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Research Article

Effect of Croscormellose Sodium in Sustained Release Layer of Valsartan in Bilayer Tablet with Clopidogrel as Immediate Drug Release and Valsartan as Sustained Drug Release

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Abstract

The aim of the study was to design and evaluate bilayer tablets of clopidogrel as immediate release and quick relief and valsartan for sustained release and check the effect of croscarmellose sodium (2%) in Carbopol for sustained release action. Bilayer tablets was prepared using direct compression method. Super disintegrants such as Crospovidone, Croscarmellose sodium were evaluated for immediate release of clopidogrel. Polymers HPMC K4, guar gum, ethyl cellulose and carbopol for controlling release of Valsartan. The compressed bilayer tablets were evaluated for weight variation, thickness, hardness, friability, drug content and *in vitro* drug release in 0.1N HCl and phosphate buffer pH 6.8. All the pre and post compression parameters were found to be within the acceptable limits. The formulations were optimized based on results of dissolution and formulations CF5 for immediate release & VF11 for sustained release. VF11 was formulated with addition of superdisentigrant and showed better controlled release and dissolution similar to VF8. The release kinetics of Valsartan was subject to curve fitting analysis in order to identify the best fit kinetic model. The regression analysis proves that VF11 follow first order release and drug release by diffusion process based on Fick's law of diffusion. The data for stability studies infer no considerable change in drug content, dissolution rates and other quality control test were within limits.

Keywords: Bilayer tablets, clopidogrel, valsartan, direct compression method.

1) INTRODUCTION:

Bilayer tablets are a type of oral solid dosage form consisting of two layers of compressed powders or granules of different drug substances that are arranged in a sandwich-like structure. The bilayer tablet is designed in a way that each layer can be made of different drug formulations, allowing for a combination of drugs with different release profiles or therapeutic effects.

The upper layer of the bilayer tablet is usually designed for immediate release of the drug substance, while the lower layer is formulated for delayed release or sustained release of the drug substance. The immediate-release layer provides a quick onset of action, while the delayed-release layer provides a prolonged duration of action. [1,2]

Bilayer tablets are commonly used in the pharmaceutical industry for various therapeutic applications and offer several advantages over conventional single-layer tablets, such as improved drug efficacy, reduced side effects, and better patient compliance.

Clopidogrel is an antiplatelet drug while Valsartan is an angiotensin II receptor blocker (ARBs).

Clopidogrel dose is 75mg once a day, belongs to BCS class II , half-life 6 hrs and absorption from upper part of GIT, Clopidogrel require immediate action. Therefore, it might be more suitable to incorporate clopidogrel as an immediate-release layer in the bilayer tablet formulation. This would allow for rapid drug release and absorption into the bloodstream to achieve its desired effect promptly.

Valsartan dose is 40mg, BCS class II , bioavailibility 25-35 % , well absorbed orally, half-life 6 hours, stable in Git fluid and used for long-term management of high blood pressure. It would be more beneficial to formulate valsartan as a sustained-release layer in the bilayer tablet. This would result in a slower and controlled drug release over an extended period, helping to maintain a consistent concentration of the drug in the body and provide prolonged antihypertensive effects.

Therefore, an attempt has been made in the combination of bilayer tablets of clopidogrel and valsartan.[3]

2) MATERIALS AND METHODS:

2.1 Collection of drug and excipients: Clopidogrel bisulfate, Valsartan (Cipla Ltd), Hydroxypropyl methylcellulose (HPMC), guar gum, ethyl cellulose, Carbopol (Emcure Pvt Ltd),

Polyvinylpyrrolidone (Colorcon India Pvt. Ltd), Crospovidone, Croscarmellose sodium (JRS Pharma Pvt Ltd), Magnesium stearate, talc (Emcure Pvt Ltd), Microcrystalline cellulose (Signet Chemical Coporation Pvt Ltd, Nirajan Laboratory).[4]

2.2 Preformulation Studies:

Organoleptic properties: Take a small quantity of sample and spread it on the white paper and examine it visually for colour, odour and texture.

Solubility studies: Different solvents were subjected for solubility studies of clopidogrel and valsartan can be practically insoluble in water. An excess amount (saturation point) of the sample was placed in contact with distilled water. The samples were shaken for 24 hours in an orbital shaker. The supernatant was filtered through a whatmann filter paper. The filtrate was suitably diluted to 10 ppm and analyzed spectrophotometrically at 272 nm & 342 nm. All experiments were conducted in triplicate.

Melting point: Determination of melting point of drug was done by capillary method using melting point apparatus.

Determination of λmax: The solution was taken to determine absorption maxima. Initially blank buffer solution was kept and scanned in the region of 200-400nm. Then sample was kept for analysis and scanned in the same region.[5,6]

Calibration curve of clopidogrel:

Preparation of standard stock solution: 10 mg of Clopidogrel was dissolved in 10ml of 0.1N HCl from this 1 ml was taken and made upto 10 ml to give a concentration of (1000 µg/ml).

Scanning: From the stock solution 100 µg/ml was prepared in 0.1N HCl and UV scan was taken between 200 to 400 nm.

Calibration curve of Clopidogrel in 0.1N HCl: The standard solutions were prepared by proper dilutions of the primary stock solution with absolute 0.1N HCl to obtain working standards in the concentration range of 5-30 µg/ml of pure sample of Clopidogrel.

Preparation of sample solution: Samples were taken from dissolution medium at different time intervals. From these different concentrations were made 2,4,6,8,10 µg/ml. The absorbance was observed at 272 nm respectively using UV visible spectrophotometer (Lab India UV 3000+). Then calibration curve of clopidogrel was plottted as the graph between absorbance value (nm) on Y-axis and concentration (µg/ml) on X-axis.

Calibration curve of valsartan:

Preparation of standard stock solution: 10 mg of Valsartan was dissolved in few ml of methanol and make up to 10 ml with 6.8 phosphate buffer , from it 1 ml was taken and made uto 10ml to give a concentration of (1000 µg/ml)

Scanning: From the stock solution 100µg/ml was prepared in 6.8 phosphate buffer and UV scan was taken between 200 to 400 nm.

Calibration curve of Valsartan in 6.8 phosphate buffer:

The standard solutions were prepared by proper dilutions of the primary stock solution with 6.8 phosphate buffer to obtain working standards in the concentration range of 5-30 µg/ml of pure sample of Valsartan.

Preparation of sample solution: Samples were taken from dissolution medium at different time intervals. From these different concentrations were made 2,4,6,8,10 µg/ml. The absorbance was observed at 342 nm respectively using UV visible spectrophotometer (Lab India UV 3000+). Then calibration curve of clopidogrel was plottted as the graph between absorbance value (nm) on Y-axis and concentration (µg/ml) on X-axis.[7,8]

Drug – excipient compatibility study:

FTIR spectrum was taken for pure drug and physical mixture of excipients with drug were the results revealed that there was no physical change observed. Hence the selected excipients were suitable for the preparation of matrix tablets.[9]

2.3 Formulation and Development:

Formulation development of valsartan as sustained release:

The sustained release ingredients were accurately weighed and added into the blender in ascending order. The powder mix was blended for 20 min. to obtain uniform distribution of the drug in formulation and subjected for preformulation studies. Tablets were prepared by direct compression method with 14 mm stainless steel punch using rotary press (Karnavati Minitab, India). Compression force for all the tablets was adjusted to get tablets of hardness 4-6 kg/cm^2 . Hardness was measured by Monsanto type hardness tester (Coslab).[10,11]

Table 1: Composition of various tablets prepared valsartan as SR layer

Ingredients	VF1	VF2	VF3	VF4	VF5	VF6	VF7	VF8	VF9	VF10	**VF11**
Valsartan	40	40	40	40	40	40	40	40	40	40	**40**
Guar gum	60	-	-	-	90	-	-	-	-	30	**-**
HPMC K4	-	60	-	-	-	90	-	-	-	-	**-**
Ethyl cellulose	-	-	60	-	-	-	90	-	30	-	**-**
Carbopol	-	-	-	60	-	-	-	90	60	60	**90**
Croscarmellose	-	-	-	-	-	-	-	-	-	-	**6**
Poly vinyl pyrrolidine K30	15	15	15	15	15	15	15	15	15	15	**15**
Talc	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	**7.5**
Magnesium Stearate	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	**7.5**
Micro crystalline cellulose	170	170	170	170	140	140	140	140	170	170	**134**
Total weight	300	300	300	300	300	300	300	300	300	300	**300**

Formulation development of clopidogrel as immediate release:

The immediate release ingredients were accurately weighed and added into the blender in ascending order. The powder mix was blended for 20 minutes to obtain uniform distribution of the drug in formulation and subjected for preformulation studies. All the formulation components were passed through sieve #60, weighed, mixed, and compressed into tablet using 14 mm punch on Rotary tablet minipress-I.[12,13]

Table 2: Composition of various tablets prepared clopidogrel as IR layer

Ingredients (mg)	CF1	CF2	CF3	CF4	**CF5**	CF6	CF7
Clopidogrel	75	75	75	75	**75**	75	75
Crospovidone	6.25	-	12.5	-	**18.75**	-	25
Croscarmellose	-	6.25	-	12.5	**-**	18.75	-
Polyvinylpyrolidone	12.5	12.5	12.5	12.5	**12.5**	12.5	12.5
Magnesium stearate	6.25	6.25	6.25	6.25	**6.25**	6.25	6.25
Talc	6.25	6.25	6.25	6.25	**6.25**	6.25	6.25
Micro crystalline cellulose	143.75	143.75	137.5	137.5	**131.25**	131.25	112.5
Total weight	250	250	250	250	**250**	250	250

Formulation of Bilayer Tablet: In the present study bilayer tablet was prepared manually using multiple station punching machine. Accurately weighed amount of sustained release powder mix was fed manually into die cavity. Sustained release layer was compressed at mild compression force. After that accurately weighed immediate release powder mix was manually fed into the die on sustained release layer and compressed using 14 mm circular shape flat punch on Rotary tablet minipress-I. CF5 batch from clopidogrel immediate release layer and VF11 batch from valsartan sustained release layer were selected to form Optimized bilayer tablet by direct compression method. Composition of bilayer tablet was shown in table no.3[14,15]

Table 3: Formulation of optimize bilayer tablet of clopidogrel immediate release layer and valsartan sustained release layer.

S.NO.	**Formulation of clopidogrel Immediate release Layer (CF5)**		**Formulation of valsartan sustained release Layer (VF8)**	
	Ingredients	**Formulation**	**Ingredients**	**Formulation**
1	Clopidogrel	75	Valsartan	40
2	Crospovidone	18.75	Carbopol	90
3	Poly vinyl pyrrolidine K30	12.5	Poly vinyl pyrrolidine K30	15
4	Talc	6.25	Talc	7.5
5	Magnesium stearate	6.25	Magnesium Stearate	7.5
6	Micro crystalline cellulose	131.25	Micro crystalline cellulose	140
7	Total weight	250	Total weight	300
Total weight of the tablet = 550				

TABLET CHARECTERIZATION:

Flow Properties:

1) Angle of Repose: The flow property was determined by measuring the Angle of Repose. In order to determine the flow property, the Angle of Repose was determined. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal.

Angle of repose= $\tan^{-1}$ (h/r)

Where,

h = height of a pile (2 cm)

r = radius of pile base.

2) Bulk density: Bulk density of a compound varies substantially with the method of crystallization, milling or formulation. Bulk density was determined by pouring blend into a graduated cylinder. The bulk volume and weight of the powder was determined. The bulk density was calculated by using the following formula.

Bulk density=Weight of sample in gram/ volume occupied by the sample

3) Tapped density: It is the ratio of total mass of the 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. If the difference between the two volumes is less than 2%, this volume is considered as final tapped volume. The tapped density was calculated by using the following formula

Tapped density= Wt of sample in gram/Tapped volume

4) Compressibility Index or Carr's Index: Carr's index is measured using the values of bulk density and tapped density. The following equation is used to find the Carr's index.

% Compressibility =

Tapped density-Bulk density/Tapped density×100

5) Hausner's ratio: It indicates the flow properties of the powder and ratio of tapped density to the bulk density of the powder or granules.[16,17]

Hausner ratio= tapped density/ bulk density

EVALUATION OF TABLETS
Post compression parameters

1) Thickness and diameter: Thickness of tablet is important for uniformity of tablet size. Thickness was measured using vernier caliper. It was determined by checking ten tablets from each batch.

2) Hardness test: The resistance of tablets to breakage, under conditions of storage, transportation or handling before usage depends on its hardness. The hardness of tablet was measured by Monsanto hardness tester. Ten tablets from the batch were used for hardness studies and results are expressed in Kg/cm^2.[18]

3) Weight variation test: Ten tablets were selected at random, individually weighed in a single pan electronic balance and the average weight was calculated.

Table 4: The uniformity of weight was determined according to I.P specification

S.No.	Average weight of tablet	Percentage
1	80 mg or less	± 10%
2	More than 80mg and less than 250mg	± 7.5%
3	250 mg or more	± 5%

4) Friability: This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Initial weight of 20 tablets is taken and these are placed in the friabilator, rotating at 25 rpm for 4min. The difference in the weight is noted and expressed a percentage. It should be preferably between 0.5 to 1.0%.

$$\%friability = (W_1-W_2)/W_1 \times 100$$

Where, W_1= weight of tablets before test

W_2 = weight of tablets after test

5) Disintegration test: For a drug to be absorbed from a solid dosage form after oral administration, it must be in solution, and the first important step toward this condition is usually the break-up of the tablet; a process known as disintegration. The disintegration test is a measure of the time required under a given set of conditions for a group of tablets to disintegrate into particles which will pass through a 10 mesh screen. Generally, the test is useful as a quality assurance tool for conventional dosage forms.[19]

Disintegration time: Uncoated tablet for immediate release: 5-30 minutes.

Uncoated tablet for sustained release: 8-12 hrs.

6) *In vitro* Dissolution Studies for immediate release layer of Clopidogrel: *In vitro* drug release studies were carried out using USP XXIV dissolution apparatus type II, with 900ml of dissolution medium maintained at 37±5°C for 1 hr, at 75 rpm, 0.1 N HCl was used as a dissolution medium. 5ml of sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn were filtered through 0.45µ membrane filter, and drug release in each sample was analyzed after suitable dilution by UV Spectrophotometer at 272nm.

Dissolution Conditions:

Medium : 0. 1N HCl
Type of Apparatus: USP –XXIV (paddle type)
RPM : 75
Volume : 900 mL
Run time : 1hour
Temperature : 37± 0.5° C

7) *In vitro* dissolution studies of Valsartan: *In vitro* drug release studies were carried out using USP XXIV dissolution apparatus type II, with 900ml of dissolution medium maintained at 37± 0.5°C for 12 hr, at 50 rpm, 6.8 phosphate buffer was used as a dissolution medium 5ml of sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn were filtered through 0.45µ membrane filter, and drug release in each sample was analyzed after suitable dilution by UV Spectrophotometer at 342nm.

Dissolution Conditions:

Medium : 6.8 phosphate buffer
Type of Apparatus : USP –XXIV (paddle type)
RPM : 50
Volume : 900mL
Run time : 12 hours
Temperature : 37±0.5° C
Time intervals : 0.5, 2, 4, 6, 8, 10, 12 hrs

8) Kinetic Studies: The following plots were made: cumulative % drug release vs time (zero order kinetic model);log cumulative of % drug remaining vs time (first order kinetic model); cumulative % drug release vs square root of time (higuchi model); cumulative % drug release vs time (peppas model). The regression coefficient R^2 value nearer to 1 indicates the model best fits the release mechanism

9) Stability studies: The formulation CF5 & VF11 was selected and the stability studies were carried out at 25±2°C, 60±5°C % RH (Long term stability condition), 30 ±2°C, 65±5°C % RH (intermediate condition) and 40±2°C, 75±5°C (accelerated conditions), the tablets were packed in amber colour screwcap container and kept in above said condition for period of six months. The tablets were analyzed periodically for their physical appearance and *in-vitro* drug release.

10) Dissolution study of Clopidogrel and Valsartan from bilayer tablet: The dissolution studies of optimized clopidogrel and valsartan bilayer tablet was studied by conducting dissolution using USP Type II dissolution apparatus. Tablets were placed in 900ml of 0.1N HCL at 37±0.5° C at 75 rpm for 1 hour and then changed to 900ml of 6.8 phosphate buffer at 37±0.5° C at 50 rpm. 5ml of sample were withdrawn at the intervals of every 10 min initially for one hour in 0.1 in 0.1N HCl and then in 6.8 phosphate buffer samples were withdrawn every 1 hour. Sampling was carried out and every time replaced with fresh 5ml of buffer. The absorbance of solution was recorded at 275 nm for clopidrogel and 342 nm for Valsartan using buffer as blank. The result was calculated as Percentage drug release of clopidogrel and valsartan.[20,21]

3) RESULTS AND DISCUSSION:

3.1 Preformulation Studies:

a. Organoleptic properties

Table 5: Organoleptic Properties Of clopidogrel & valsartan:

S.No.	Organoleptic Properties Of clopidogrel		Organoleptic Properties Of valsartan	
	Parameters	**Drug**	**Parameters**	**Drug**
1	Colour	White, crystalline powder,	Colour	White, crystalline powder,
2	Odour	Odorless	Odour	Odorless
3	Taste	Slightly bitter	Taste	Bitter
4	Appearance	Fine crystalline powder	Appearance	Fine crystalline powder

b. Melting point determination:

Table 6: Melting point determination of both clopidogrel & valsartan.

Drug	Reported melting point	Observed melting point
Clopidogrel	158-160°C	158°C
Valsartan	116-117°C	116°C

Observation: The melting point of clopidogrel & valsartan observed melting point was found to be 158°C & 116°C.

C. Solubility results

Table 7: solubility of clopidogrel and valsartan in various solvents.

Solvents	Solubility of clopidogrel	Solubility of valsartan
Chloroform	0.05 mg/ml	0.15mg/ml
Water	0.001 mg/ml	0.005 mg/ml
Methanol	0.25 mg/ml	0. 35 mg/ml
Ethanol	0.25 mg/ml	0.45 mg/ml
0.1NHCL	0. 15mg/ml	0. 15mg/ml
6.8 phosphate buffer	0. 09mg/ml	0.20 mg/ml

Observation: clopidogrel was found to soluble in methanol, ethanol and 0.1NHCL

Valsartan was found to be soluble in methanol, ethanol 6.8 phosphate buffer.

D. UV-Spectroscopy-Analysis of Drug

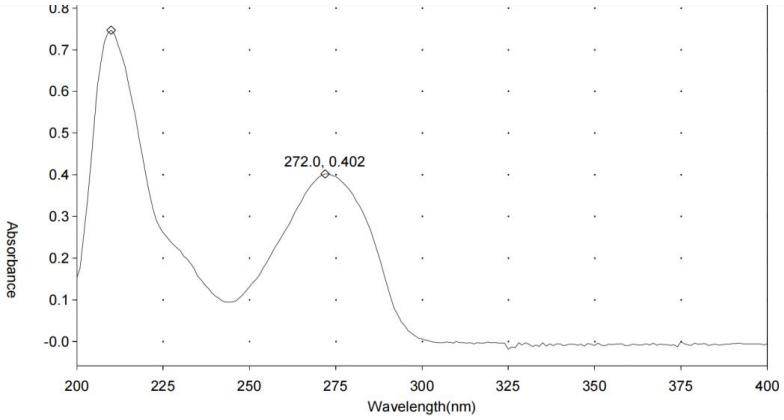

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Figure 1: Determination of λ max of clopidogrel in 0.1NHCLby thermospectronic-vision prosoftware V1.06

Observation: Solution of clopidogrel concentration of 10 ug/ml was scanned in the range of wavelength 200-300 nm. The absorption spectrum was found to be sharp and maximum at wavelength of 272nm therefore , it was selected as the wavelength for detection in 0.1NHCl.

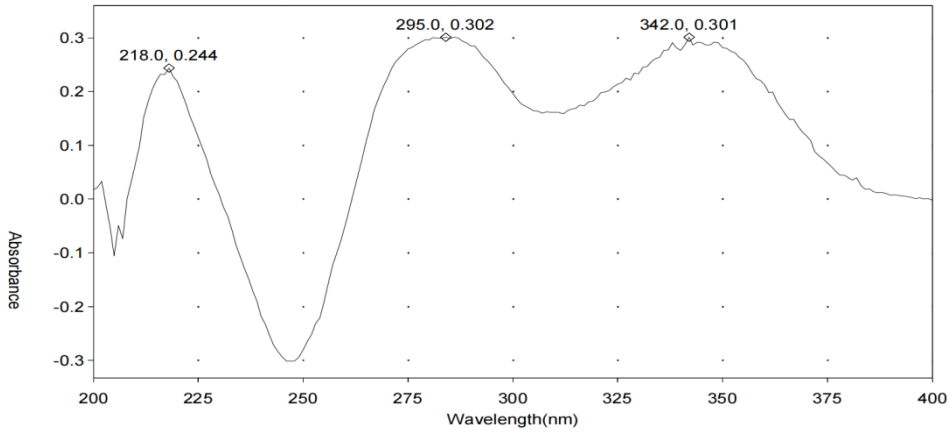

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Figure 2: Determination of λ max of valsartan in phosphate buffer 6.8 by thermospectronic-vision prosoftware V1.06

Observation: Solution of valsartan concentration of 10 ug/ml was scanned in the range of wavelength 200-400 nm. The absorption spectrum was found to be sharp and maximum at wavelength of 342nm therefore , it was selected as the wavelength for detection in phosphate buffer pH6.8

E. Calibration curve:

Table 8: CALIBRATION CURVE DATA OF CLOPIDOGREL IN 0.1 N HCL & VALSARTAN PHOSPHATE BUFFER 6.8

S.No.	calibration curve data of clopidogrel		calibration curve data of valsartan	
	Concentration	Absorbance at 272nm	Concentration	Absorbance at 342nm
1	0	0	0	0
2	5	0.125±0.015	5	0.25±0.02
3	10	0.223± 0.026	10	0.300±0.081
4	15	0.351±0.030	15	0.584±0.051
5	20	0.466±0.051	20	0.732±0.068
6	25	0.540±0.047	25	0.861±0.074
7	30	0.691±0.054	30	0.923±0.078
	Standard deviation n=3		Standard deviation n=3	

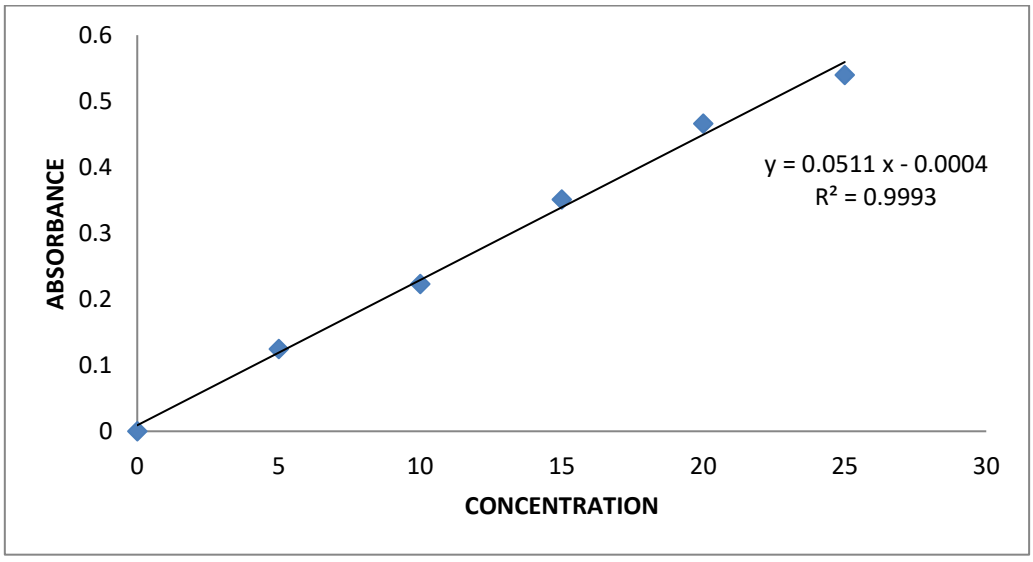

Figure 3: calibration curve data of clopidogrel.

Observation:- R^2 value of clopidogrel was found to be 0.9993 and indicate that it obeys beer's lambert's law in concentration range of 2-10 µg/ml. The standard graph of clopidogrel showed good linearity with R^2 of 0.9993, which indicates that it obeys "Beer- Lamberts" law

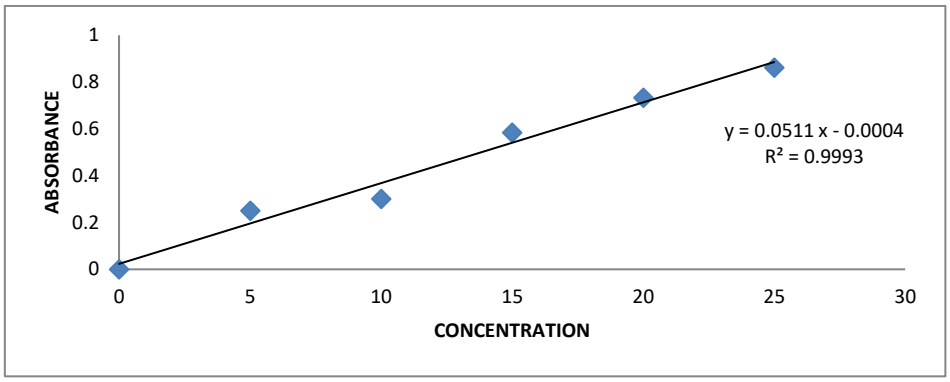

Figure 4: calibration curve data of valsartan.

Observation:- R^2 value of valsartan was found to be 0.9993 and indicate that it obeys beer's lambert's law in concentration range of 2-10 µg/ml. The standard graph of clopidogrel showed good linearity with R^2 of 0.9993, which indicates that it obeys "Beer- Lamberts" law

F(i)-Drug excipient compatibility for clopidogrel by FTIR Spectroscopy:

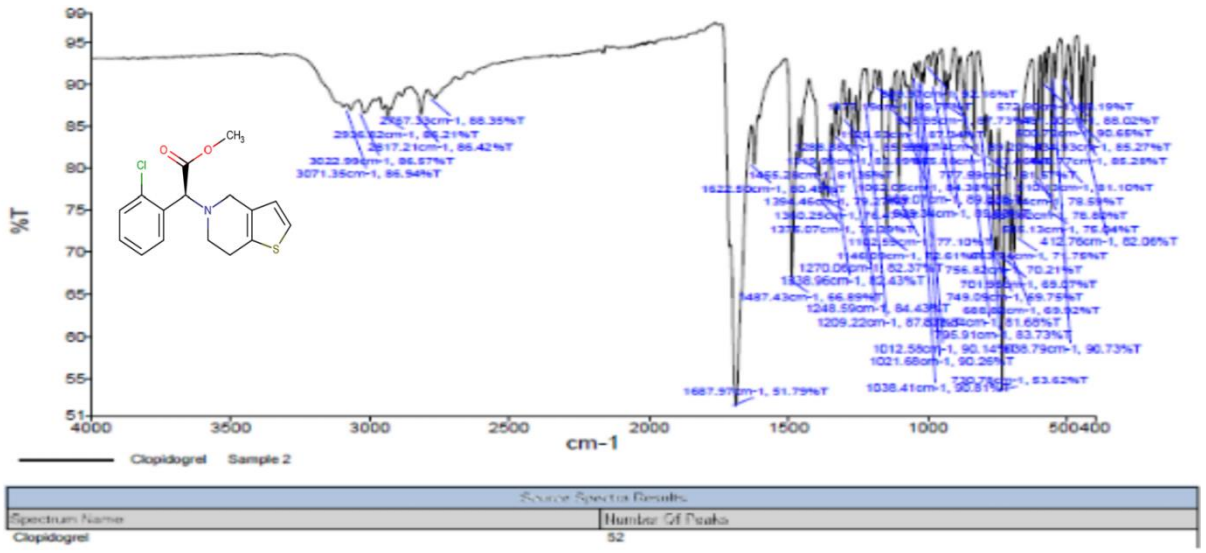

Figure 5: FTIR spectra of clopidogrel pure drug.

Observation: No peak change in the FTIR spectra of clopidogrel pure drug.

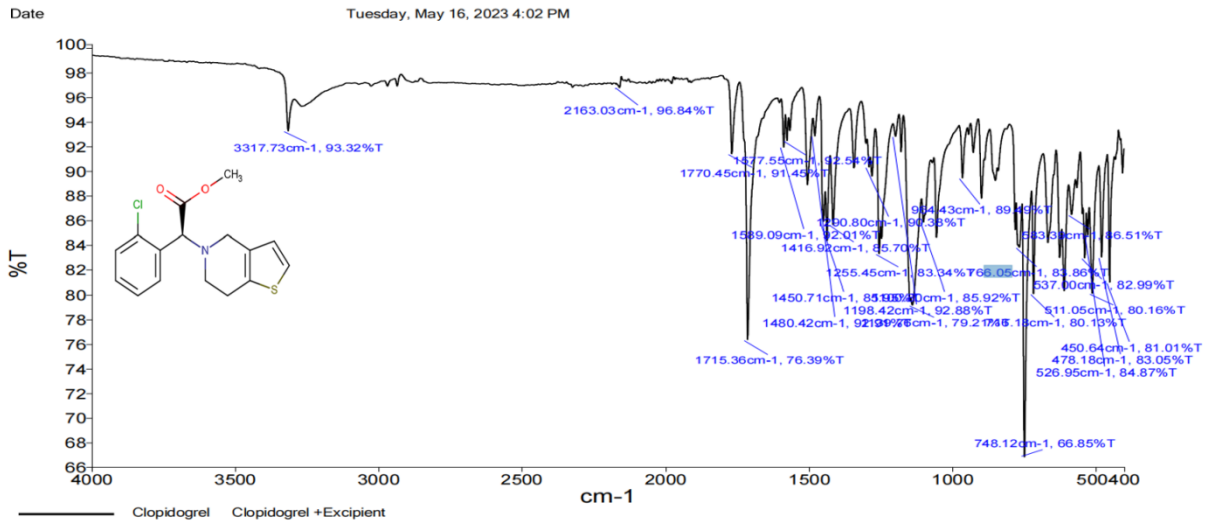

Figure 6: FTIR spectra of clopidogrel + excipient.

Observation: There are no change of functional group as it is assume there is no interaction between clopidogrel+excipient

F(ii)-Drug excipient compatibility for valsartan by FTIR Spectroscopy:

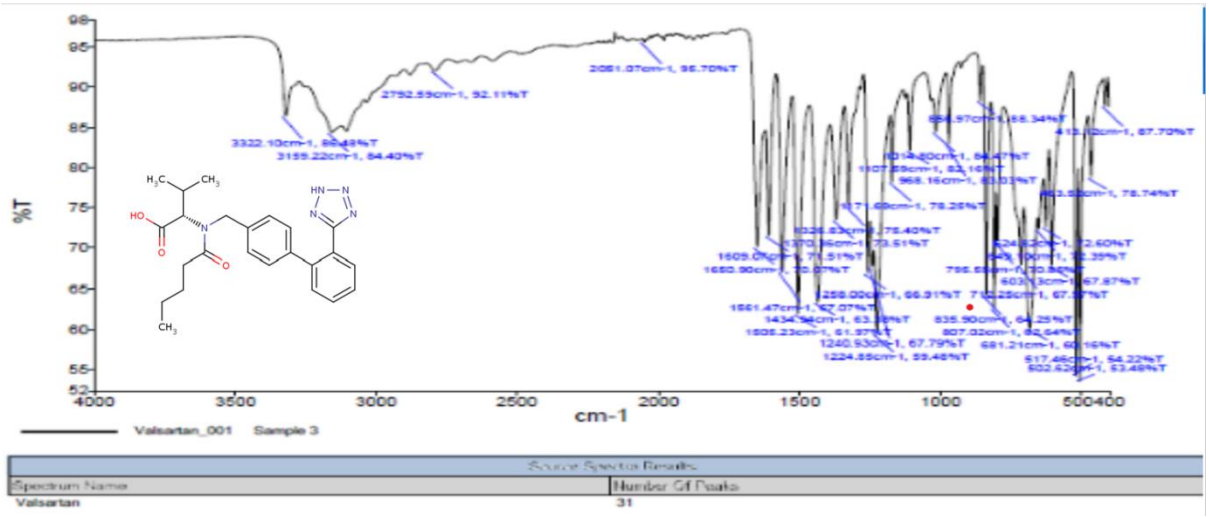

Figure 7: FTIR spectra of valsartan pure drug.

Observation: No peak change in the FTIR spectra of valsartan pure drug.

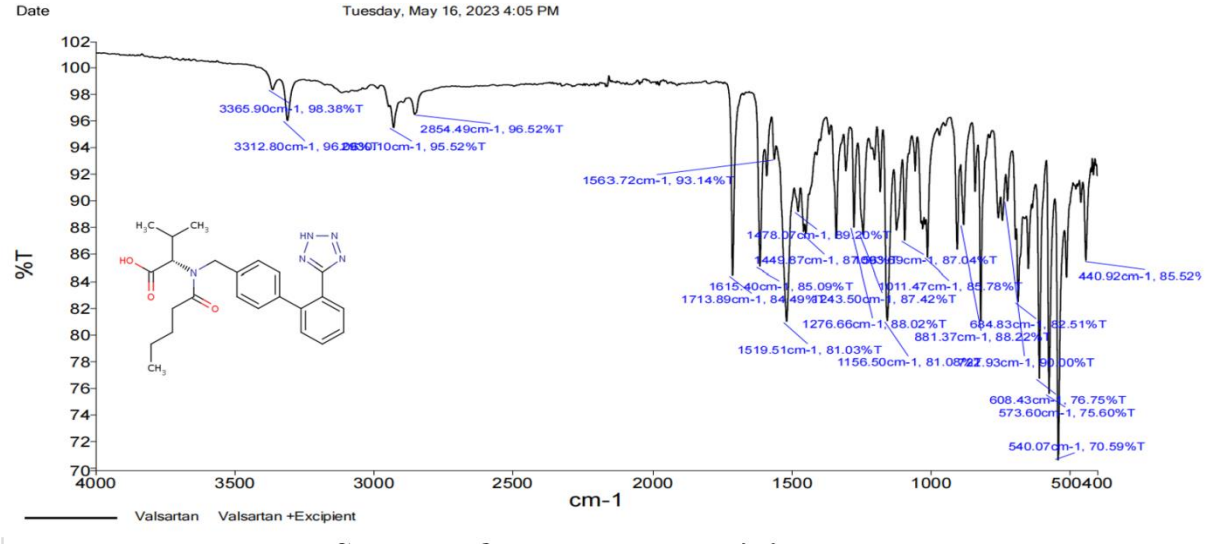

Figure 8: FTIR spectra of valsartan + excipient.

Observation: There are no change of functional group as it is assume there is no interaction between valsartan+excipient

Discussion: Infrared studies were carried out to confirm the compatibility between the drug and selected excipients. From the spectra it was observed that there was no major shifting, as well as, no loss of functional peaks between the spectra of the drug and excipients. This indicated no interaction between the drug and other excipients

3.2-EVALUATION OF PRE & POST COMPRESSION PARAMETERS FOR CLOPIDOGREL AND VALSARTAN:

Evaluation parameters of powder blend for clopidogrel (immediate release layer) & valsartan (sustained release layers):

The powder blends of both immediate release and sustained release layer of different formulations of bilayer tablets were evaluated for various physical properties. The bulk densities for the powder blend of immediate release and sustained release layer of various formulations values indicated satisfactory flow behaviour.

Evaluation of optimized bilayer tablet of clopidogrel immediate release layer and valsartan sustained release Layer:

Optimized bilayer tablet was prepared from optimized Formulation of clopidogrel immediate release Layer (CF5) and valsartan sustained release Layer (VF11). This tablet was subjected only to *in vitro* drug release study to check the drug release was as per given specifications

Evaluation of precompression and post compression parameters of Bilayer Tablet:

All the Prepared tablet formulations were subjected for precompression and post compression evaluation such as bulk density, tapped density, Hausner's ratio and Carr's index. Results of precompression evaluations of formulation mixtures are shown in

table(9,10,11,12). From the results of Compressibility (Carr's) index and Hausner's ratio it can be clearly concluded that the clopidogrel & valsartan tablet blend were having excellent flow properties, fair to good compressibility. All the prepared bilayer tablets were subjected to compendial test for post compression evaluation such as friability, hardness, thickness, uniformity of weight, disintegration time & content uniformity results.

3.2.1 PRECOMPRESSION EVALUATION OF CLOPIDROGEL:

Table 9: Results of precompression evaluation of clopidogrel immediate release layer.

Formulations	Angle of Repose (θ)	Loose bulk density (g/ml)	Tapped density (g/ml)	%Compressibility
CF1	23.7	0.31	0.36	13.88
CF2	27.6	0.29	0.35	17.14
CF3	25.5	0.34	0.42	19.04
CF4	26.7	0.35	0.41	14.63
CF5	**24.5**	**0.41**	**0.48**	**14.58**
CF6	26.4	0.40	0.47	14.89
CF7	25.2	0.37	0.43	13.95

3.2.2 POST COMPRESSION EVALUATION OF CLOPIDROGEL TABLET

Table 10: Results of post compression evaluation of clopidogrel immediate release layer.

Formulations	Average weight (mg)	Thickness (mm)	Hardness Kg/cm²	Friability (%)	Disintegration Time	Drug content (%)
CF1	248	3.04	5	0.16	32 sec	96.9
CF2	249	3.12	5	0.20	32 sec	99.4
CF3	247	3.20	5	0.14	24 sec	97.6
CF4	249	3.16	5	0.12	25 sec	99.4
CF5	**250**	**3.15**	**5**	**0.15**	**18 sec**	**98.7**
CF6	251	3.19	5	0.19	20 sec	98.5
CF7	250	3.20	5	0.18	20 sec	98.7

3.3.1 PRECOMPRESSION OF VALSARTAN TABLETS

Table 11: Results of precompression evaluation of valsartan sustained release layer.

Formulations	Angle of Repose (θ)	Loose bulk density (g/ml)	Tapped density (g/ml)	%Compressibility
VF1	24.32	0.30	0.36	16.66
VF2	23.15	0.34	0.40	15.00
VF3	22.40	0.32	0.37	13.51
VF4	23.45	0.29	0.37	21.62
VF5	23.32	0.37	0.43	11.62
VF6	22.05	0.37	0.46	20.05
VF7	21.42	0.31	0.38	18.42
VF8	21.50	0.33	0.40	17.05
VF9	22.37	0.32	0.39	17.94
VF10	21.01	0.38	0.43	13.51
VF11	**21.45**	**0.31**	**0.39**	**17.05**

3.3.2 POST COMPRESSION EVALUATION OF VALSARTAN TABLET

Table 12: Results of post compression evaluation of valsartan sustained release layer.

Formulations	Average Weight (mg)	Thickness (mm)	Hardness	Friability (%)	Drug content (%)
VF1	298	3.12	4.2	0.16	99.8
VF2	299	3.24	5.1	0.14	97.6
VF3	300	3.16	5.2	0.08	99.65
VF4	300	3.25	5.4	0.14	96.25
VF5	299	3.48	5.6	0.11	99.15
VF6	299	3.26	5.2	0.10	98.8
VF7	298	3.42	5.4	0.08	89.6
VF8	300	3.27	5.0	0.07	98.43
VF9	298	3.59	5.1	0.16	87.36
VF10	299	3.18	5.4	0.12	90.48
VF11	**300**	**3.25**	**5.5**	**0.8**	**99.42**

3.4-IN VITRO DISSOLUTION STUDY OF CLOPIDOGREL & VALSARTAN BILAYER TABLETS:

Table 13: *In vitro* dissolution study of clopidogrel

Time in minutes	Cummulative percent drug release						
	CF1	CF2	CF3	CF4	**CF5**	CF6	CF7
5	10.2±0.21	7.8±0.23	17.1±0.34	20.1±0.42	**22.15**±0.48	20.6±024	30.1±0.21
10	19.4±0.32	16.11±0.33	30.2±0.45	35.8±0.53	**68.4**±0.50	45.4±0.53	51.2±0.53
15	28.1±0.43	29.14±0.35	47.26±0.63	50.6±0.65	**84.7**±0.32	70.1±0.61	74.8±0.59
30	33.4±0.54	42.9±0.56	63.8±0.82	76.5±0.79	**100.2**±0.41	86.4±0.74	99.7±0.76
45	40.6±0.65	57.6±0.67	71.5±0.93	89.2±0.83	**100.2**±0.41	99.8±0.9	99.7±0.76
60	50.7±0.67	70.8±0.69	80.1±0.33	100.8±0.94	**100.2**±0.41	99.8±0.9	99.7±0.76

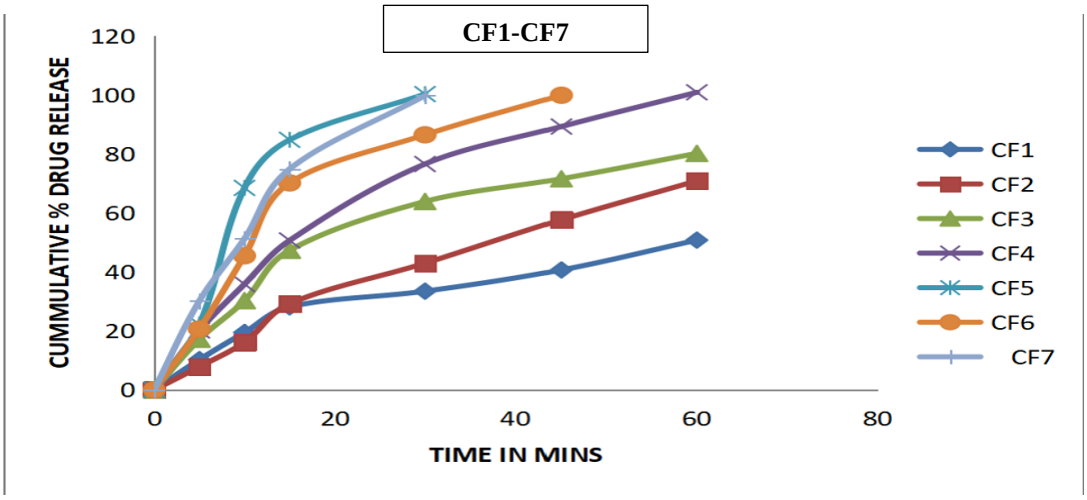

Figure 9: *In vitro* diffusion studies of clopidogrel formulation(CF1-CF7)

Table 14: *In vitro* dissolution study of valsartan

Time in hrs.			Cumulative percent drug release								
	VF1	VF2	VF3	VF4	VF5	VF6	VF7	VF8	VF9	VF10	**VF11**
0.5	11.2± 0.23	17.8±0.21	12.35±0.24	16.24±0.26	14.25±0.32	12.4±0.34	10.1±0.35	11.02±0.22	18.35±0.31	16.26±0.27	**11.01**±0.21
1	24.31±0.25	26.4±0.24	20.34±0.25	26.34±0.28	24.05±0.36	20.1±0.37	18.2±0.21	17.35±0.26	20.26±0.34	24.36±0.78	**14.32**±0.34
2	46.21±0.26	39.41±0.26	31.16±0.27	34.74±0.22	36.45±0.38	28.7±0.39	30.6±0.24	26.37±0.29	33.21±0.36	30.15±0.65	**20.33**±0.56
3	59.7± 0.28	58.43±0.29	41.28±0.26	44.26±0.23	47.26±0.41	42.9±0.42	41.8±0.28	38.26±0.30	39.27±0.38	40.82±0.63	**30.24**±0.67
4	78.8± 0.32	76.14±0.32	59.44±0.32	66.37±0.30	58.35±0.43	53.4±0.45	50.2±0.31	50.37±0.32	52.28±0.39	58.34±0.23	**40.35**±0.78
6	99.8± 0.34	97.6±0.35	82.78±0.34	87.26±0.37	79.16±0.47	70.1±0.48	64.9±0.33	67.26±0.34	59.35±0.42	66.27±0.89	**62.22**±0.89
8	99.8± 0.34	97.6±0.35	99.65±0.49	96.25±0.36	92.25±0.49	83.1±0.50	76.3±0.35	75.42±0.39	69.27±0.44	70.34±0.92	**80.40**±0.92
10	99.8± 0.34	97.6±0.35	99.65±0.49	96.25±0.36	99.15±0.52	98.8±0 0.5	82.5±0.36	84.27±0.41	78.37±0.46	78.75±0.95	**91.23**±0.45
12	99.8± 0.34	97.6±0.35	99.65±0.49	96.25±0.36	99.8±0.54	99.8±0.55	89.6±0.40	98.43±0.42	87.36±0.55	90.48±0.32	**99.42**±0.34

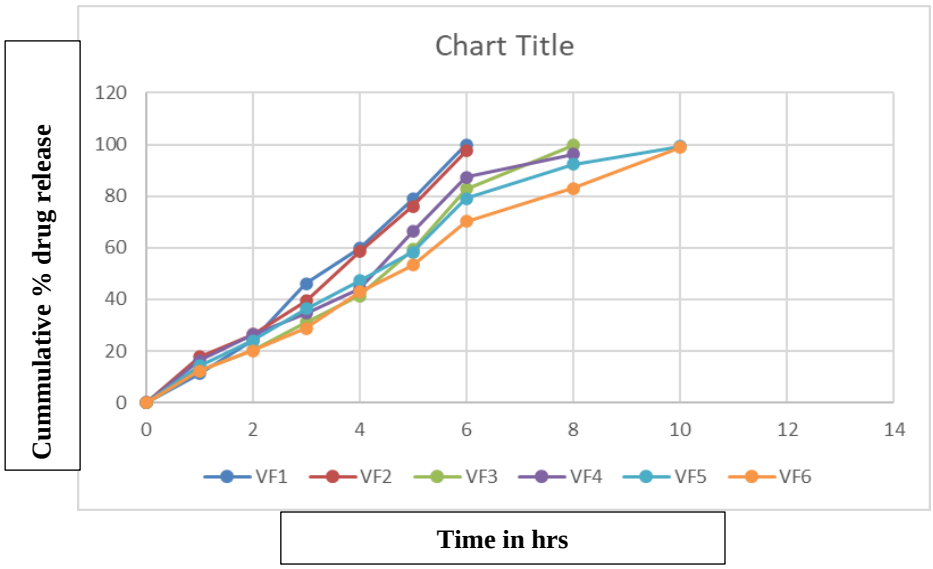

Figure 10: *In vitro* diffusion studies of valsartan formulation(VF1-VF6)

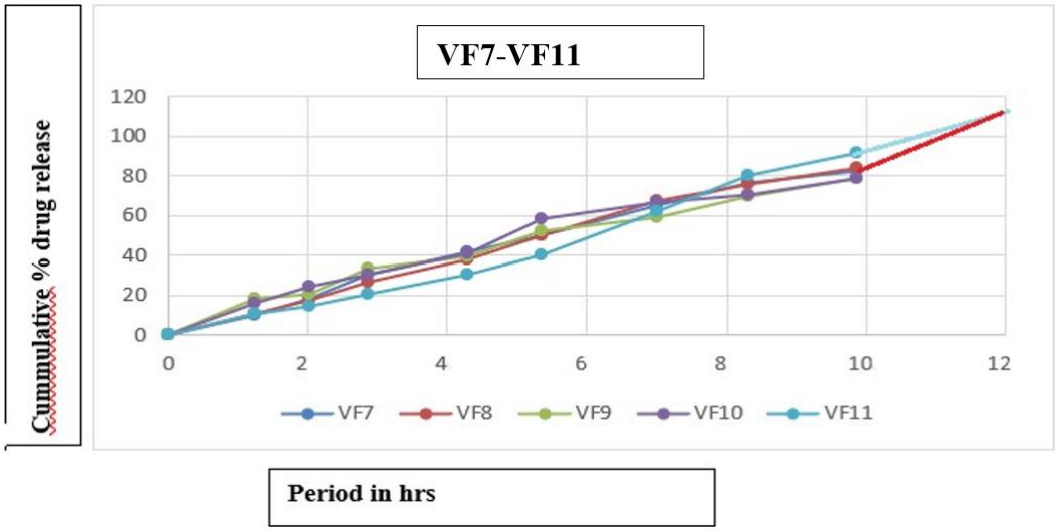

Figure 11: *In vitro* diffusion studies of valsartan formulation(VF7-VF11)

Table 15: *In vitro* Dissolution profile of optimized bilayer tablets

S.NO	Sampling time	Percentage drug released (%)	
		Clopidogrel	Valsartan
1	15 mins in 0.1 N HCL	84.7	5.03
2	30 mins 0.1 N HCL	100.2	11.02
3	1 hr (6.8 PO_4 buffer)	-	17.35
4	2 hr (6.8 PO_4 buffer	-	26.37
5	3 hr (6.8 PO_4 buffer	-	38.26
6	4 hr (6.8 PO_4 buffer	-	50.37
7	6 hr (6.8 PO_4 buffer	-	67.26
8	8 hr (6.8 PO_4 buffer	-	75.42
9	10 hr (6.8 PO_4 buffer	-	84.27
10	11 hr (6.8 PO_4 buffer	-	98.43
11	12 hr (6.8 PO_4 buffer	-	99.42

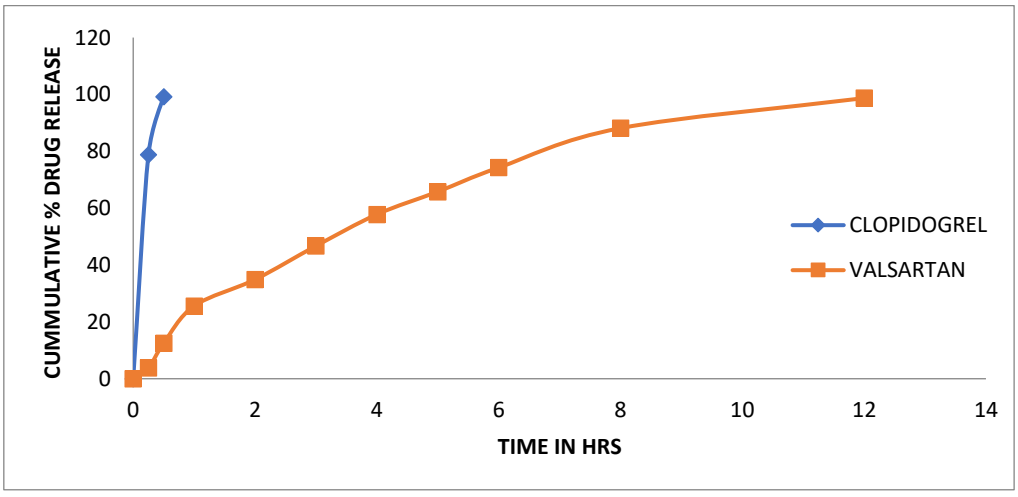

Figure 12: In *vitro* Dissolution profile of optimized bilayer tablets

KINETIC STUDIES:

Table 16: Release kinetics of optimised valsartan formulation

PARAMETERS	ZERO ORDER	FIRST ORDER	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	7.95972	0.150413	30.074283	1.1091223
Intercept	11.01832	2.176431	8.4000224	2.0120624
Correlation	0.936480	0.988211	0.9605634	0.9090615
R^2	0.772746	0.965594	0.9872591	0.5313055

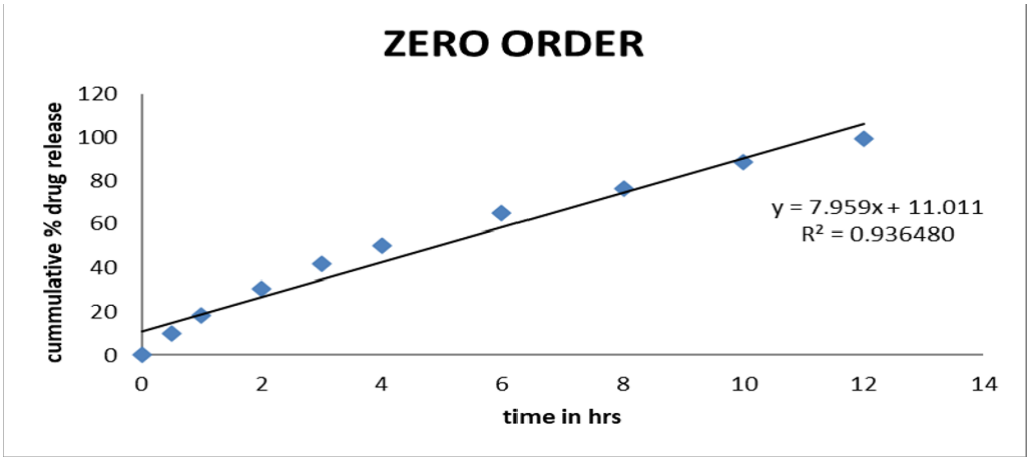

Figure 13: Zero order release graph for VF11 sustained release formulation

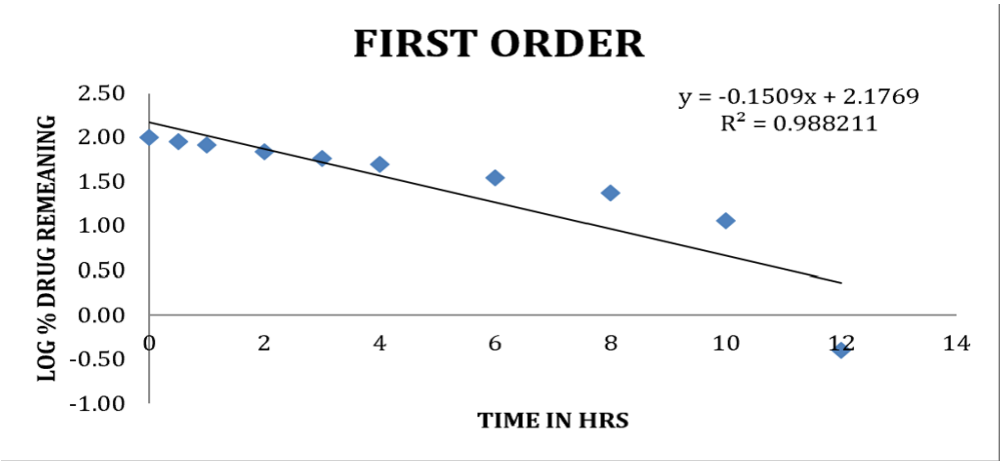

Figure 14: First order release graph for VF11 sustained release formulation

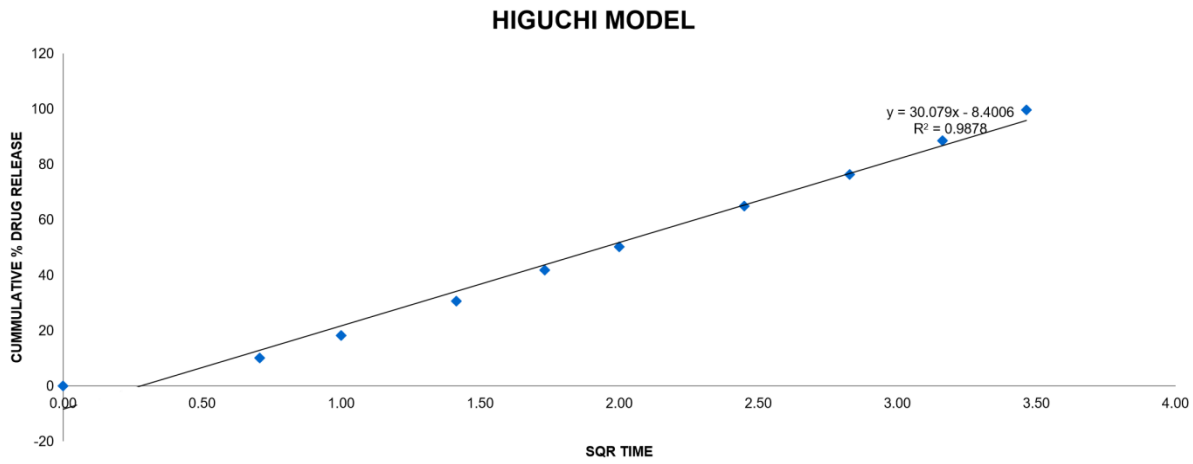

Figure 15: Higuchi model graph for VF11 sustained release formulation

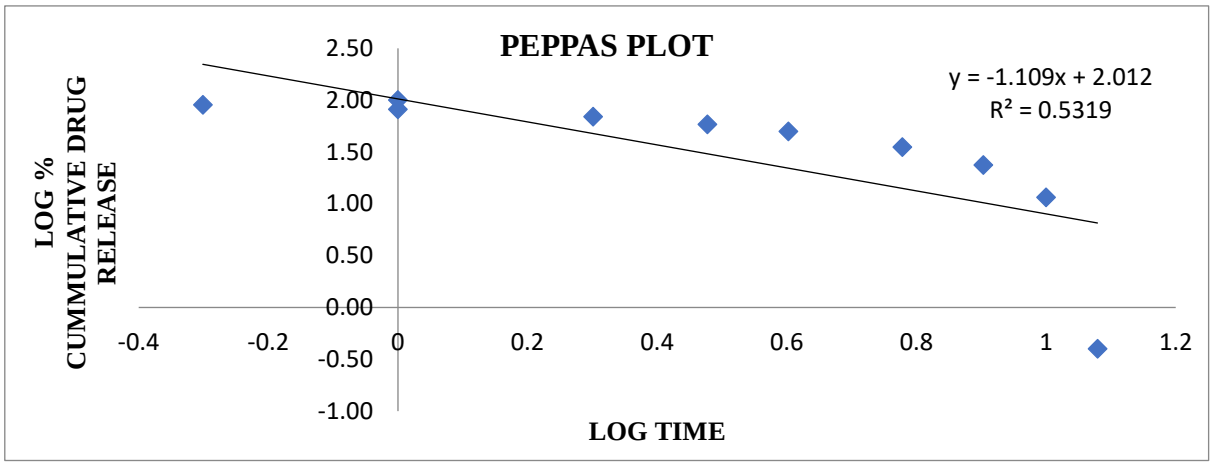

Figure 16: Peppas model for VF11 sustained release formulation

Discussion: The optimised formulation VF11 optimised was analyzed for the drug release mechanism. The best correlation coefficient value (0.988211) indicates the best release mechanism (Higuchi release kinetics).

STABILITY STUDIES

Optimized formulations of bilayer tablet were subjected to stability studies as per ICH guidelines. Various parameters such as Physical appearance, drug content, disintegration time and *in vitro* dissolution profile release were measured before and after 30, 60 and 90 days of stability. Results of stability studies are shown in table(17,18,19,20). Physical appearances of all formulations did not show any significant changes.

Table 17: Stability studies of optimized formulation of clopidogrel

S No	Time in mins	Initial	Cumulative % Drug Release (mean SD) (n=3)								
			25±2⁰C,60±5%RH			30 ±2⁰C,65±5⁰C % RH			40±2⁰C,75±5%RH		
			1st Month	3rd Month	6th Month	1st Month	3rd Month	6th Month	1st Month	3rd Month	6th Month
1	15 mins	82.7	84.7	84.6	84.5	83.7	83.8	82.8	81.7	81.6	81.5
2	30 mins	100.2	100.2	100.1	100	100.2	100	100.1	100.	100.2	100.1

Table 18: Stability studies of optimized formulation of valsartan

S. No	Time in hrs	Initial	Cumulative % Drug Release (mean SD) (n=3)								
			25±2⁰C,60±5%RH			30 ±2⁰C,65±5⁰C % RH			40±2⁰C,75±5%RH		
			1st Month	3rd Month	6th Month	1st Month	3rd Month	6th Month	1st Month	3rd Month	6th Month
1	0.5	11.02	11.02	11.01	11.00	11.02	11.00	11.01	11.02	11.00	11.00
2	1	17.35	17.35	17.34	17.33	17.35	17.34	17.35	17.35	17.33	17.32
3	2	26.37	26.37	26.35	26.34	26.36	26.35	26.34	26.37	26.34	26.33
4	3	38.26	38.26	38.25	38.24	38.26	38.25	38.23	38.26	38.22	38.21
5	4	50.37	50.37	50.36	50.35	50.38	50.36	50.35	50.37	50.34	50.33
6	6	67.26	67.26	67.25	67.24	67.27	67.25	67.24	67.26	67.24	67.23
7	8	75.42	75.42	75.41	75.40	75.43	75.41	75.40	75.42	75.41	75.40
8	10	84.27	84.27	84.26	84.25	84.28	84.26	84.25	84.27	84.24	84.23
9	12	98.43	98.43	98.42	98.41	98.44	98.42	98.41	98.43	98.41	98.40

Table 19: Stability studies of optimized post compression parameters of clopidogrel

S.No	Parameters	Initial	Clopidogrel optimized parameters								
			25±2⁰C,60±5%RH			30 ±2⁰C,65±5⁰C % RH			40±2⁰C,75±5%RH		
			1st Month	3rd Month	6th Month	1st Month	3rd Month	6th Month	1st Month	3rd Month	6th Month
1	Average weight (mg)	250	250	249	249	249	250	249	250	248	249
2	Thickness (mm)	3.15	3.15	3.15	3.15	3.15	3.15	3.15	3.15	3.15	3.15
3	Hardness Kg/cm2	5	5	5	5	5	5	5	5	5	5
4	Friability (%)	0.15	0.15	0.14	0.13	0.13	0.15	0.14	0.15	013	0.14
5	Disintegration Time	32 sec	32 sec	24 sec	25 sec	33 sec	32 sec	31 sec	18 sec	20 sec	20 sec
6	Drug release in 30 mins	100.2	100.2	100.1	100	100.2	100.2	100.1	100.2	100	100.1

Table 20: Stability studies of optimized post compression parameters of valsartan

S.No	Parameters	Initial	valsartan optimized parameters								
			25±2⁰C,60±5%RH			30 ±2⁰C,65±5⁰C % RH			40±2⁰C,75±5%RH		
			1st Month	3rd Month	6th Month	1st Month	3rd Month	6th Month	1st Month	3rd Month	6th Month
1	Average weight (mg)	300	300	301	299	300	301	299	300	299	249
2	Thickness (mm)	3.25	3.25	3.25	3.25	3.25	3.25	3.25	3.25	3.25	3.25
3	Hardness Kg/cm2	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
4	Friability (%)	0.07	0.07	0.06	0.05	0.04	0.06	0.05	0.07	0.05	0.04
5	Drug release in 2hrs	26.37	26.37	26.36	26.35	26.36	26.35	24.34	25.34	25.31	25.30
6	Drug release in 4hrs	50.37	50.37	50.35	50.35	50,36	50.34	50.33	50.27	50.28	5029
7	Drug release in 12hrs	98.43	98.43	98.42	98.41	98.43	98.42	98.41	98.43	98.42	98.41

Discussion: Results of stability studies showed that there is no significant change in above mentioned parameters after elevated temperature and humidity conditions during stability studies. Thus it can be proved from the stability studies that the prepared formulation is stable and not much affected by elevated humidity and temperature conditions.

CONCLUSION

The aim of the study was to formulate and evaluate clopidogrel & valsartan of bilayer ablets. Preformulation studies indicated better solubility of clopidogrel & valsartan in 0.1NHCL and 6.8 phosphate buffer . FTIR analysis revealed no interaction between drug and excipients, the Absorption maxima of clopidogrel & valsartan was found to be 272 nm & 342 nm respectively. The formulated and optimised clopidogrel immediate release formulation CF5 exhibited acceptable average weight variation (250), average thickness (3.12), average hardness (5) , friability (0.15), disintegration time (32 sec), drug content (98.7)

The optimized formulation of valsartan sustained release VF11 exhibited satisfactory average weight variation (300), average thickness (3.27), average hardness (6.0) , friability (0.07), drug content (98.42).

The percent drug release of clopidogrel & valsartan was determined to be 100.2 % and 98.42% respectively, indicating good content uniformity. Stability studies indicated that clopidogrel and valsartan were more stable at 25±20°C, 60±5%RH, 30±20°C,65±5%RH, and 40±20°C, 75±5%RH compared to other temperatures.

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