUCTION

Hypertension or high blood pressure occurs when the high cardiac output exerts pressure on the arterial wall as the blood flow increases. The present available conventional dosage form used in the treatment of hypertension cannot produce the desired therapeutic effect for prolonged period of time and thus dose fluctuation and missing of dose chances are more[1]. The reason for using fixed dose combination therapy is to obtain controlled blood pressure by employing two antihypertensive drugs

with different mode of action and enhance the compliance by using single tablet that is taken once a day[2].

Some 600 million people worldwide have high blood pressure and nearly 3 million die every year as a direct result. Yet eight out of every 10 people with hypertension are not being treated adequately, according to the International Society of Hypertension (ISH). Combination drug therapy is recommended for patients whose blood pressure does not fall to optimal levels with single-drug treatment. Bilayer tablet is novel idea for successful development of controlled release formulation.

Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as loading dose and second layer is maintenance dose[3]. It is envisaged that the proposed work is designed as the Bilayer tablet of hydrochlorothiazide and candesartan. One layer of the bilayer tablet contains the hydrochlorothiazide as instant release, and the remaining second layer contains the candesartan as control Layer. Hydrochlorothiazide is a thiazide diuretic which prevents the patient from absorbing an excessive amount of electrolytes, that can reason fluid retention. Candesartan is an angiotensin II receptor antagonists. Candesartan keeps blood vessels from narrowing, which lowers blood stress and improves blood go with the flow. The combination of Hydrochlorothiazide and Candesartan is used to treat excessive blood pressure (hypertension)[4].

MATERIAL AND METHODS

Materials

Candesartan and Hydrochlorothizide (Chandra Labs, Hyderabad); HPMC K 4 M, HPMC K15 M, Guargum, Microcrystaline cellulose, IPA, Sodium starch glycolate, Crospovidone (MYL CHEM, Mumbai) Cross Magnesium stearate, PVP, carmellose sodium, Aerosil, (S.D.Fine Chemical Ltd, Mumbai).

Method

Preformulation[5]

Physiochemical Properties of candesartan and hydrochlorothiazide

Organoleptic evaluation

It refers to the evaluation by sensory characters-colour, taste, appearance, odor.

Solubility (at room temp)

We will check the solubility of both of drugs in water, hot water, 0.1N HCL, 0.1 NaOH, acetone, ethanol, chloroform, methanol at room temperature.

Melting point

It is one of the parameters to judge the purity of drugs. In case of pure chemicals, melting points are very sharp and constant. Since the drugs contain the mixed chemicals, they are described with certain range of melting point. A small quantity of powder was placed into a fusion tube. That tube is placed in the melting point determining apparatus containing castor oil. The temperature of the castor oil was gradual increased automatically and read the temperature at which powder started to melt and the temperature when all the powder gets melted.

Bulk density

A known quantity of powder was poured into the measuring cylinder carefully level the powder without compacting, if necessary and read the unsettled apparent volume, Vo, to the nearest graduated unit. Calculate the bulk density, in gm per ml gm/cc, by the formula

Bulk density = Bulk Mass/ Bulk Volume

Compressibility index (Carr's index)

Compressibility index (C.I.) is an important measure that can be obtained from the bulk and tapped densities. Carr's index a material having values of less than 20% to 30% is defined as the free flowing material. Shown in Table No.1. It can be calculated as per given formula:

$$C.I = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} * 100$$

Hausner ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density.

Hausner ratio = Tapped density / Bulk Density

Angle of Repose

The angle of repose is a relatively simple technique for estimating the flowability of a powder through a funnel and fall freely onto a surface. The height and diameter of the resulting cone is measured and using the following equation, the angle of repose can be calculated.

$\tan \theta = h/r$

Where h, r is the relatively height and radius of the powder cone. For maximum pharmaceutical powders, the angle of repose values range form 25 to 45, with decrease values indicating better flow traits. Values of angle of repose $\leq$ 30 usually indicate a free flowing material and angle $\geq$40 suggest a poorly flowing material.

DETERMINATION OF λ max. OF HYDROCHLOROTHIAZIDE

Accurately weighed amount of 100 mg hydrochlorothiazide was transferred into a 100ml volumetric flask. 20 ml 0.1N HCl of was added to dissolve the drug and volume was made up to 100 mL with the 0.1N HCl. The resulted solution had the concentration of 1mg/ml which was labeled as 'stock'. From this stock solution 10ml was taken and diluted to 100 ml with 0.1N HCl which has given the solution having the concentration of 100mcg/ml. Necessary dilutions were made by using this second stock to give the different concentrations of hydrochlorothiazide (1-12 mcg/mL) solutions. The spectrum of this solution was run in 200-400 nm range in U.V spectrophotometer (Corporation-BL-220H). The absorbances of above solutions were recorded at λ_{max} (272 nm) of the drug using double beam UV-Visible spectrophotometer. Standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis).

DETERMINATION OF λmax. OF CANDESARTAN

Accurately weighed amount of 100 mg Candesartan was transferred into a 100ml volumetric flask. 20 ml of 6.8pH phosphate buffer was added to dissolve the drug and volume was made up to 100 ml with6.8pH phosphate buffer. The resulted solution had the concentration of 1mg/ml which was labeled as 'stock'. From this stock solution 10ml was taken and diluted to 100 ml with 6.8pH phosphate buffer which has given the solution having the concentration of 100 mcg/mL. Necessary dilutions were made by using this second solution to give the different concentrations of Candesartan (1-5 mcg/mL) solutions. The absorbances of above solutions were recorded at λ_{max} (255nm) of the drug using double beam UV-Visible spectrophotometer. Standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis).

Formulations

Preparation of Candesartan Sustained Release layer and immediate release layer

Sustained Release Formulations

In the formulations prepared, the release retardants included HPMC K4 M, HMPC K 15M and Guargum, MCC were used as filler. Magnesium stearate (MS) were used as lubricants and PVP as binder. For preliminary studies to optimize the SR formulations, a weighed quantity of above lubricated drug mixture blend was fed manually into the die and directly compressed using 12 mm flat faced punch of 16 station Cad mach compression machine to get SR tablets. Nine formulation batches were made in order to achieve desired disintegration time and drug release. Formulation compositions of different sustained release batches are given in the (Table No.2).

Immediate release formulations

In the formulations prepared, the release enhancers included were SSG, CP and CCS, MCC were used as filler. Magnesium stearate (MS) were used as lubricants and PVP+IPA as binder. For preliminary studies to optimize the IR formulations, a weighed quantity of above lubricated drug mixture blend was fed manually into the die and directly compressed using 8 mm flat faced punch of 16 station Cadmach compression machine to get IR tablets. Nine formulation batches were made in order to achieve desired disintegration time and drug release.

Formulation compositions of different immediate release batches are given in the (Table No.3).

Preparation of Bilayer Tablets

So as to put together bilayer drugs, the dissolution take a look at changed into carried out for each layers of IR with the purpose of selecting the fine formulation. Based on dissolution behavior, formulations of Immediate release optimized layer were selected for bilayer tablet. Optimized immediate release layer was compressed with nine formulations of sustained release layer with optimum hardness of 6–8 kg/cm2 to form bilayer tablets. Compression was made by using 12 mm punches. The total weight of each bilayer tablet was 330 mg, containing 12.5 mg of hydrochlorothiazide in immediate-release layer and 16 mg of Candesartan in sustained release layer. Prepared bilayer tablets was optimized and evaluated for various post compression parameters and in vitro dissolution studies.

Evaluation of Post Compression parameters

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, Friability and in vitro-dissolution characters.

Physical Appearance

The overall look of a pill, its identification and widespread elegance is important for consumer attractiveness, for control of lot-to-lot uniformity and tablet-to-pill uniformity. The control of general appearance involves the measurement of size, shape, colour, presence or absence of odour, taste etc.

Size and Shape

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness may be measured through micro-meter or by way of different tool. Tablet thickness should be controlled within a ± 5% variation of standard value.

Weight variation test

This is an in process quality control test to ensure that the manufacturers control the variation in the weight of the compressed tablets, different pharmacopoeia specify these weight variation tests.. These tests are primarily based on the comparison of the weight of the individual tablets (xi) of a sample of tablets with an upper and lower percentage limit of the observed sample average (x-mean). The USP has provided limits for the average weight of uncoated compressed tablets. These are applicable when the tablet contains 50mg or more of the drug substance or when the latter comprises 50% or more, by weight of the dosage form.

Method

Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Now not greater than tablets ought to differ of their common weight by using extra than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Friability[7]

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability take a look at is cautiously associated with tablet hardness and designed to assess the capability of the tablet to resist abrasion in packaging, coping with and shipping. It is usually measured by the use of the Roche friabilator.

Method

Some of drugs are weighed and located inside the equipment in which they are exposed to rolling and repeated shocks as they fall 6 inches in every turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss because of abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

The percentage friability changed into decided by the components:

% friability = $(W_1-W_2) / W_1$ X 100

W_1 = Weight of tablets before test, W_2 = Weight of tablets after test

***In vitro* Dissolution Studies**

In vitro drug release studies have been carried out the usage of USP dissolution apparatus II, with 900ml of dissolution medium maintained at 37±1°C for 12 hr, at a hundred rpm, 0.1 N HCl (pH 1.2) turned into used as a dissolution medium for first 2h observed with the aid of pH 6.8 phosphate buffer for similarly 10 hr. 5ml of pattern was withdrawn at predetermined time periods changing with an same quantity of drug free dissolution fluid. The samples withdrawn have been filtered via 0.45µ membrane clear out, and drug content in each sample turned into analyzed after appropriate dilution with the aid of UV Spectrophotometer and cumulative percent drug release changed into calculated.

Kinetic Analysis of Dissolution Data

To analyze the in vitro release data various kinetic models were used to describe the release kinetics. The 0 order rate describes the structures where the drug release rate is impartial of its awareness (Hadjiioannou *et al.,* 1993). The first order describes the release from system where release rate is concentration dependent (Bourne, 2002). Higuchi (1963) described the release of drugs from insoluble matrix as a rectangular root of time dependent manner based on Fickian diffusion. The Hixson-Crowell cube root law describes the release from systems where there is a change in surface area and diameter of particles or tablets (Hixson and Crowell, 1931).

FTIR Studies

FTIR studies were performed on drug and the optimized formulation using Corporation japan. The samples were analyzed between wavenumbers 4000 and 400 cm^{-1}.

RESULTS AND DISCUSSION

Preformulation Study

Organoleptic Properties (Color, odor, taste and appearance)

Determination of solubility

Drug: Candesartan

Soluble in methanol and DMSO, dimethylsulfoxide, and N, N-dimethylformamide, sparingly soluble in ethanol, propylene glycol,

Drug: HCTZ

Soluble in methanol water and DMSO, and very slightly soluble in hexane, dichloromethane, and methylbenzene.

Ultraviolet Visible (UV-visible) spectroscopy

Drug sample showed wavelength of maximum absorption (λ-max) 255nm.

Standard Graph of Candesartan in 6.8pH phosphate buffer

The results of release studies of formulations F1 to F9 are shown. The release of drug depends only on the nature and amount of superdisintegrants. As the percentage of superdisintegrants increased the release also increased. Based on this F5 was optimised as the maximum drug release was observed with in 20min.

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of the drug and the optimized method had been recorded in range of 4000-400 cm. Candesartan showed some prominent and characteristic peaks. In the optimized formulation, the presence of all the characteristic peaks of the Candesartan indicates that no interaction was occurred between the drug and the excipients.

Stability Studies

Formulation batch F3 was packed and charged at both room temperature (30±2°C and 65±5% RH). The tablets were evaluated for assay and dissolution profile testing at 0 and 3 months. The data for stability studies revealed that no considerable differences in drug content and dissolution rates were observed. The results of drug content and dissolution rate after 3 months are given in Table No.15.

DISCUSSION

The purpose of the present work was to develop an optimized bilayer tablet for hypertensive patients using candesartan and hydrochlorthiazide as a model drug candidate to improve the therapeutic efficacy and to prolong the drug release. The compatibility of polymers and excipients along with pure drugs was evaluated using FTIR studies. In the present study, nine formulations (SR & IR) with variable concentration of polymers (HPMC K4 M, HPMC K15 M, Crospovidone, Sodium Starch Glycolate, Cros Carmellose Sodium) prepared by direct compression method and evaluated for physiochemical properties and in vitro drug release invitro drug release. The results indicated that optimized the gastric fluid, formulation F5 of immediate release with F3 of sustained release layer on immersion in 0.1N HCl solution for 2 hour and then at pH 6.8 phosphate buffer at 37±0.50C. The formulation has shown maximum drug release at 99.4% in 12 hrs when compared with marketed formulation.

Table No.1: Acceptance Criteria

S. No	Flow properties	Angle of repose(θ)	Compressibility Index (%)	Hausner ratio
1.	Excellent	25-30	<10	1.00-1.11
2.	Good	31-35	11-15	1.12-1.18
3.	Fair	36-40	16-20	1.19-1.25
4.	Passable	41-45	21-25	1.26-1.34
5.	Poor	46-55	26-31	1.35-1.45
6.	Very poor	56-65	32-37	1.46-1.59
7.	Very very poor	> 66	>38	>1.6

Table No.2: Composition of Candesartan sustained release tablets

S.No	FORMULATION (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	API	16	16	16	16	16	16	16	16	16
2	HPMC K100M	70	87.5	105		-	-	-	-	-
3	Guar gum	-	-	-	70	87.5	105		-	-
4	HMPC K 15M	-	-	-	-	-	-	70	87.5	105
5	MCC	121	103	86	121	103	86	121	103	86
6	Mg.stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
7	PVP	16	16	16	16	16	16	16	16	16
8	Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
9	Total	230	230	230	230	230	230	230	230	230

Table No.3: Composition of hydrochlorothiazide immediate release tablets

S.No	FORMULATION (mg).	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	API	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
2	MCC	70	65	61	70	65	61	70	65	61
3	PVP +IPA	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4
4	SSG	9	13.5	18	-	-	-	-	-	-
5	CP	-	-	-	9	13.5	18	-	-	-
6	CCS	-	-	-	-	-	-	9	13.5	18
7	Mg.stearate	2	2	2	2	2	2	2	2	2
8	Aerosil	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
9	Total weight	100	100	100	100	100	100	100	100	100

Table No.4: Limits for Tablet Weight variation test

S.No	Average weight of tablet (mg)	% Difference allowed
1	130 or less	10 %
2	From 130 to 324	7.5 %
3	> 324	5 %

Table No.5: Results of identification tests of drug

S.No	Parameter	Candesartan	HCTZ
1	Color	White	Off white
2	Odor	Odorless	Odorless
3	Taste	Tasteless	Tasteless
4	Appearance	Crystalline powder	Amorphous powder

Melting point determination

Drug: Candesartan

Table No.6: Results of Melting point determination test of drug

S.No	Reported Melting Point	Observed Melting Point
1	176 – 185	178

Drug: HCTZ

Table 7: Results of Melting point determination test of drug

S.No	Reported Melting Point	Observed Melting Point
1	273 – 275	274

Table No.8: Physical Properties of Pre compression Blend for sustained release formulations

S.No	Formulations	Angle of repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's ratio	Flow property
1	F1	33.49	0.214±0.13	0.251±0.1	14.74±0.2	1.17±0.4	Good
2	F2	31.24	0.308±0.15	0.364±0.15	15.38±0.1	1.18±0.3	Good
3	F3	25.05	0.276±0.22	0.322±0.3	9.28±0.2	1.11±0.12	Excellent
4	F4	33.97	0.341±0.13	0.388±0.15	12.11±0.3	1.13±0.21	Good
5	F5	34.97	0.341±0.13	0.388±0.15	12.11±0.3	1.13±0.21	Good
6	F6	31.32	0.445±0.11	0.49±0.5	9.183±0.8	1.101±0.1	Excellent
7	F7	33.45	0.489±0.65	0.56±0.6	12.678±0.4	1.145±0.3	Excellent
8	F8	28.65	0.71±0.14	0.813±0.1	12.669±0.2	1.145±0.1	Excellent
9	F9	30.65	0.445±0.1	0.49±0.5	9.183±0.8	1.101±0.5	Excellent

Table No.9: Physical Properties of Pre compression Blend for immediate release formulations

S.No	Formulations	Angle of Repose (°)	Buk Density	Tapped Density	Carr's Index	Hausner's Ratio	Flow Property
1	F1	28	0.31±0.1	0.52±0.1	12.3±0.3	1.13±0.5	Excellent
2	F2	25	0.32±0.3	0.5±0.23	11.1±0.1	1.16±0.4	Excellent
3	F3	26	0.38±0.2	0.56±0.32	13±0.1	1.18±0.8	Excellent
4	F4	27	0.35±0.5	0.51±0.1	11.8±0.5	1.17±0.11	Excellent
5	F5	30	0.33±0.8	0.53±0.2	9.123±0.8	1.06±0.14	Excellent
6	F6	31	0.32±0.1	0.51±0.02	8.568±0.11	1.1±0.15	Good
7	F7	34	0.3±0.9	0.54±0.8	9.8±0.15	1.11±0.18	Good
8	F8	35	0.39±0.7	0.53±0.9	9.67±0.12	1.09±0.88	Good
9	F9	35	0.32±0.8	0.5±0.1	8.3±0.11	1.11±0.2	Good

Table No.10: Physical Evaluation of Sustained Layer

S.No	Formulation	Hardness (kg/cm^2)	Thickness (mm)	Weight Variation (mg)	Friability (%)	Drug content (%)
1	F1	7.3 ±0.44	3.84±0.17	252±1.48	0.32±0.1	92.25±1.37
2	F2	7.6±0.31	3.92±0.25	248±0.54	0.3±0.2	96.58±0.80
3	F3	7.6±0.40	3.80±0.80	249±0.41	0.36±0.14	99.32±2.47
4	F4	7.5±0.55	3.82±0.20	252±1.64	0.31±0.12	101.23±0.88
5	F5	7.7±0.57	3.98±0.66	249±1.14	0.34±0.3	99.54±1.25
6	F6	7.6±0.30	3.93±0.25	250±0.83	0.35±0.1	97.33±1.87
7	F7	7.5±0.57	3.85±0.71	252±0.67	0.32±0.1	96.68±1.99
8	F8	7.6±0.60	3.95±0.89	254±0.43	0.32±0.12	97.55±1.14
9	F9	7.7±0.45	3.83±0.69	252±0.57	0.3±0.12	98±5.57

Table No.11: Physical Evaluation of Immediate Layer

S.No	Formulation	Hardness (kg/cm^2)	Thickness (mm)	Weight (mg)	Friability (%)	Drug content (%)
1	F1	4.3 ±0.44	2.54±0.17	180±1.48	0.36±0.2	98.25±1.37
2	F2	4.6±0.31	2.62±0.25	178±0.54	0.39±0.1	95.28±0.80
3	F3	4.6±0.40	2.50±0.80	179±0.41	0.43±0.11	99.12±2.47
4	F4	4.5±0.55	2.52±0.20	181±1.64	0.32±0.21	101.22±0.88
5	F5	4.6±0.57	2.58±0.66	183±1.14	0.34±0.14	100.24±1.25
6	F6	4.5±0.30	2.53±0.25	185±0.83	0.58±0.15	99.53±1.87
7	F7	4.6±0.57	2.65±0.71	183±0.67	0.54±0.11	96.28±1.99
8	F8	4.5±0.60	2.65±0.89	180±0.43	0.37±0.12	95.35±1.14
9	F9	4.6±0.45	2.53±0.69	182±0.57	0.58±0.13	98±1.57

Table 12: Cumulative percentage drug release for immediate layer

S.No	Dissolution time(Min)	Cumulative Percentage drug release								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	5	24	30	38	39	48	50	26	32	39
2	10	40	51	56	57	63	61	39	46	48
3	15	53	64	63	75	84	83	51	68	72
4	20	66	78	79	90	99	101	69	76	80
5	30	75	87	85	103			80	83	93
6	45	89	101	98				93	97	101
7	60	105	-	-				102	-	

***In-Vitro* Drug Release Studies for SR tablets**

Table No.13: Cummulative percentage drug release layer

S.No	Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0	0	0	0	0	0	0	0	0
2	1	38.5	45.9	25.5	26.3	23.9	22.7	28.1	32.6	31.4
3	2	45.7	72.2	39.2	33.2	36.9	31.4	33.5	49.3	45.9
4	3	53.8	80.7	46.5	40.1	49.7	45.9	52.7	67.4	57.3
5	4	70.4	92.4	55.2	45.6	53.9	57.3	60.3	72.6	80.7
6	5	84.9		68.5	55.2	63.8	80.7	72.4	85.4	94.9
7	6	93.6		75.9	63.8	70.4	94.9	78.3	95.8	
8	8			81.3	73.6	75.8		80.1		
9	10			93.2		84.9				
10	12			99.1		92.2				

Table No.14: Comparison of cummulative percentage drug release with that of the marketed product

S.No	Time (hrs)	Bilayered tablet	Marketed Product
Dissolution medium 0.1N HCL			
1	0	0	0
2	1	28	30
3	2	50	45
6.8pH phosphate buffer			
4	3	53	54
5	4	60.8	59.3
6	5	70.4	64
7	6	78.5	70.4
8	8	84.3	74.3
9	10	90.7	81.2
10	12	99.4	88.3

Table No.15: Kinetic analysis of dissolution data

S.No		ZERO	FIRST	HIGUCHI	PEPPAS
		% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
1	Slope	7.130237581	0.148386652	28.80262917	1.130864595
2	Intercept	25.14578834	2.113566968	3.079176248	0.967376994
3	Correlation	0.923139266	0.919266506	0.99279152	0.736026248
4	R 2	0.852186104	0.845050909	0.985635001	0.541734638

Table No.15: Stability Studies data

S.No	Parameters	Storage conditions	
		Initial release	Room Temperature 30±2 °C and 65±5%RH
		0 months	3 months
1	% Drug Content	99.32±2.47	99.26±1.53

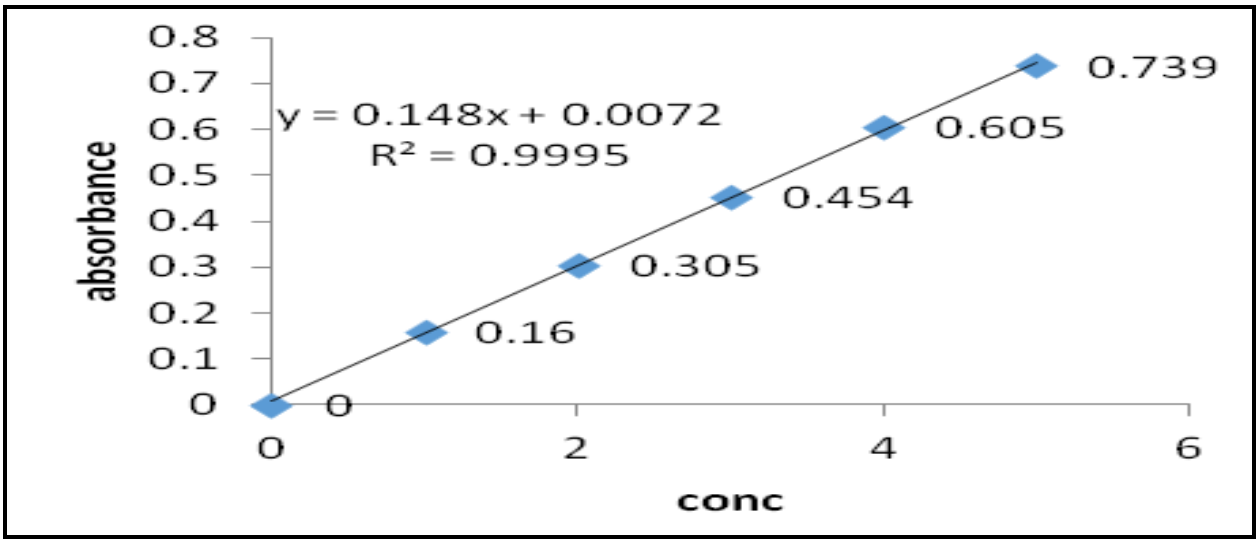

Figure No.1: Standard graph of Candesartan in 6.8pH phosphate buffer

Calibration curve data for HCTZ in pH 0.1N Hcl

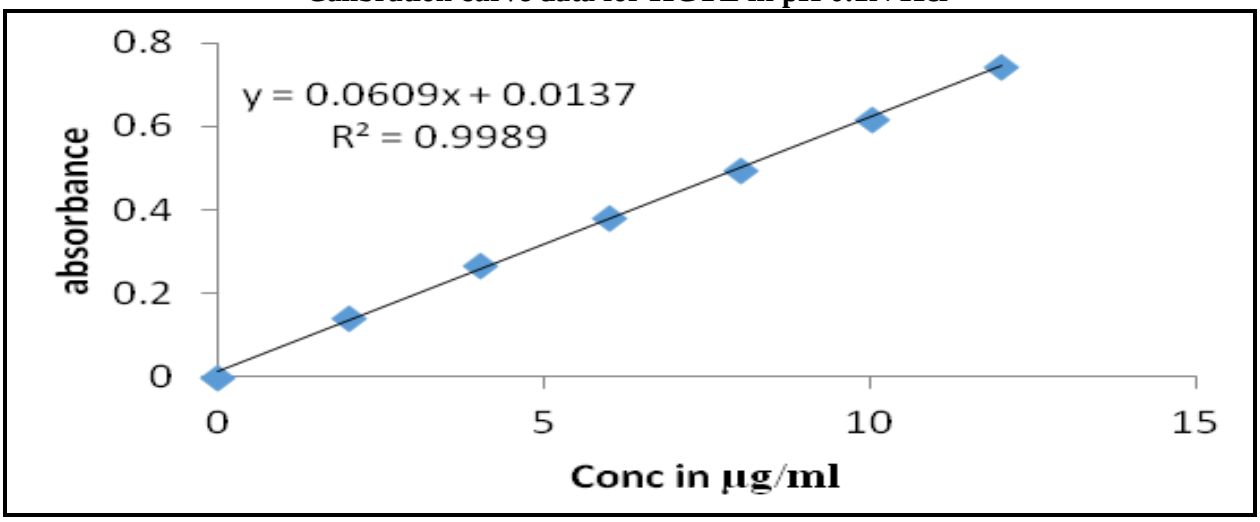

Figure No.2: Standard graph Of HCTZ in pH 0.1N HCl

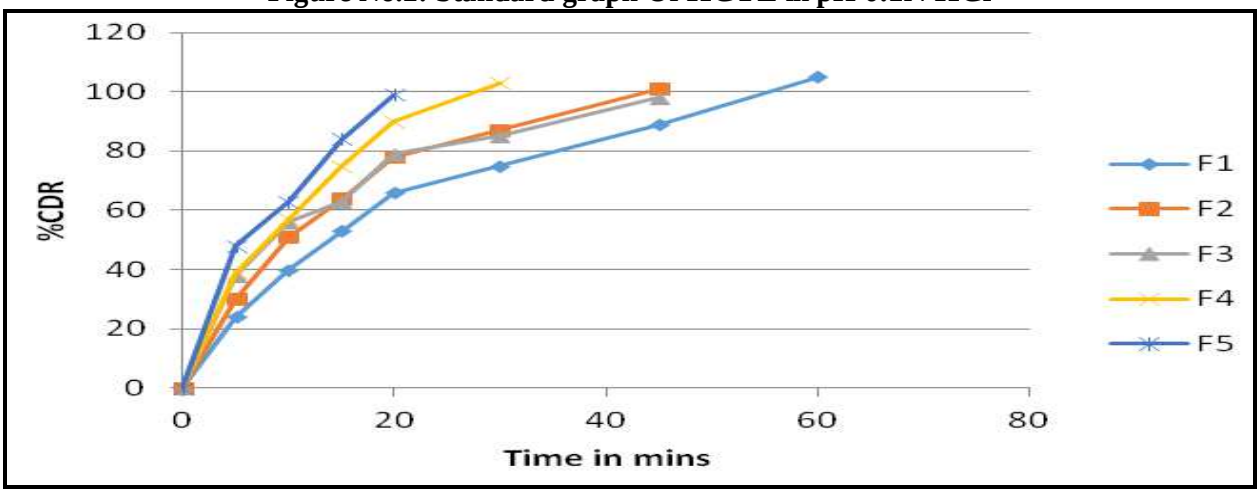

Figure No.3: Dissolution graph for formulations F1-F5

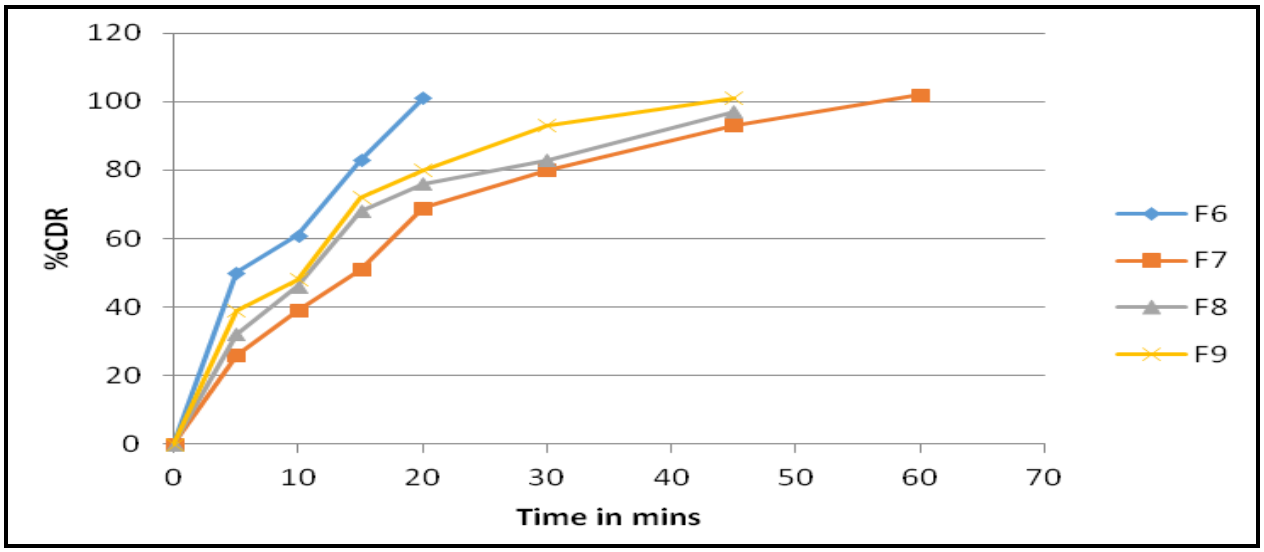

Figure No.4: Dissolution graph for formulations F6-F9

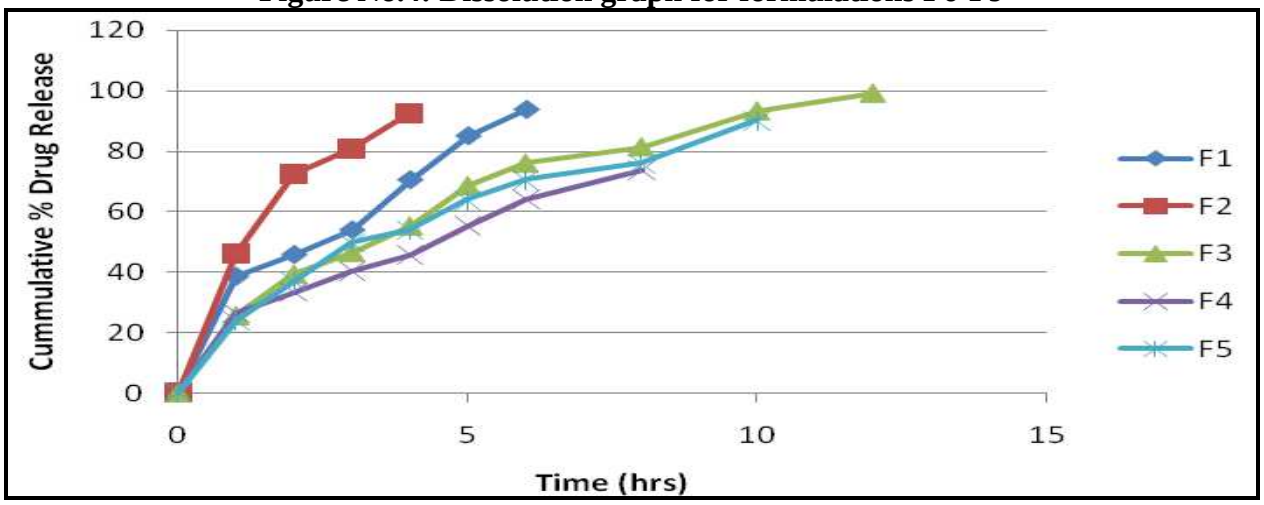

Figure No.5: Dissolution graph for formulations F1-F5

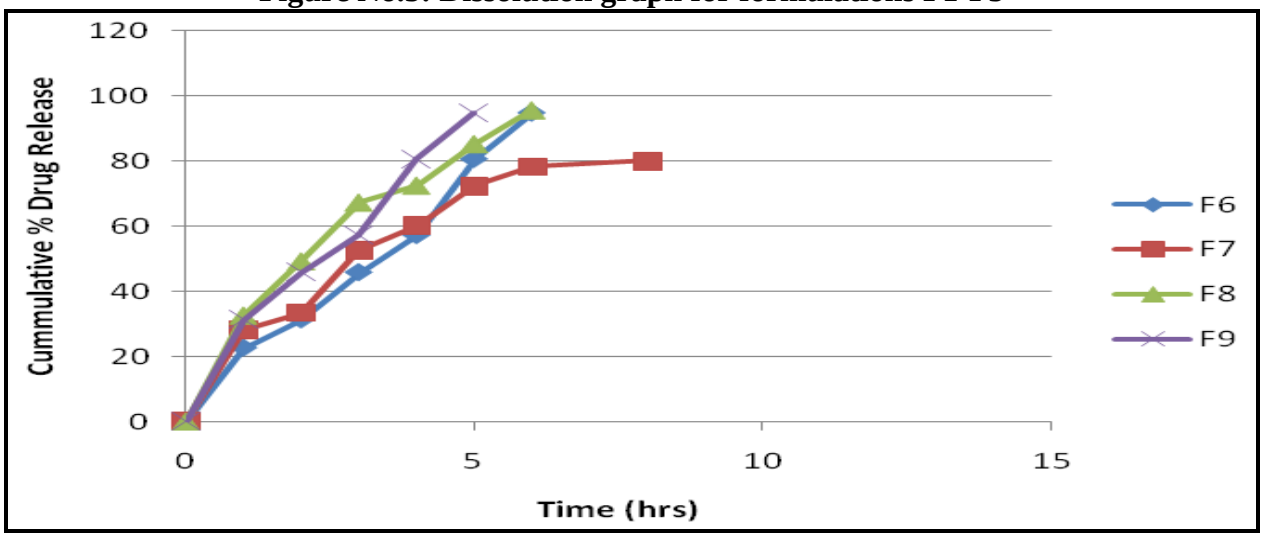

Figure No.6: Dissolution graph for formulations F6-F9

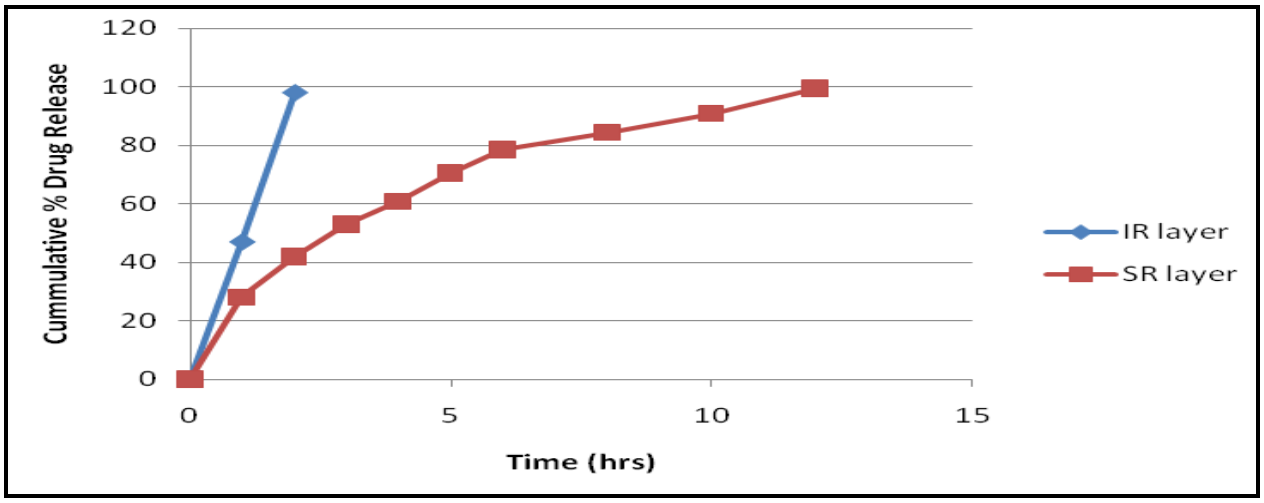

Figure No.7: Cummulative percentage drug release of bilayered tablet

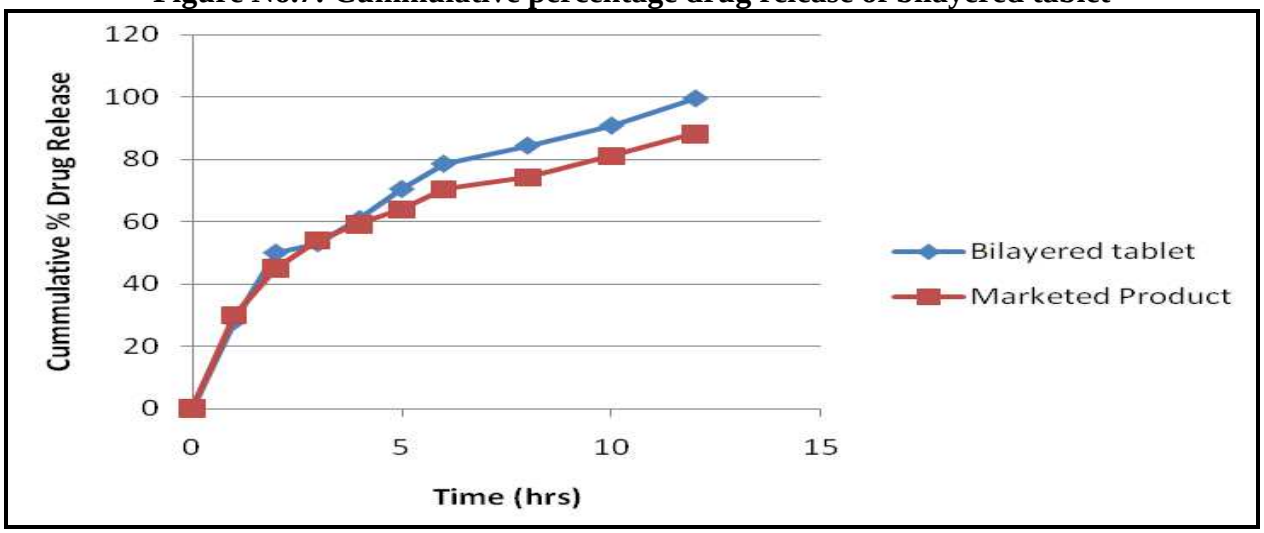

Figure No.8: Comparison of cumulative percentage drug release with that of the marketed product

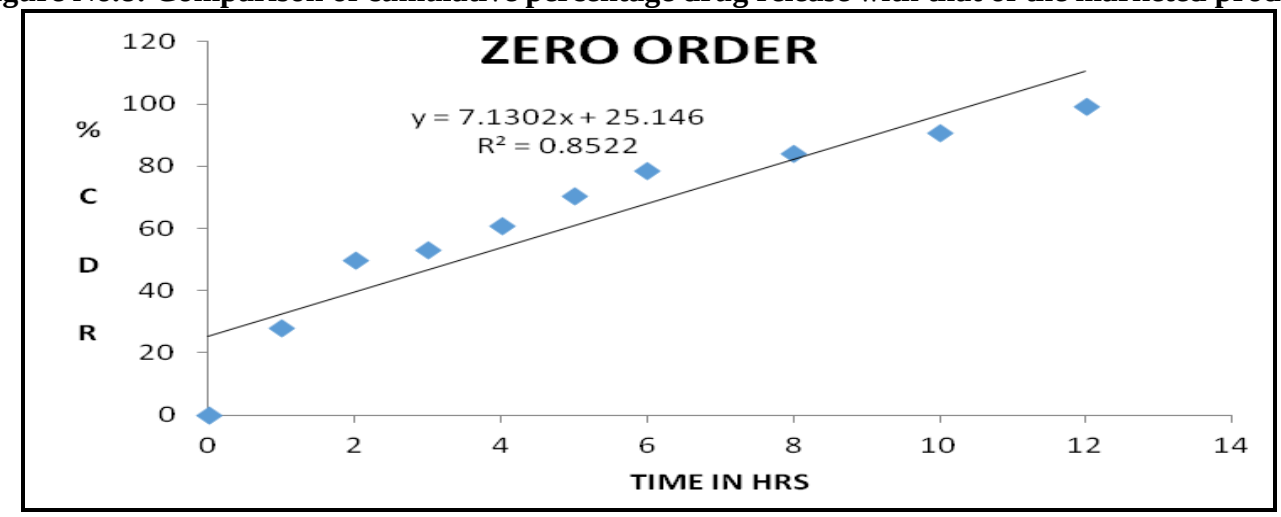

Figure No.9: Zero order graph for F3 formulation

Figure No.10: First order graph for F3 formulation

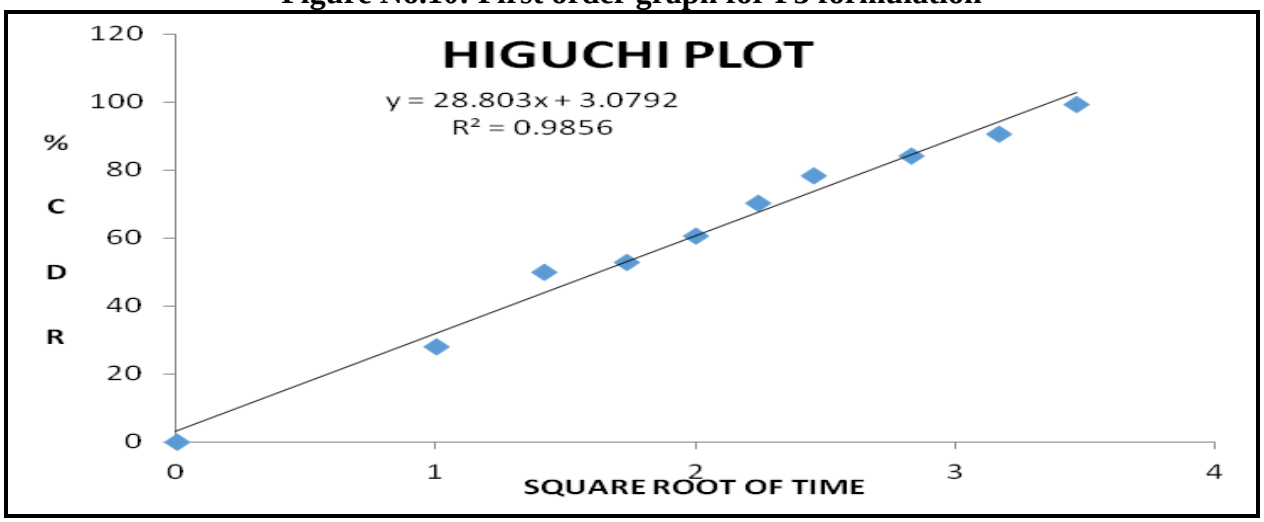

Figure No.11: Higuchis model graph for F3 formulation

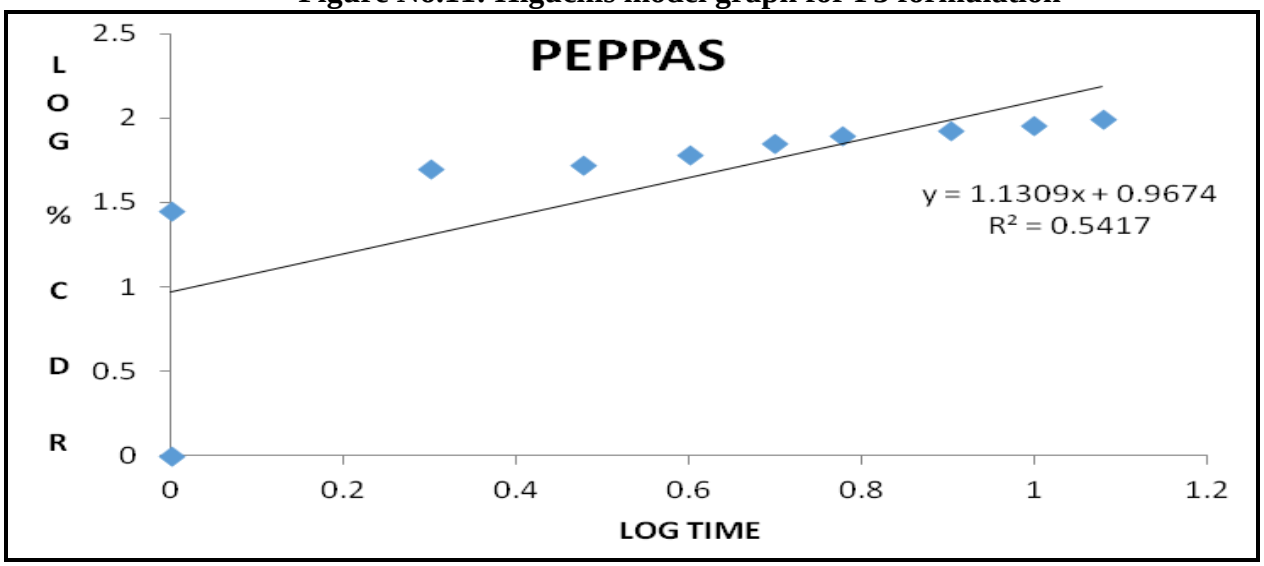

Figure No.12: Peppas model graph for F3 formulation

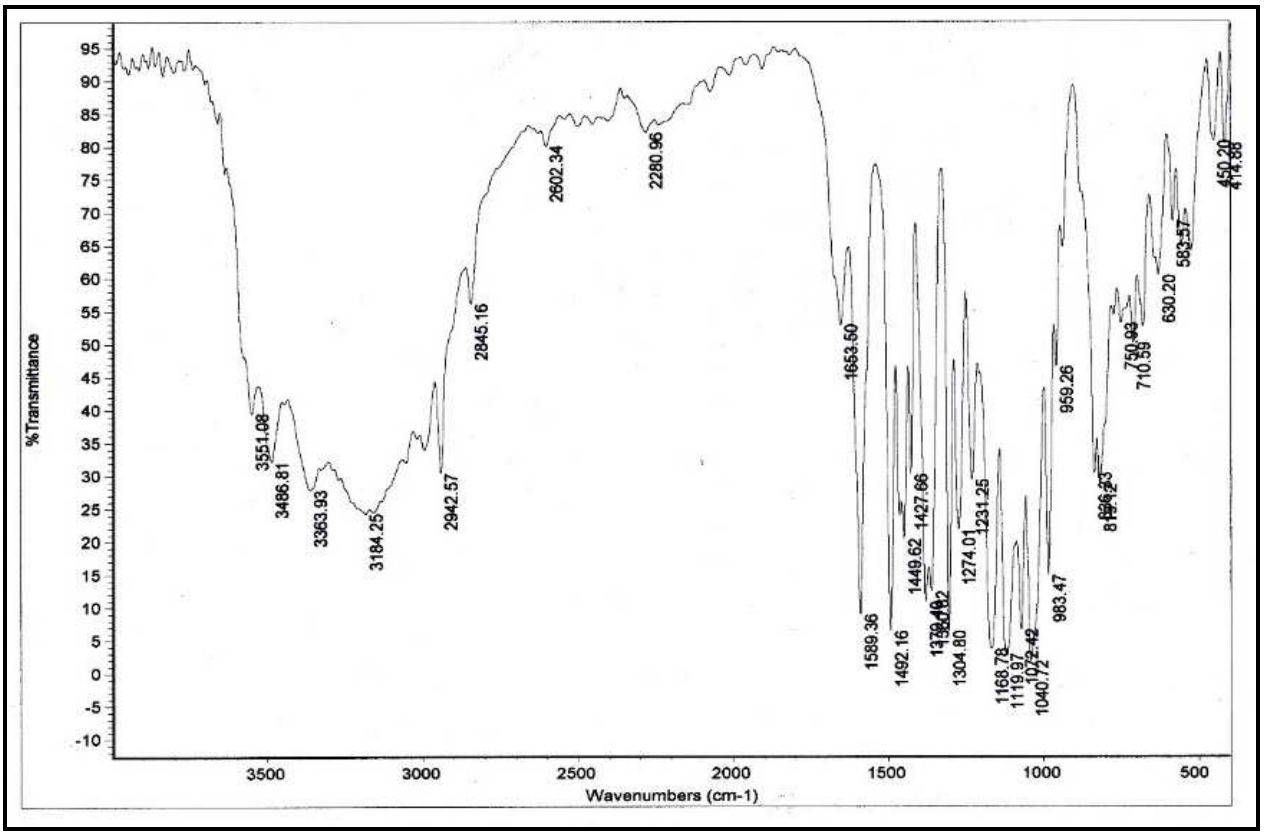

Figure No.13: FTIR of Candesartan pure drug

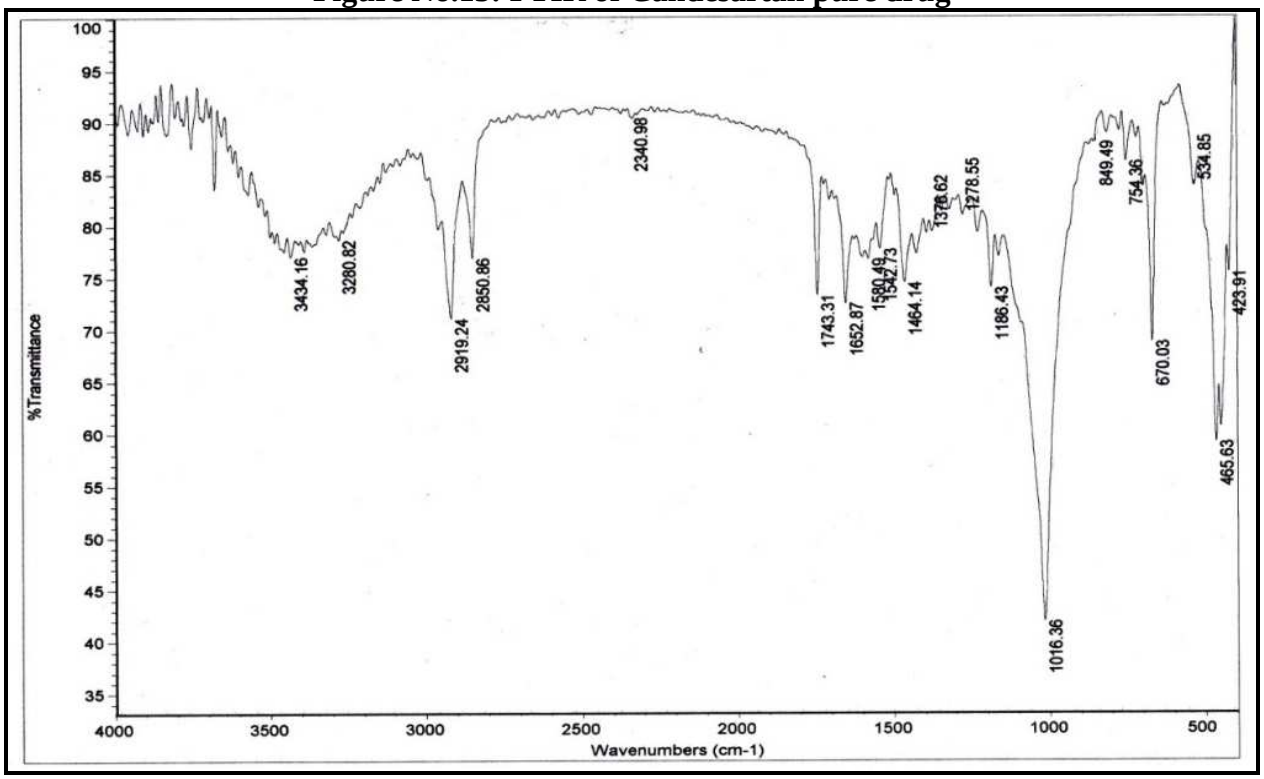

Figure No.14: FTIR of hydrochlorothiazide pure drug

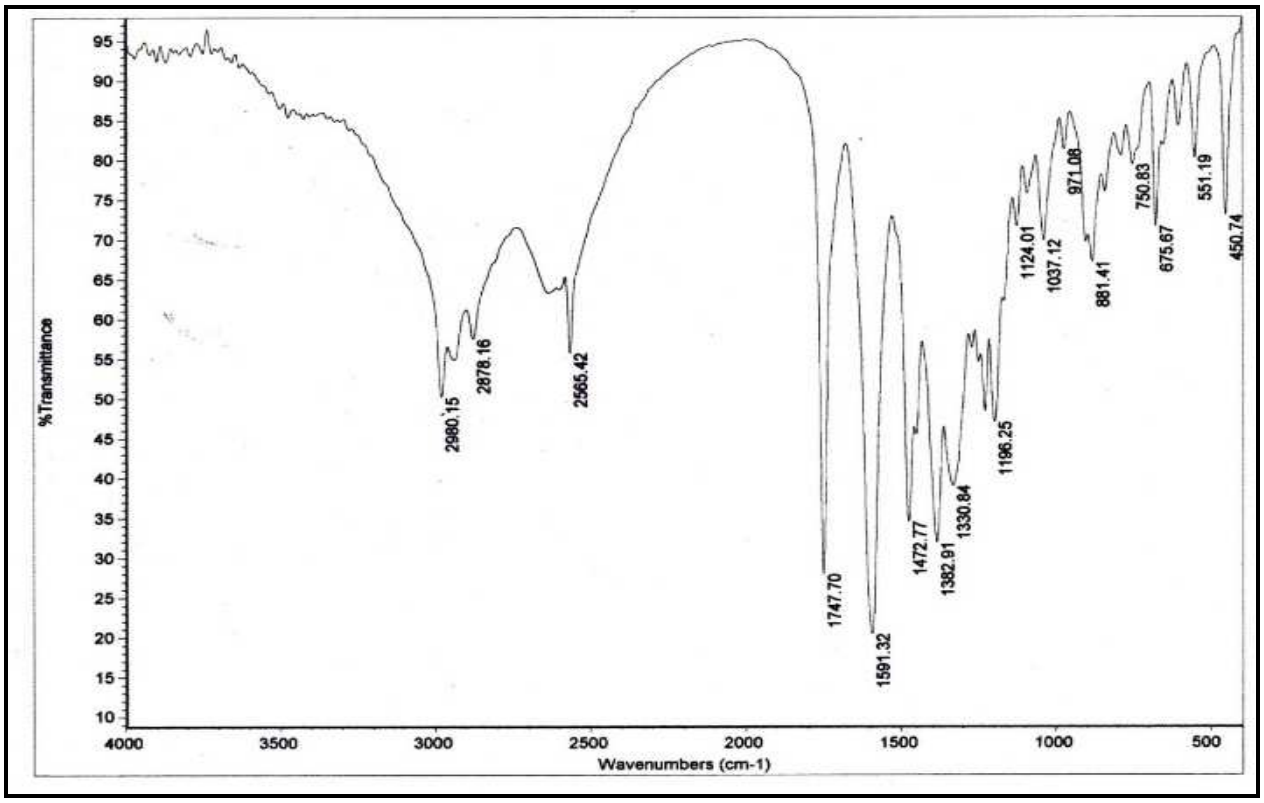

Figure No.15: FTIR of bilayered optimized formulation

CONCLUSION

Candesartan is a potent, long-acting, non-peptide tetrazole derivative, angiotensin II receptor antagonist having high selectivity for the AT1 subtype (angiotensin I). Candesartan reduces the blood pressure and is an effective antihypertensive agent in patients with mild to moderate hypertension.

The polymers and excipients along with the pure drug was found to be compatible when evaluated using FTIR.

The standard calibration curve of candesartan and hydrochlorthiazide in 6.8 phosphate buffer and 0.1N HCl respectively showed good correlation with regression value 0.999 and 0.998 respectivley.

To enhance the permeability and bioavailability, nine formulations (SR and IR) with various polymers at different concentrations were formulated.

Candesartan (16mg) and hydrochlorthiazide (12.5mg) was successfully formulated to 330mg tablet by using direct compression method.

The resulted bilayer tablet composed of HPMC K4 M 105mg (F3) and Crospovidone 13.5mg (F5) in sustained and immediate release respectively. With other excipients showed the maximum drug release in desired time.

When in-vitro dissolution studies were carried out, the optimized formula was better than marketed product with drug release 99.4% in 12hrs.

The formulation followed Zero Order and Higuchi's kinetic with the regression value 0.8522 and 0.9856 respectively.

Finally the optimized tablet was further evaluated for hardness, friability, thickness, % CDR.

The data for stability studies revealed that no considerable differences in drug content and dissolution rates for a period of 3 months as per ICH guidelines.

Resulting in improving patient compliance and convenience

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Most importantly, none of this would have been possible without the love and patience of my family and friends who has aided and encouraged me throughout this Endeavour.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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