FORMULATION, DEVELOPMENT AND CHARACTERIZATION OF SUSTAINED RELEASE BILAYERED TABLET OF VALSARTAN AND PIOGLITAZONE HCl

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ABSTRACT

Valsartan is a drug used to treat high blood pressure and congestive heart failure. Pioglitazone is a drug that reduces the amount of glucose (sugar) in the blood. It is in a class of anti-diabetic drugs called thiazolidinediones that are used in the treatment of type 2 diabetes. The main objectives of sustained release bilayered tablet of Valsartan and Pioglitazone HCl is that antihypertensive and antidiabetic both drugs can be given in one dosage form. It gives sustained release of both drugs upto 12hr and decrease the chances of Myocardial Infraction which is due to Pioglitazone HCl. In the present research the comparative study between HPMC K4M, HPMC K15M & HPMC K100M was performed. Sustained release bilayered tablets were prepared by different concentration of polymers (45%, 55%, 65%). The powder mixture of Valsartan and other ingredients, Pioglitazone HCl and other ingredients were evaluated for various physical properties such as bulk density, tapped density, angle of repose, carr's index and hausner's ratio. The bilayered tablets were evaluated by different parameters such as hardness, friability, weight variation, drug content uniformity, Swelling Index, and *In vitro* drug release. The optimized formulation (F9) containing 65% HPMC K15M in Valsartan layer and 65% HPMC K100M in Pioglitazone HCl layer shows in vitro drug release upto 12 hrs.

Keywords: Sustained release, Bilayer tablet, Valsartan, Pioglitazone HCl, Hypertension, Diabetes type II.

INTRODUCTION

In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bilayer tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance. Bilayer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation and to enable the development of different drug release profiles (immediate release with extended release). Despite their advantages, due to the use of different materials and complex geometric boundaries between the adjacent layers, the mechanical structures of this drug delivery system have become quite intricate, requiring

complicated tablet architectures as well as patient-friendly administration which pose serious challenges to the pharmaceutical scientists/engineers. One of the major challenges is lack of sufficient bonding and adhesion at the interface between the adjacent compacted layers which is often the result of an interfacial crack driven by residual stresses in the tablet propagating a finite distance within the tablet and leads to delamination (layer-separation) which may not always be apparent immediately after compaction (e.g., during storage, packaging, shipping).[1,2]

Diabetes mellitus is a group of metabolic diseases characterized by elevated blood glucose levels (hyperglycemia) resulting from defects in insulin secretion, insulin action or both. Insulin is a hormone manufactured by the beta cells of the pancreas, which is required to utilize glucose from digested food as an energy source. Chronic hyperglycemia is associated with microvascular and macrovascular complications that can lead to visual impairment, blindness, kidney disease, nerve damage, amputations, heart disease, and stroke.[3]

Pioglitazone is an oral drug that reduces the amount of glucose (sugar) in the blood. Pioglitazone hydrochloride belongs to BCS class-II and a member of the thiazolidinedione class (TZD) with hypoglycemic action. Pioglitazone lowers the level of glucose in the blood by reducing the production and secretion of glucose into the blood by the liver. In addition, Pioglitazone may alter the blood concentrations of lipids (fats) in the blood.[4,5]

Arterial hypertension is a major cause of morbidity and mortality because of its association with coronary heart disease, cerebro-vascular disease and renal disease. The hypertension optimal treatment study indicates that the treatment goal is to reduce blood pressure to 140/85 mm Hg. Hypertension is a chronic elevation of blood pressure that, in the long-term, causes end-organ damage and results in increased morbidity and mortality. Blood pressure is the product of cardiac output and systemic vascular resistance. It follows that patients with arterial hypertension may have an increase in cardiac output, an increase in systemic vascular resistance, or both. In the younger age group, the cardiac output is often elevated, while in older patients increased systemic vascular resistance and increased stiffness of the vasculature play a dominant role. Vascular tone may be elevated because of increased adrenoceptor stimulation or increased release of peptides

such as angiotensin or endothelins. The final pathway is an increase in cytosolic calcium in vascular smooth muscle causing vasoconstriction. Several growth factors, including angiotensin and endothelins, cause an increase in vascular smooth muscle mass, termed vascular remodelling. Both an increase in systemic vascular resistance and an increase in vascular stiffness augment the load imposed on the left ventricle; this induces left ventricular hypertrophy and left ventricular diastolic dysfunction.[6]

Valsartan is an oral medication that is used to treat high blood pressure and congestive heart failure. It belongs to a class of drugs called angiotensin receptor blockers (ARBs). Angiotensin, formed in the blood by the action of angiotensin converting enzyme (ACE), is a powerful chemical that attaches to angiotensin receptors found in many tissues but primarily on smooth muscle cells of blood vessels. Angiotensin's attachment to the receptors causes the blood vessels to narrow (vasoconstrict) which leads to an increase in blood pressure (hypertension). Valsartan blocks the angiotensin receptor. By blocking the action of angiotensin, Valsartan dilates blood vessels and reduces blood pressure.[7]

MATERIALS AND METHODS

Valsartan (Cadila Pharmaceuticals), Pioglitazone HCl (Aarti Drugs,Mumbai), HPMC K4M, HPMCK15M, HPMC K100M (Polymer), Dicalcium Phosphate (Diluent), Magnesium Stearate (Lubricant) and Talc (Glidant).

FORMULATION OF SUSTAINED RELEASE BILAYERED TABLETS OF VALSARTAN AND PIOGLITAZONE HCl:

Bilayered tablets of Valsartan and Pioglitazone HCl were prepared by direct compression method. Accurate amount of the active ingredients and all additives were homogenously blended using geometric dilution method after passing through 40# sieve, Magnesium stearate and talc was added at last for lubrication and mix thoroughly into polythene bag. Finally, the tablets were prepared by using 12 mm flat punch by rotary tablet punching machine. (Table 1)

TABLE 1: FORMULATION OF BATCH F1 TO F9 BY DIRECT COMPRESSION METHOD

Table I: For Layer 1 : Valsaratan

Ingredients	Quantity in mg		
	F1	**F2**	**F3**
Valsartan	40	40	40
HPMCK4M	135	-	-
HPMCK15M	-	135	-
HPMCK100M	-	-	135
Dicalcium Phosphate	122	122	122
Magnesium stearate	1.5	1.5	1.5
Talc	1.5	1.5	1.5
Total Weight	300	300	300

Table II: For Layer 2 : Pioglitazone HCl

Ingredients	Quantity in mg		
	F4	**F5**	**F6**
Pioglitazone HCl	30	30	30
HPMCK4M	135	-	-
HPMCK15M	-	135	-
HPMCK100M	-	-	135
Dicalcium Phosphate	132	132	132
Magnesium stearate	1.5	1.5	1.5
Talc	1.5	1.5	1.5
Total Weight	300	300	300

Table III: BIlayer Tablet Of Valsartan and Pioglitazone HCl

Ingredients	Quantity in mg		
	F7	**F8**	**F9**
Valsartan	40	40	40
HPMCK15M	135	165	195
Dicalcium Phosphate	122	92	62
Magnesium stearate	1.5	1.5	1.5
Talc	1.5	1.5	1.5
Pioglitazone HCl	30	30	30
HPMCK100M	135	165	195
Dicalcium Phosphate	132	102	72
Magnesium stearate	1.5	1.5	1.5
Talc	1.5	1.5	1.5
Total Weight	600	600	600

Preformulation Studies:

Angle of repose:

The angle of repose of powder was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted at a distance of 2 cm from the flat surface. The powder was allowed to flow through the funnel freely onto the surface until the pile of powder touches the lower end of funnel. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

$= \tan^{-1} h/r$

Where, h and r are the height and radius of the powder cone respectively.

Bulk density and Tapped density

Both bulk density (BD) and tapped density (TD) were determined by pouring 10 g of powder from each formula into a 50 mL measuring cylinder. The cylinder was tapped three times onto a hard surface from the height of 2 cm at 2 second intervals. This volume was considered as a bulk volume. The tapping was continued until no further change in volume was noted. This volume was considered as a tapped volume. BD and TD were calculated using the following formulas

BD = weight of the powder/volume of the packing

TD = weight of the powder/tapped volume of the packing

Compressibility index

The compressibility index of the Powder was determined by Carr's compressibility index

Carr's index (%) = [(TD – BD) × 100]/TD [8]

Haushner's ratio

Flow properties of powder was determined by Hausner's ratio using following formula:

H = Tapped density / Bulk density

A Hausner ratio greater than 1.25 is considered of poor flow ability.[9]

2. Evaluation of tablet:

Appearance:

Tablets were evaluated for its size, shape, colour, odor, taste etc.

Thickness and Diameter:

The size of tablets was measured by Vernier calipers.

Weight variation test

To study weight variation, 20 tablets of each formulation was weighed using an electronic balance and the test was performed according to the official method.[10]

Hardness and friability

For each formulation, the hardness and friability of 6 tablets was determined using the Hardness tester and the friabilator.[11,12]

In Vitro release **studies**

Release of the prepared tablets was determined up to 12 hour using U.S.P type II paddle type dissolution rate test apparatus. For first 2 hrs, 700 ml of 0.1 N HCl was used as dissolution medium and pH 6.8 phosphate buffer for the rest of the period as dissolution medium. The paddle was allowed to rotate at a speed of 50 rpm and 37 ± 0.5ºC temperature was maintained throughout the experiment. Samples of 10 ml were withdrawn at the interval of 10 min and dissolution medium were replaced with same volume of fresh dissolution media after each withdrawal. The samples were analyzed for drug contents at 248 nm and 268 nm in 0.1 N HCl solution and for pH 6.8 buffer solution absorbances were measured at 248nm and 280nm using UV- VIS. [13,14]

Drug content uniformity

10 Tablets were taken for drug content uniformity. Each tablet was crushed and dissolved in 0.1 N HCl solution and solution is filtered and absorbance was measured at 248 nm and 268 nm.

Swelling index

Measurement of the swelling index was carried out to gain an insight into the phenomenon of polymer hydration and to evaluate the extent of media penetration within the tablets. The swelling index was determined by equilibrium weight gain method. The study was carried out in petriplate. The tablets was accurately weighed, placed in petriplate, immersed in 0.1 N HCl solution for 2 hrs and then immersed in pH 6.8 buffer solution for 10 hr. At regular intervals of 1,2,3,4 hrs and up to 12 hrs tablet was weighted. The tablet was blotted lightly with the tissue paper to remove excess test liquid and re-weighed. The swelling index (SI) of each tablet was calculated according to the following equation:

S.I. = $\{(Wt - W_0) / W_0\} \times 100$

Where- W_0 = initial weight,

t= final weight [15]

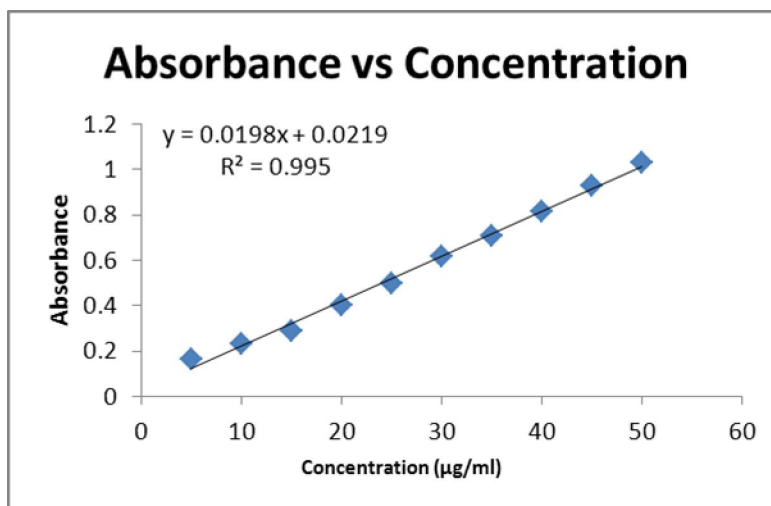## RESULTS

Standard Curve of Valsartan and Pioglitazone HCl:
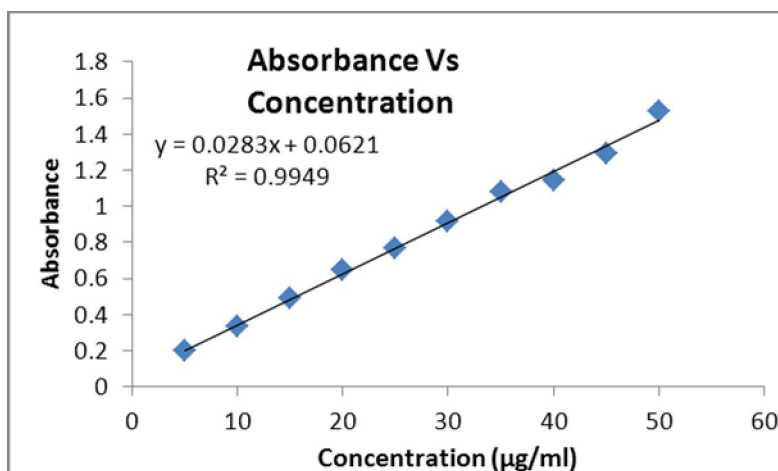

Figure 1: Standard Curve of Valsartan in 0.1 N HCl

Figure 2: Standard Curve of Valsartan in 6.8 pH Buffer
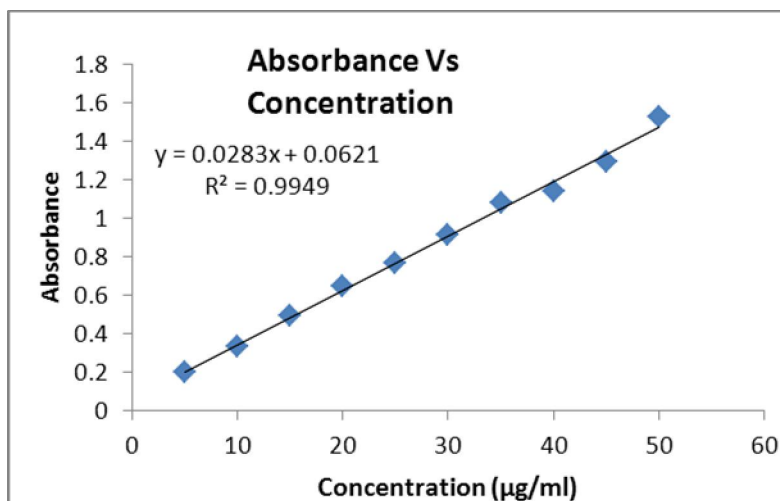
Figure 3: Standard Curve of Pioglitazone HCl in 0.1 N HCl
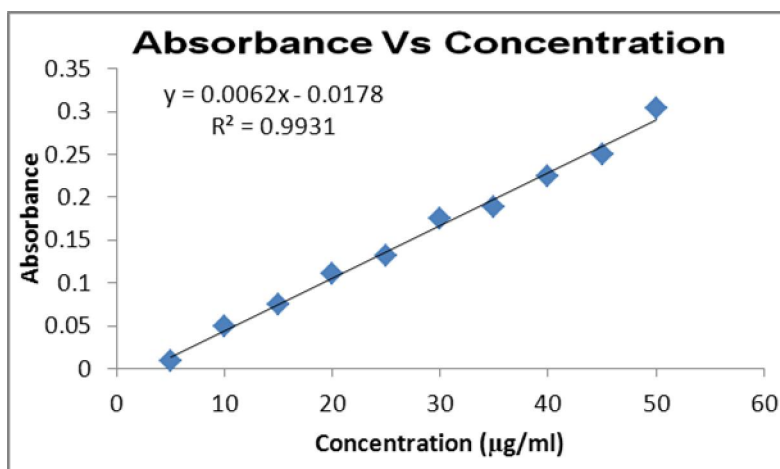

Figure 4: Standard Curve of Pioglitazone HCl in 6.8 pH buffer

Preformulation study of Powder mixture:

TABLE 2: BULK DENSITY, TAPPED DENSITY, ANGLE OF REPOSE, CARR'S COMPRESSIBILITY INDEX AND HAUSNER'S RATIO

Sr. No.	Formulation code	Bulk density	Tapped density	Angle of repose	Carr's compressibility index	Hausner ratio
1	F1	0.8197 ± 0.0067	0.9466 ± 0.0184	26 ± 0.5525	13.393 ± 1.039	1.1547 ± 0.013
2	F2	0.7958 ± 0.0097	0.8956 ± 0.0123	27.157 ± 0.5965	11.126 ± 2	1.1255 ± 0.025
3	F3	0.8067 ± 0.017	0.8983 ± 0.0122	27.1511 ± 0.2724	10.202 ± 1.05	1.1137 ± 0.013
4	F4	0.8380 ± 0.01	0.9435 ± 0.0152	26.01 ± 0.55	11.175 ± 0.528	1.1258 ± 0.006
5	F5	0.8242 ± 0.0103	0.9588 ± 0.023	26.20 ± 0.86	14.01 ± 0.996	1.1631 ± 0.013
6	F6	0.8130 ± 0.006	0.9555 ± 0.014	25.732 ± 0.2698	14.908 ± 0.5795	1.175 ± 0.008
7	F7 Valsartan	0.7916 ± 0.0095	0.9038 ± 0.0168	26.5723 ± 0.5730	12.40 ± 0.597	1.141 ± 0.007
8	F7 Pioglitazone	0.8022 ± 0.0098	0.9259 ± 0.008	26.97 ± 0.891	13.358 ± 1.52	1.1544 ± 0.020
9	F8 Valsartan	0.7865 ± 0.0125	0.8851 ± 0.0156	26.491 ± 0.99	11.141 ± 0.2647	1.1253 ± 0.003
9	F8 Pioglitazone	0.7959 ± 0.0130	0.8826 ± 0.019	26.668 ± 0.595	9.815 ± 1.225	1.108 ± 0.015
10	F9 Valsartan	0.80462 ± 0.019	0.9012 ± 0.021	26.10 ± 0.70	10.722 ± 0.3123	1.120 ± 0.0039
11	F9 Pioglitazone	0.7957 ± 0.0036	0.90 ± 0.008	25.973 ± 0.555	11.667 ± 1.167	1.1322 ± 0.014

Evaluation of Tablets

TABLE 3: HARDNESS, THICKNESS, DIAMETER, PERCENTAGE FRIABILITY AND WEIGHT VARIATION OF FORMULATION F1 TO F9

Formulation	Hardness (kg/cm^2) n=6	Thickness (mm) n=3	Diameter (mm) n=3	% Friability n=6	Weight variation (mg) n=20
F1	4.118 ± 0.0516	2.323 ± 0.011	12.523 ± 0.023	0.635 ± 0.034	299.55 ± 4.22
F2	4.246 ± 0.0502	2.336 ± 0.011	12.556 ± 0.005	0.682 ± 0.137	297.75 ± 4.29
F3	4.138 ± 0.0526	2.31 ± 0.01	12.53 ± 0.02	0.608 ± 0.044	299.25 ± 2.863
F4	4.334 ± 0.0466	2.326 ± 0.005	12.523 ± 0.005	0.728 ± 0.082	299 ± 2.714
F5	4.126 ± 0.052	2.333 ± 0.015	12.506 ± 0.005	0.715 ± 0.048	298.3 ± 3.04
F6	4.25 ± 0.038	2.316 ± 0.011	12.526 ± 0.005	0.557 ± 0.134	299.8 ± 3.3
F7	4.134 ± 0.036	3.613 ± 0.015	12.55 ± 0.017	0.4775 ± 0.04	601.05 ± 2.94
F8	4.2 ± 0.057	3.646 ± 0.015	12.52 ± 0.01	0.5246 ± 0.07	598.55 ± 3.50
F9	4.214 ± 0.0251	3.64 ± 0.01	12.54 ± 0.011	0.7 ± 0.095	599.95 ± 3.47

TABLE 4: CONTENT UNIFORMITY AND SWELLING INDEX OF FORMULATION F1 TO F9

Batch	Drug content uniformity (%), n=10	Swelling Index (%) n=3
F1	96.03947368	135.12 ± 0.90
F2	98.25	148.84 ± 0.644
F3	94.82894737	165.85 ± 1.08
F4	97.24074074	136.93 ± 0.192
F5	93.94444444	148.19 ± 1.214
F6	94.44444444	164.02 ± 0.242
F7 Valsartan	96.5954549	132.20 ± 0.787
F7 Pioglitazone HCl	93.42189368	
F8 Valsartan	96.97258393	146.3 ± 0.508
F8 Pioglitazone HCl	96.30051409	
F9 Valsartan	95.80578313	149.12 ± 0.512
F9 Pioglitazone HCl	96.07662139	

TABLE 5: *In-vitro* **DISSOLUTION OF BATCH F1 TO F6**

TIME (Min)	% DRUG RELEASE					
	F1	F2	F3	F4	F5	F6
30	4.912 ± 0.296	14.092 ± 0.243	6.263 ± 0.243	14.340 ± 1.496	12.910 ± 0.197	7.0430 ± 0.149
60	9.339 ± 0.2813	15.859 ± 0.515	9.463 ± 0.191	30.130 ± 0.388	26.320 ± 0.269	10.558 ± 0.49
90	9.563 ± 0.292	16.297 ± 0.201	6.358 ± 0.105	41.660 ± 0.203	32.100 ± 0.265	20.380 ± 0.326
120	10.03 ± 0.191	15.690 ± 0.204	5.234 ± 0.103	49.730 ± 0.081	42.100 ± 0.129	23.740 ± 0.124
180	18.669 ± 0.179	18.120 ± 0.234	16.824 ± 0.298	69.299 ± 0.346	58.590 ± 0.600	27.870 ± 0.600
240	31.621 ± 0.178	24.928 ± 0.343	23.230 ± 0.311	75.248 ± 0.010	64.020 ± 1.030	30.370 ± 0.340
300	39.700 ± 0.246	26.373 ± 0.126	40.250 ± 0.243	81.655 ± 1.241	68.110 ± 0.911	44.294 ± 0.354
360	52.763 ± 0.248	33.980 ± 0.127	53.660 ± 0.447	84.52 ± 1.510	76.840 ± 1.200	51.170 ± 0.586
420	57.439 ± 0.119	57.120 ± 0.257	47.880 ± 0.364	89.610 ± 0.930	79.450 ± 0.610	56.710 ± 0.340
480	63.936 ± 0.141	64.366 ± 0.169	52.680 ± 0.228	96.553 ± 0.660	84.880 ± 0.700	65.110 ± 0.913
540	75.551 ± 0.125	76.44 ± 0.128	58.990 ± 0.062	99.350 ± 0.371	89.970 ± 0.373	72.400 ± 1.250
600	87.485 ± 0.114	83.93 ± 0.076	66.871 ± 0.122		93.700 ± 0.940	79.970 ± 0.935
660	99.78 ± 0.308	87.42 ± 0.122	73.800 ± 0.071		99.060 ± 1.245	85.000 ± 0.880
720		98.67 ± 0.078	79.490 ± 0.251			93.890 ± 0.606

TABLE 6: *In-vitro* DISSOLUTION OF BATCH F7 TO F9

| Time (min)	% DRUG RELEASE					
	F7 Valsartan	F7 Pioglitazone	F8 Valsartan	F8 Pioglitazone	F9 Valsartan	F9 Pioglitazone
30	2.939 ± 0.296	1.480 ± 0.176	3.028 ± 0.455	1.467 ± 0.373	2.234 ± 0.357	2.375 ± 0.224
60	3.460 ± 0.172	2.040 ± 0.110	4.020 ± 0.200	2.790 ± 0.114	3.960 ± 0.220	3.215 ± 0.242
90	4.185 ± 0.380	2.425 ± 0.129	4.960 ± 0.360	2.697 ± 0.155	5.690 ± 0.210	5.900 ± 0.278
120	5.626 ± 0.246	2.919 ± 0.060	5.225 ± 0.190	3.53 ± 0.09	7.160 ± 0.230	8.730 ± 0.233
180	5.163 ± 0.269	5.058 ± 1.410	8.163 ± 2.430	8.264 ± 2.846	6.350 ± 0.410	10.189 ± 1.310
240	7.041 ± 0.515	5.336 ± 2.270	8.115 ± 2.230	15.366 ± 2.200	18.860 ± 0.730	17.030 ± 3.650
300	12.070 ± 0.470	4.450 ± 0.9347	13.120 ± 0.380	22.528 ± 1.710	25.890 ± 0.660	32.630 ± 1.720
360	13.830 ± 0.326	8.480 ± 0.929	13.260 ± 0.690	28.040 ± 1.070	26.660 ± 0.463	49.090 ± 1.370
420	32.820 ± 0.153	11.370 ± 1.240	22.710 ± 0.210	43.190 ± 0.684	32.040 ± 0.930	57.020 ± 2.800
480	44.720 ± 1.080	29.200 ± 2.350	37.220 ± 1.100	47.240 ± 3.320	44.250 ± 0.570	75.250 ± 2.530
540	50.240 ± 0.440	47.130 ± 2.110	46.780 ± 0.570	56.540 ± 0.698	52.970 ± 0.524	83.600 ± 3.380
600	62.750 ± 0.019	57.260 ± 0.690	64.250 ± 0.700	59.400 ± 1.790	62.700 ± 0.730	89.520 ± 1.930
660	64.080 ± 0.130	83.040 ± 0.910	66.900 ± 1.210	78.920 ± 1.860	61.280 ± 0.400	9.310 ± 1.200
720	63.590 ± 5.100	90.231 ± 7.370	78.420 ± 3.820	84.800 ± 3.310	82.940 ± 0.930	95.480 ± 1.270
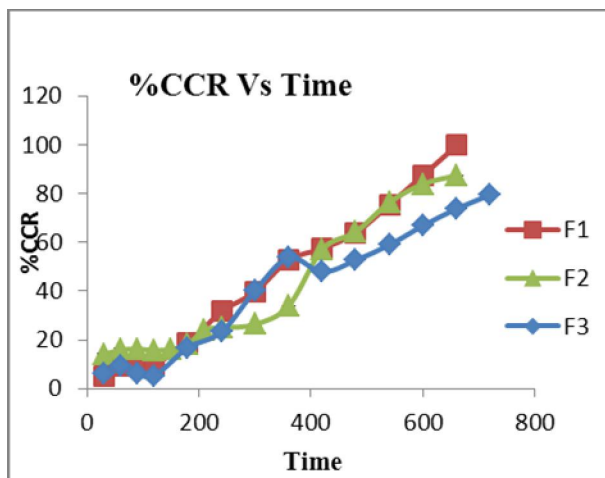
Figure 5: In-vitro dissolution profile of F1 to F3
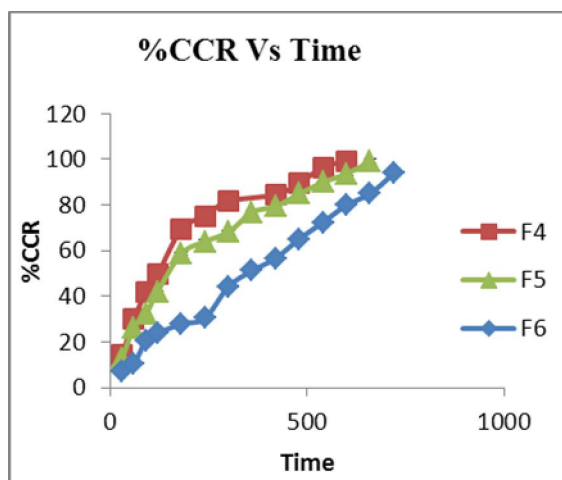

Figure 6: In-vitro dissolution profile of F4 to F6
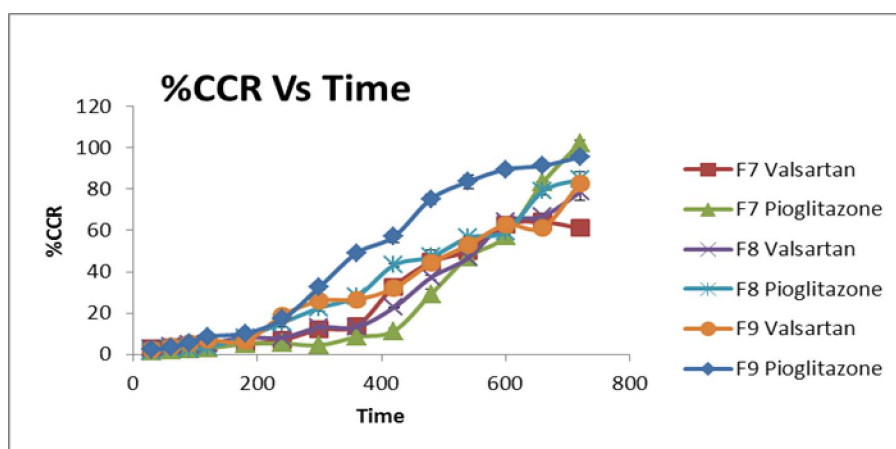

Figure 7: In-vitro dissolution profile of formulation F7 to F9

Where, %CCR = Cumulative % drug release

DISCUSSION

The use of HPMC polymer for the preparation of sustained release bilayered tablet is highly effective and easily available. These polymers such as HPMC K4M, HPMC K15M, HPMC K100M when comes into contact with aqueous environment, leads to swell. So, provide release of both drugs for sustained period of time.

The results obtained from preformulation studies such as angle of repose, bulk density, tapped density, carr's compressibility index etc. of powder mixture shows good flow property. (Table 2)

The Formulation (F9) considered as optimized formulation. The hardness of tablets found was between 4.214 ± 0.0251 kg/cm^2. Percentage friability was observed between 0.7 ± 0.095 %, which was within acceptable limit. Weight variation of tablets was found within acceptable limit as per Indian pharmacopeia (Table 3).

Percentage drug content of all the formulations were found between 93.98 to 98.25 % of drug which was within acceptable limit. Swelling index of all formulation was found in a range of 132.20 ± 0.787 to 165.85 ± 1.08. (Table 4)

In vitro dissolution of formulation F9 showed better drug release upto 12 hrs. Formulation F9 is considered as optimized formulation because of uniform and sustained release of both drug upto 12 hrs. (Figure 7)

CONCLUSION

In bilayered tablet of Valsartan and Pioglitazone HCl both layers are used as sustained release. Optimized formulation containing 65% HPMC K15M in Valsartan layer and 65% HPMC K100M in Pioglitazone HCl layer shows better drug release upto 12 hrs.

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