JOURNAL OF PHARMACEUTICAL SCIENCE AND BIOSCIENTIFIC RESEARCH (JPSBR)

(An International Peer Reviewed Pharmaceutical Journal that Encourages Innovation and Creativities)

Formulation and In-Vitro Evaluation of Novel Fixed Dose Triple Combinations of Antidiabetic and Anti-Hypertensive Drugs for Treatment of Hypertension in Diabetic Patients

Priyaranjan Pattanaik*[1], Kanubhai R. Patel[2]

1. Research Scholar, JJT University, Vidhyanagari Jhunjhun, Rajasthan, India-333001.
2. Associate Professor, Dept. of Pharmaceutics, B. M. Shah Pharmacy College, Modasa, Gujarat, India

Article history:

Received 07 Oct 2016
Accepted 30 Oct 2016
Available online 01 Nov 2016

Citation:
Pattanaik P. Patel K. R. Formulation and In-Vitro Evaluation of Novel Fixed Dose Triple Combinations of Antidiabetic and Anti-Hypertensive Drugs for Treatment of Hypertension in Diabetic Patients **J Pharm Sci Bioscientific Res**. 2016. 6(6): 816-823

For Correspondence:
Priyaranjan Pattan
Research Scholar, JJT University, Vidhyanagari Jhunjhun, Rajasthan, India-333001.

(www.jpsbr.org)

ABSTRACT:

Combination therapies are widely used to treat cardiovascular and diabetic patients. Current study is designed to develop fixed dose combination of anti diabetic and anti hypertensive drugs to treat hypertension in patients suffering from diabetics. Fixed dose combination was designed as bilayer tablets with immediate release and sustained release layers. Immediate release was loaded with drugs that required for immediate action by achieving blood level immediately and sustained release layer to maintain the drug concentration throughout the time as designed. Antidiabetic drug Alogliptin Benzoate and antihypertensive drug Valsartan were incorporated in immediate release layer to show immediate action whereas Metformin HCl was loaded as sustained release layer to maintain the drug level throughout the targeted time period. Immediate release layer was manufactured using direct mixing process with optimized disintegrant concentration for faster release. Sustained release layer of Metformin HCl was manufactured employing wet granulation approach using HPMC and POLYOX resin as release control polymer in combination. Formulation was optimized using statistical designed. Physico-chemical parameters like weight variation, hardness, friability and in-vitro dissolution of bilayer tablets were evaluated.

KEY WORDS: Fixed dose combination, Bilayer, sustained release, antidiabetic and antihypertensive, HPMC K100LVCR & POLYOX WSR 301.

INTRODUCTION:

Diabetics is serious chronic disease occurs when pancreases either does not produce sufficient insulin or body can't consume the produced insulin. Mortality rate increased due to co-existence of diabetics with cardiovascular diseases [1]. The global prevalence of diabetes has nearly doubled since 1980, rising from 4.7% to 8.5% in the adult population. The prevalence of hypertension is 1.5 – 2.0 times more in those with diabetes than in those without diabetes, where as almost one-third of the patients with hypertension develop diabetes later. Diabetes caused 1.5million, higher than optimal glucose caused an additional 2.2 million deaths, by increasing the risk of cardiovascular and other disease. Hypertension is major risk factor for cardiovascular morbidity and mortality in patients with diabetes [2-3].

Combination therapy is a common method of treating disease which requires more than one active pharmaceutical. Fixed dose combinations (FDC) are dosage forms that contain two or more active ingredients in a fix dose in the same formulation The FDC enhanced adherence rates by approximately 13% when compared to

a 2-pill Regimen. [4]

Merits of FDC (Fixed dose combination):

1. Improve patients compliances
2. Better efficacy
3. Synergistic mechanism
4. Improved ADME and drug resistance.

Demerits of FDC (Fixed dose combination):

1. Dose alteration of one drug is not possible without alteration of the other drug.
2. Increase chance of adverse effect and drug interactions.
3. Problem of frequency of admistration.

Alogliptin Benzoate is a DPP-4 inhibitor which inactivates the incretin hormone glucagon like peptide-1 (GLP-1) and glucose dependant insulinotropic polypeptide. Alogliptin is a new generation antidiabetic used for treatment of Type II diabetes either alone or combination with other antidiabetic [5]

Valsartan is an angiotensin II receptor antagonist used in the management of hypertension. (Valsartan) blocks the vasoconstrictor and aldosterone-secreting effects of Angiotensin II by selectively blocking the binding of Angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for Angiotensin II synthesis [6].

Metformin HCl is a biguanide glucose-lowering agent. Mechanism of action of Metformin includes decreased intestinal absorption of glucose, increased glucose uptake from the blood into the tissues, decreased glucose production in liver and decreased insulin requirements for glucose disposal.[7-9].

MATERIALS AND METHODS:

Materials:

Alogliptin Benzoate, Metformin HCl and Valsartan were gift sample from SPS Pharmaceuticals, Mumbai. Lactose monohydrate, Microcrystalline cellulose, Polyvinyl Pyrrolidine, HPMC K100LVCR, POLYOX WSR 301, Talc, Magnesium stearate were gift sample from pharmaceutical vendors.

Methods:

Preparation of Standard Curve for Alogliptin Benzoate

100mg of Alogliptin benzoate was weighed and transferred to 100ml of volumetric flask containing 50ml of 0.1 N HCl and sonicated for 30 minutes and volume was made up to 100ml (1mg/ml). Then the stock solution was diluted to get 2 -10 ppm solution and absorbance was measured at 222nm.Standard curve was obtained by plotting concentration vs mean peak area.

Preparation of Standard curve for Valsartan

50 mg of Valsartan was accurately weighed and transferred to 100 mL volumetric flask. The drug was dissolved in diluents and volume was made up to mark (50 ppm). Stock solution was further diluted to get concentrations of 10 to 70 ppm. Solutions of different concentration were injected and area was calculated. Standard curve was obtained by plotting concentration vs. mean peak area.

Preparation of Standard Curve of Metformin HCl

Metformin HCl 50 mg was accurately weighed and transferred to a 100 mL volumetric flask containing 50mL of diluents (Methanol: Acetonitrile in 50:50 proportion) and sonicated for 30 minutes. Stock solution was further diluted with mobile phase to get concentrations of 20 to 80 ppm. These individual solutions were then injected. Each sample was run and chromatograms were obtained. Solutions of different concentration were injected and area was calculated. Standard curve was obtained by plotting concentration vs. mean peak area.

Preparation of Immediate release Layer:

Immediate release layer containing Alogliptin and valsartan with other inactive excipients were formulated according to below formula using direct mixing process.

Table 1: Formulation trails for Immediate Release Layer Blend Preparation:

Sr. No.	B. No. / Ingredients	AV_1	AV_2	AV_3	AV_4	AV_5
		%w/w				
1	Alogliptin Benzoate	2.83	2.83	2.83	2.83	2.83
2	Valsartan	27.47	27.47	27.47	27.47	27.47
3	Lactose monohydrate	23.33	23.33	23.33	23.33	30.00
4	Microcrystalline cellulose	43.54	42.54	41.54	42.29	34.87

5	Crospovidone	1.50	2.50	3.50	2.75	2.90
6	Colloidal Silicon dioxide	0.58	0.58	0.58	0.58	0.58
7	Iron Oxide Red	0.04	0.04	0.04	0.04	0.04
8	Magnesium stearate	0.70	0.70	0.70	0.70	0.70

Manufacturing process for Immediate release Layer Blend:

Alogliptin Benzoate, Valsartan, Lactose monohydrate, Microcrystalline Cellulose, Polyvinyl Pyrolidine K30, Crospovidone and Colloidal silicon dioxide were co-sifted through 40mesh sieve. Co-sifted material was resifted through #40 mesh sieve and loaded in an octagonal blender and mixed for 10 minutes with blender at slow speed. Magnesium stearate was sifted through #60 mesh sieve and mixed with pre-lubricated blend for 5 minutes in octagonal blender.

Preparation of Sustained release layer:

Sustained release layer containing Metformin HCl was prepared by wet granulation method using combination of HPMC and POLYOX as release controlling polymer.

Table 2: Formulation trails for Sustained Release Layer Blend Preparation:

Sr. No.	Batch No / **Ingredients**	M1	M2	M3	M4	M5
				%w/w		
1	Metformin HCl	52.63	52.63	52.63	52.63	52.63
2	Microcrystalline Cellulose	33.87	31.87	29.87	29.37	28.87
3	HPMC K100LVCR	10.00	7.50	7.50	10.00	12.00
Binder						
4	Povidone K30	3.00	2.50	2.00	2.50	2.50
5	Purified water	q.s	q.s	q.s	q.s	q.s
Blending						
6	Polyox WSR 301	***	5.00	7.50	5.0	3.50
Lubrication						
7	Magnesium stearate	0.50	0.50	0.50	0.50	0.50
Total weight		100.0	100.00	100.00	100.00	100.00

Manufacturing process for Sustained release Layer Blend:

Metformin HCl, Microcrystalline cellulose, HPMC K100LVCR were sifted through #40mesh sieve. Sifted material was loaded into a rapid mixture granulator and mixed for 10 minutes. Binder solution was prepared by dissolving Povidone K30 in Purified water. Dry mix blend was granulated adding binder solution slowly. Kneading was continued till desired consistency of granules was achieved. Wet granules were dried and passed through #24 mesh. Oversized granules were milled through suitable screen and passed through #30 mesh. Polyox WSR 301 was sifted through #40 mesh sieve and added to dried granules in an octagonal blender and mixed for 10 minutes. Magnesium stearate was sifted through #60mesh sieve and mixed with pre-lubricated blend for 5 minutes in octagonal blender.

Blend Properties Characterization:

Determination of Angle of Repose:

10 g granules were loaded on funnel with 6mm orifice and allowed to fall at once on the flat surface to form a heap. The height of the heap was measured. The diameter of the heap was measured at three different ends and the average was taken. The angle of repose is defined as,

$$\tan \theta = h/r$$

Where, θ = angle of repose, h = height of the heap and r = radius of the heap.

Bulk Density (BD) and Tapped Density (TD)

The bulk density and tapped density of granules were determined separately by the cylinder method. An accurately weighed 25 g of granules were transferred to 100 mL graduated cylinder. Initial volume and final volume after 500 taps and 750 taps were noted. Calculate the bulk density and tapped density by the following formula.

BD = Mass of the granules (W) / Initial volume of the granules (V_0)

TD = Mass of the granules (W) / Tapped volume of the granules (Vf)

Carr's Index and Hausner's Ratio:

Carr's compressibility index was used to determine compressibility index. Hausner's ratio is a number that is correlated to the flowability of a powder. The formula for Carr's index and Hausner's ratio is mentioned below.

Carr's index (%) = [(TD-BD) X100] / TD

Hausner's ratio = TD / BD

Preparation of Bilayer Tablets

Bilayer tablets were prepared by using double rotary bi-layer compression machine. The prepared granules of each layer were compressed using 19.50 × 8.50 mm, 'D' tooling standard concave, flat faced modified capsule shaped punch. Both the prepared granules were added to two different hoppers. The bottom or first layer of sustained release metformin HCl was compressed first, which was then followed by filling of the die cavity by the second immediate release layer Alogliptin and valsartan .Both the layers were identified on the basis of colour.

CHARACTERIZATION OF BILAYER TABLETS

Appearance: Tablets were observed visually for surface characteristics and appearance of dark or colour spots.

Determination of Uniformity of Weight (USP/NF):

20 tablets were taken and they were weighted together and individually by an analytical balance. The individual variations were studied from the mean weight of each set. The average weight and its related standard deviations were carried out.

Determination of Thickness (**USP/NF**)**:**

Thickness was measured individually for 10 pre-weighed tablets by using a Vernier Caliper. The average thickness and its related standard deviations were evaluated

Determination of Hardness (**USP/NF**)

Tablet hardness was measured using Electrolab hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kilopond (kp) and the average hardness, and its related standard deviations were reported.

Determination of Friability (**As per USP/NF**):

Ten (10) tablets were de-dusted and weighed. They were loaded on Electrolab Friabilator. Tablets were rotated at 25 rpm for 4 min (100 rotations). The tablets were then de-dusted and re-weighed to determine the loss in weight. Friability was calculated using following formula,

Friability (%) = 100 (Loss in weight / initial weight)

Invitro Drug Release Study: (USP/NF-34)

In-vitro drug release study for the bi-layer tablets was conducted by using a six station USP type II apparatus (Electrolab Tablet dissolution tester USP). Alogliptin layer of test formulation and its reference product (Nesina 6.25 mg, USA) were analysed in 0.01N HCl as dissolution medium at 37 ± 0.5°C, 900 mL, apparatus II (paddle) and at a rotation speed of 75 rpm. Samples at 5, 10, 15, 30, 45 and 60 min were analyzed by using HPLC at 222 nm.

Valsartan layer of test formulation and its reference product (Diovan 80mg, USA) were analysed in Phosphate buffer Ph6.8 as dissolution medium at 37 ± 0.5°C, 900 mL, apparatus II (paddle) and at a rotation speed of 75 rpm. Samples at 5, 10, 15, 30, 45 and 60 min were analyzed by using HPLC at 272 nm. Metformin HCl layer of test formulation and its reference product (Glucophage XR, Bristol Mayers Squibb, USA) were analysed as per USP dissolution (711), at 37 ± 0.5°C, apparatus II (paddle), at a rotation speed of 100 rpm in phosphate buffer (pH = 6.8) for 12 h. Samples were analyzed at 233nm. The amount of drug present in the samples was calculated with the help of appropriate calibration curve constructed from reference standard.

Factorial Design for optimization of Metformin Sustained release Layer:

Factorial designs are used in experimental where effect of different factors or condition on experimental results is to be elucidated. Factorial designs are designs of choice for simultaneous determinations of effects of several factors and their interactions. A 2^3 factorial design was used to investigate the effects of three components (factors) - binder (PVP K30), Polymer (HPMC K100LVCR) and Polymer (Polyox WS301) - on the drug release from the sustained release layer . Two levels were chosen for each factor in this experiment as shown in table. Low and high levels refer to low and high concentrations pre-selected for the - binder (PVP K30), Polymer (HPMC K100LVCR) and Polymer (Polyox WS301)

Table 3: High and low levels of each factor in the design experiment.

Factor	Low level (mg)	High level (mg)	Response
Factor A (PVP K30)	1.5	3.5	**Dissolution**
Factor B (HPMC K100LVCR)	10	14	
Factor C (Polyox WSR 301)	**2.0**	**5.0**	

A total of eight trials were performed in random order to avoid any bias.

Table 4: Trials based on the level of factors (PVP K30, HPMC K100LVCR and Polyox WS301) effect on drug release.

Experimental code	Factor A PVP K30	Factor B HPMC K100LVCR	Factor C Polyox WS301
(D1)	- (1.5)	- (10)	**- (2.0)**
(D2)	+ (3.5)	- (10)	**- (2.0)**
(D3)	- (1.5)	+ (14)	**- (2.0)**
(D4)	+ (3.5)	+ (14)	**- (2.0)**
(D5)	- (1.5)	- (10)	**+(5.0)**
(D6)	+ (3.5)	- (10)	**+(5.0)**
(D7)	- (1.5)	+ (14)	**+(5.0)**
(D8)	**+ (3.5)**	**+ (14)**	**+(5.0)**

'-' sign denotes the low level of each factor and '+' sign denotes the high level for each factor.

Bilayer tablets were manufactured using final blend of immediate release layer and individual sustained release layer prepared as per experimental design.

RESULT & DISCUSSION:

Standard Curve of Alogliptin Benzoate:

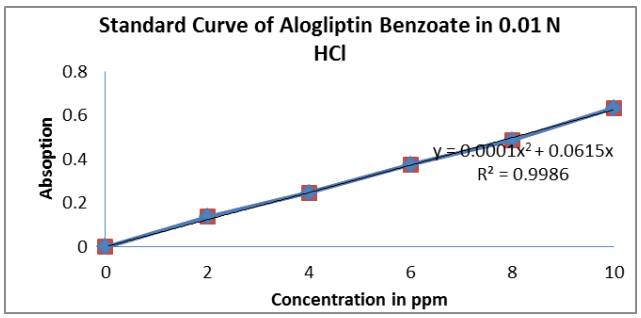

Figure 1: Standard curve of Alogliptin benzoate in 0.01N HCl.

Standard Curve of Valsartan:

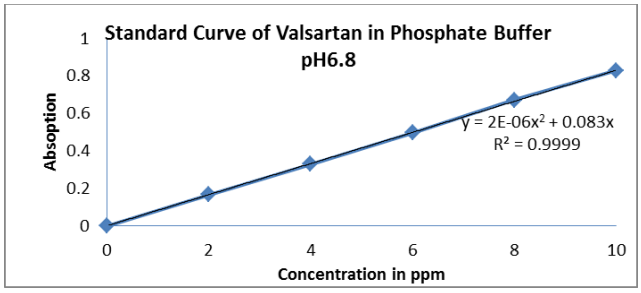

Figure 2: Standard curve of Valsartan in Phosphate Buffer pH6.8

Standard Curve of Metformin HCl:

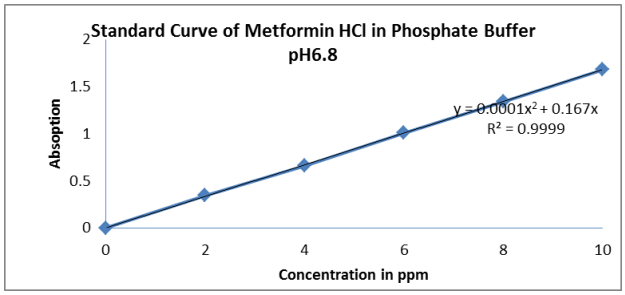

Figure 3: Standard curve of Metformin HCl in Phosphate Buffer pH6.8

Characterization of Alogliptin and Valsartan Blend:

Table 5: Blend characterization of Immediate release Layer

Batch No.	AV_1	AV_2	AV_3	AV_4	AV_5
Angle of Repose (°)	32	28	29	24	30
Bulk density (g / mL)	0.42	0.46	0.44	0.48	0.41
Tapped density (g / mL)	0.63	0.64	0.65	0.61	0.60
Carr's Index (%)	33.33	28.13	33.31	21.31	31.67
Hausner Ratio	1.50	1.39	1.48	1.27	1.46

Table 6: Blend characterization of Sustained release Layer

Batch No.	M1	M2	M3	M4	M5
Angle of Repose (°)	30	25	28	21	26
Bulk density (g / mL)	0.53	0.49	0.48	0.49	0.52
Tapped density(g / mL)	0.64	0.59	0.64	0.61	0.59
Carr's Index (%)	17.19	16.95	25.00	19.67	16.13
Hausner Ratio	1.21	1.20	1.33	1.24	1.13

Physico-chemical characterization of Bilayer tablets:

Table 7: Physical characterization of Bilayer Tablets.

Formulation	AV_1+M1	AV_2+M2	AV_3+M3	AV_4+M4	AV_5+M5
Average Weight (mg) (n=20)	1252 ± 0.014	1247 ± 0.010	1249 ± 0.015	1253 ± 0.013	1248 ± 0.019
Mean Thickness (mm) (n=10)	6.42 ± 0.007	6.38 ± 0.002	6.40 ± 0.010	6.38 ± 0.008	6.41 ± 0.005
Mean Hardness (Kp) (N=10)	12.43 ± 0.18	14.45 ± 0.12	13.88 ± 0.16	14.55 ± 0.10	14.12 ± 0.20
Friability (% mean weight loss) (n=10)	0.32 ± 0.15	0.36 ± 0.02	0.30 ± 0.08	0.37 ± 0.11	0.34 ± 0.20

Data shown; mean ± RSD (n= number of observations).

Release profile of valsartan formulation and its reference product in Phosphate Buffer Ph6.8.

Table 8: Dissolution profiles of Valsartan from Bilayer Tablets

Time (min)	Cumulative Amount of Drug Released in mg					
	AV_1	**AV_2**	**AV_3**	**AV_4**	**AV_5**	**RLD**
0	0.0	0.0	0.0	0.0	0.0	0.0
5	32.1 ± 3.08	41.6 ± 2.25	51.0 ± 3.44	43.9 ± 2.87	45.2 ± 3.12	46.8 ± 2.85
10	44.7 ± 1.97	51.6 ± 2.04	61.8 ± 2.66	54.6 ± 0.99	56.3 ± 1.8	55.2 ± 1.10
15	48.3 ± 1.08	59.8 ± 1.35	73.5 ± 1.32	58.9 ± 1.50	63.8 ± 1.02	62.7 ± 2.10
30	52.9 ± 1.80	62.2 ± 1.55	78.2 ± 1.12	67.9 ± 1.48	70.6 ± 1.10	70.1 ± 1.29
45	58.2 ± 1.45	68.8 ± 1.15	81.1 ± 1.05	74.5 ± 1.09	78.5 ± 1.00	76.8 ± 1.03
60	62.5 ± 1.16	70.5 ± 1.68	83.3 ± 1.09	79.9 ± 2.10	81.9 ± 1.52	82.5 ± 1.00

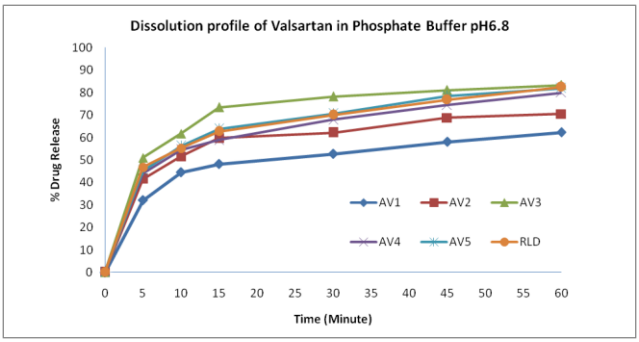

Figure 4: Graphical presentation of Valsartan release in Phosphate buffer pH6.8.

Release profile of Alogliptin Benzoate from immediate release layer and Reference product in 0.01N HCl

Table 8: Dissolution profiles of Alogliptin Benzoate from Bilayer Tablets

Time (min)	Cumulative amount of drug released in mg					
	AV_1	**AV_2**	**AV_3**	**AV_4**	**AV_5**	**RLD**
0	0.0	0.0	0.0	0.0	0.0	0.0
5	68.2 ± 3.46	74.9 ± 2.78	82.0 ± 3.71	78.1 ± 2.69	80.5 ± 2.32	80 ± 3.78
10	84.5 ± 2.32	88.2 ± 2.11	91.9 ± 2.09	90.8 ± 1.44	89.8 ± 1.27	88.5 ± 1.37
15	92.1 ± 1.23	92.9 ± 0.95	94.8 ± 1.17	94.3 ± 1.23	95.8 ± 1.33	94.6 ± 1.32
30	96.2 ± 1.22	95.1 ± 0.91	96.8 ± 0.98	95.5 ± 1.12	96.1 ± 1.48	94.7 ± 1.78
45	97.6	98.1	99.2	97.0	96.5	96.8

	± 1.03	± 0.89	± 1.12	± 1.05	± 1.20	± 1.38
60	97.8	98.0	100.1	98.6	96.9	98.1
	± 1.22	± 1.43	± 1.80	± 1.35	± 1.24	± 1.56

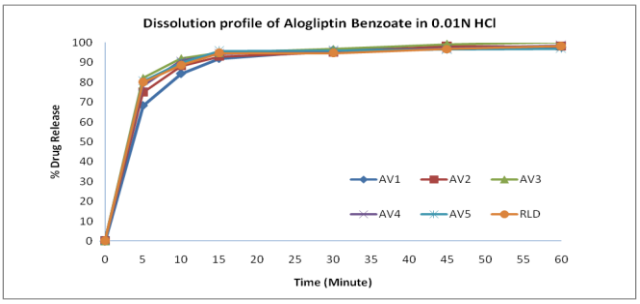

Figure 5: Graphical presentation of Alogliptin benzoate release in 0.01N HCl.

Table 9 Release profile of Metformin HCl formulation and its reference product in pH 6.8 phosphate buffer for 12 h

Time (min)	Cumulative Amount of Drug Released in mg					
	M1	**M2**	**M3**	**M4**	**M5**	**M**
0	0.0	0.0	0.0	0.0	0.0	0.0
1	65.1	53.2	48.2	39.2	32.5	31.6
	± 2.18	±2.51	±2.10	±1.88	±1.55	±1.92
3	82.2	76.3	66.0	52.6	44.7	43.2
	±2.0	±2.10	±1.55	±1.19	±1.69	±1.23
6	96.7	84.8	76.2	64.1	56.3	54.1
	±2.13	±1.54	±1.94	±1.10	±1.08	±0.99
8	98.9	96.9	92.3	75.3	67.0	66.5
	±1.58	±1.43	±1.11	±1.50	±0.90	±1.10
10	99.1	100.0	98.7	82.5	76.8	77.9
	±1.23	±1.10	±1.56	±1.82	±1.02	±0.90
12	100.2	100.4	99.2	91.9	89.2	90.0
	±1.75	±1.02	±1.52	±1.09	±0.49	±1.10

Data shows mean ± RSD (n=6).

Table 10: Physico-chemical Parameters of Bilayer Tablets manufactured based on DOE:

Formulation	D_1	D_2	D_3	D_4	D_5	D_6	D_7	D_8
Average Weight (mg) (n=20)	1250 ± 0.012	1248 ± 0.012	1252 ± 0.012	1253 ± 0.013	1251 ± 0.011	1250 ± 0.009	1247 ± 0.016	1251 ± 0.011
Mean Thickness (mm) (n=10)	6.45 ± 0.003	6.43 ± 0.052	6.44 ± 0.008	6.42 ± 0.003	6.38 ± 0.008	6.40 ± 0.006	6.45 ± 0.009	6.42 ± 0.005
Mean Hardness (Kp) (N=10)	14.00 ± 0.11	14.12 ± 0.13	13.09 ± 0.13	13.95 ± 0.12	14.09 ± 0.19	14.25 ± 0.20	14.55 ± 0.19	14.00 ± 0.12
Friability (% mean weight loss) (n=10)	0.27 ± 0.12	0.29 ± 0.08	0.35 ± 0.06	0.30 ± 0.09	0.28 ± 0.09	0.28 ± 0.10	0.27 ± 0.13	0.31 ± 0.10

Dissolution of Metformin HCl in Phosphate buffer pH6.8

Time (Hour)	% Drug Release							
1	44.2 ± 0.92	41.7 ± 2.18	35.5 ± 2.22	35.1 ± 2.10	29.1 ± 1.98	28.6 ± 2.11	22.0 ± 2.43	22.5 ± 1.49
3	65.7 ± 1.23	64.0 ± 1.42	47.0 ± 1.15	46.8 ± 1.45	40.2 ± 1.62	40.5 ± 1.85	30.5 ± 1.28	29.70± 1.25
10	92.8 ± 1.05	92.2 ± 10.2	82.0 ± 0.92	82.1 ± 1.06	72.0 ± 1.01	71.9 ± 0.89	63.4 ± 1.12	62.8 ± 1.08

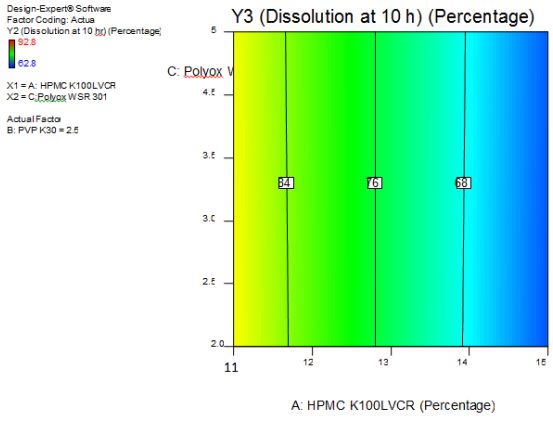

Figure 6: Effect of X1 and X2 on Dissolution at 10h

CONCLUSION:

Result from current experiment concluded that bilayer tablets manufactured by immediate release layer of formulation trial AV5 and sustained release of formulation M5 were found optimized formula where the physiochemical properties of bilayer tablets are comparable to marketed sample. With increasing concentration of Crospovidone, dissolution of both Alogliptin Benzoate and Valsartan increased resulting faster systemic availability. Release of Metformin HCl from sustained release depends on the concentration of HPMC K100LVCR and Polyox WSR301. Concentration of PVPK30 has no significant effect on dissolution profile. Considering in-vitro studies, the final test formulation was similar and the dose of single dose can be reduced considering synergistic action. Statistical design provides a range of concentrations of HPMC K100LVCR, PVPK30 and Polyox WSR 301where there is no significant change in in-vitro dissolution was observed and within that range formulation is similar to the reference product.

REFERENCES:

1. Bastaki, S. (2005) "Diabetes mellitus and its treatment. " Int. J. Diabetes & Metabolism; 13: 111-134.

2. Bakris, G., Williams, M., Dworkin, L., Elliott, W., Epstein, M., Toto, R., Tuttle, K., Douglas, J., Hsueh, W., Sowers, J. (2000) "Preserving renal function in adults with hypertension and diabetes: a consensus approach." Am. J. Kid. Dis.; 36: 646-661

3. Arauz-Pacheco, C., Parrott, M., Raskin, P. (2002) "The treatment of hypertension in adult patients with diabetes (Technical Review)." Diabetes Care; 25: 134–147.

4. Chan, P. Wong, P., Liu, I., Tzeng T., Yang, T., Cheng, J. (2003) "Antihyperglycemic action of angiotensin II receptor antagonist, valsartan, in streptozotocin-induced diabetic rats." J. Hyper.; 21: 761-769.

5. Chandira, M., Venkateswarlu, B., Shankarrao, J., Bhowmik, D., Jayakar, B. and Narayana, T. (2010) "Formulation and evaluation of extended release tablets containing Metformin HCl." Int. J. ChemTech Res.; 2 (2): 1320-132

6. Bhimarao, B., Shivale, D. and Pokharkar, V. (2009) "Preparation and characterization of spherical crystals of valsartan for direct compression method." Int. J. Phar. Res. Dev.; 1: 29-35

7. Aulton, M. (2002) "Pharmaceutics- The science of dosage form design." Matrix System, Second Edi.; 296-300.

8. Bailey, C., Path, M., Turner, M. (1996) "Metformin." N. Engl. J. Med.; 334: 574-579.

9. Budavari, S., ONeil, M., Smith, A., Heckelman, P. (2001) "The Merck Index ."; 1767.