Research Article

Formulation Development and Evaluation of Modified Release Tablet using a Fixed Dose Combination of Antidiabetic Agents

Nishit Gohel[1*], D M Patel[2], Komal Patel[3], Jignasa Modi[4]
[1]School of Pharmacy, RK University, Rajkot and Parul Institute of Pharmacy and Research, Vadodara, Gujarat, India.
[2]Shri Sarvajanik Pharmacy College, Mehsana, Gujarat, India.
[3]Parul Institute of Pharmacy, Parul University, Vadodara, Gujarat, India.
[4]Bhagwan Mahavir College of Pharmacy, Surat, Gujarat, India.
***Corresponding author's E-mail:** nishitgohel@gmail.com

Received: 05-12-2016; **Revised:** 26-01-2017; **Accepted:** 14-02-2017.

ABSTRACT

The present invention relates to formulate the bilayer tablet of antidiabetic agents comprising Vildagliptin (VLD) immediate release layer and Metformin Hydrochloride (MET) sustained release layer. VLD makes pancreas to produce insulin which helps to improve the glycaemic control in body and MET makes a better use of insulin in body. Both drugs does not alter pharmacokinetics of one another and hence attempt was made to formulate bilayer tablet of these two drugs to improve patient compliance, bioavailability, reduce dosing frequency and reduce GI side effect of MET. VLD (50mg) layer contained Cross Povidone as a super disintegrant and MET (500mg) layer composed different hydrophilic controlled release polymers like, HPMC K100M CR, Carbopol 934P and PVP K30 as a binder. The tablets were evaluated for all physicochemical properties. In-vitro drug release studies were performed as per USP in phosphate buffer pH 1.2 and phosphate buffer pH 6.8, using USP type I apparatus (Basket type). Based on *in vitro* drug release data for formulations A5 and F8 were selected as the optimized formulations. VLD immediate release layer (F4) contained 2.25% Cross povidone and MET sustained release layer (F8) contained combination of polymers, HPMC K100M CR and Carbopol 934P 15% and 7.5% respectively. The result obtained for formulation A5F8 showed that VLD was released 98.90% in 30 minutes and MET was released 98.92% for 12 hours satisfactorily. Optimized formulation observed to follow Higuchi model when different kinetic models were applied. The stability studies revealed no significant changes in physical and chemical properties of optimized formulation.

Keywords: Bilayer Tablet, Antidiabetic agents, Vildagliptin, Metformin Hydrochloride, Cross povidone, HPMC K100M CR, Carbopol 934P.

INTRODUCTION

Diabetes mellitus type 2 (Noninsulin dependent diabetes Mellitus or adult-onset diabetes) is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency. Non-insulin dependent diabetes mellitus is a major and growing public health problem throughout the world. Number of patients diagnosed with type II diabetes will be more than double to 300 million before 2025 according to recent estimates[1]. Normal plasma glucose levels maintenance is a key factor in reducing the risk of developing diabetes complications[2-3].

Metformin is a biguanide antihyperglycemic agent used in the treatment of non-insulin dependent diabetes mellitus (NIDDM). Metformin is the only antidiabetic drug that has been conclusively shown to prevent the cardiovascular complications of diabetes and it is one of only two oral antidiabetic medicines, in the World Health Organization Model List of Essential Medicines[4]. In spite of its favorable clinical response and lack of significant draw backs, chronic therapy with metformin hydrochloride suffers from certain problems. The marketed immediate release products need to be administered 2-3 times daily. The current metformin therapy is associated with high incident of GI side effects seen in about 30% of patients[5]. Moreover inherent compressibility, very high solubility (i.e. >300 mg/ml at 25° C), initial burst effect of drug from immediate release tablets and less bioavailability (60%) due to saturable absorption process can lead to difficulty in providing an optimum therapeutic effect from a single formulation.

The fixed dose combination of a Vildagliptin (DPP-4 Inhibitor) with Metformin allows a broad and complementary spectrum of anti-diabetic actions. Such fixed dose combination does not increase the risk of hypoglycemia, does not promote weight gain, and does not cause adverse effects caused by various other oral anti diabetic combinations.

Both the drugs have a complimentary and possibly synergistic effect on glycemic control and reduced glycosylated heamoglobin[6].

Hence, attempts were made to formulate bilayer tablet, containing immediate release Vildagliptin layer and sustained release Metformin Hydrochloride layer. Bi-layer 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 initial dose and second layer is as maintenance dose[7].

Such formulation can offer longer transit time in the stomach and can act as an *in vivo* reservoir that releases drug at a controlled rate continuously over a prolonged time for absorption in the stomach and the intestine.

As Bi-layer tablets offer several advantages over conventional therapy, it is proposed in the present study to develop a competitive formulation of both drugs by using different polymers alone or in combination, in order to get the prolonged release and their effect on release pattern[8-12].

MATERIALS AND METHODS

Materials

Metformin HCl was received as a gift sample from IPCA Laboratories Limited, Mumbai, India.

Vildagliptin was obtained as a gift sample from Mylan Laboratories Limited, Nashik, India.

Methocel® K100M CR (HPMC) was collected as a gift sample from Colorcon Asia Pvt. Ltd.

Avicel PH101 (Microcrystalline cellulose) and Magnesium stearate was collected as a gift sample from Signet corporation.

All other excipients and chemicals were purchased by ensuring pharmacopoeial grade and analytical grades respectively.

Methods

Preformulation Study of Drugs

Preformulation studies were carried out to investigate physicochemical properties of drug substance alone and in combination with other drug as well as excipients.

Following studies were performed to characterize drugs and their interaction with and excipients.

Identification of Drugs by Melting Point

Melting point was determined by taking small amount of pure drug in a different capillary tube closed at one end.

The capillary tube was placed in an electrically operated digital melting point apparatus and the temperature at which the drug melts was recorded.

Identification of Drugs and Compatibility Study by FTIR Spectroscopy

FTIR of pure drugs, their mixture with excipients as well as mixture of both drugs was taken and spectrum was recorded.

Sample pellets were prepared by mixing individual drugs, both drugs together and drugs along with excipients uniformly with an approximately 10-15% of dry KBr powder.

Sample was scanned in the region of 4000-500 cm^{-1} using a Bruker Alpha spectrophotometer. Scanned spectrum of pure drug was compared with standard range.

Analytical Method

Absorption maxima λmax for Vildagliptin and Metformin HCl was determined by scanning standard stock solutions of both drugs between 200-400nm in UV spectrophotometer.

From the linearity of both drugs from standard calibration curves, simultaneous estimation was carried out by Q-Absorption ratio method.

For Q-absorption ratio method λ_{max} of Metformin HCl i.e. 236 nm is selected and isoabsorption point is selected at 220 nm.

Calibration curve is recorded for both at 236 and 220 nm, and absorptivity value for drug at particular wavelength was considered from that value of slope.

Simultaneous estimation was carried out using following equation.

X = 236 nm, Y = 220 nm

$C_X = (Q_M-Q_Y) \times A1 / (Q_X-Q_Y) \times a_{X1}$

$Cy = (Q_M-Q_X) \times A1 / (Q_Y-Q_X) \times a_{Y1}$

Cx = Concentration of Metformin HCl

Cy = Concentration of Vildagliptin

Q_X = Ratio of absorptivity of X at λ2 and at λ1

Q_Y = Ratio of absorptivity of Y at λ2 and at λ1

a_{X1} = Absorptivity of X at λ1

a_{Y1} = Absorptivity of Y at λ1

Q_M = Q absorbance ratio of sample at λ2 and at λ1

A1 = Absorbance of X at λ1

Preparation of Bilayer Tablets

Preparation of Vildagliptin Immediate Release Layer

Different batches of immediate release layer of Vildagliptin (A1 to A9) were prepared by direct compression technique as per the composition given in the Table 1.

Vildagliptin, microcrystalline cellulose and superdisintegrant were passed through sieve no. 40# and thoroughly mixed in a polybag for approximately 5 minutes.

This blend was lubricated with magnesium stearate and talc for 2 minutes and processed for direct compression by using 16 mm punch at 10 station tablet press at an average weight of 200 mg.

Preparation of Metformin HCl Sustained Release Layer

Different batches of sustained release layer of Metformin HCl (C1 to C12) were prepared by wet granulation technique as per the composition given in Table 2.

Metformin HCl, HPMC K100M CR, HPMC K4M, Carbopol 934P and Lactose monohydrate were passed through sieve no.40# and mixed in polybag for 10 minutes.

Above mixture was granulated with PVP K30 solution using water and Isopropyl alcohol as a solvent.

Wet milling was carried out through sieve no. 18 # and then dried in tray dryer at 400C to get desired loss on drying. Dried blend was passed through mesh no.22 #. Finally mixture was lubricated with Aerosil and Magnesium stearate for 5 minutes.

Preparation of Bilayer Tablets

Bilayer tablets were prepared by the same method as mentioned for individual layers. Composition of Bilayer tablets was same as that of formulation A5C11.

Evaluation of Powder Blends

Before compression the lubricated blends were evaluated for different parameters like bulk density, tapped density, angle of repose, Carr's index and Hausner's ratio to determine the flow behaviour.

Evaluation of Tablets

Prepared tablets of both layers were evaluated for physical parameters like, hardness, thickness, weight variation and friability. Tablets of Vildagliptin layer were evaluated for disintegration time also.

For hardness testing, Mosanto hardness tester and for friability, Roche friabilator, Electrolab, were used. Weight variation was performed as per the official method. Digital vernier caliper was used to measure thickness and Electrolab disintegration test apparatus was used to determine disintegration time for Vildagliptin layer.

Drug Content Estimation

Twenty tablets were selected randomly and average weight was calculated. Tablets were crushed in a mortar and accurately weighed amount of average tablet was taken from the crushed blend.

The drug content in each tablet was estimated after suitable dilution at λ_{max} 232 nm of Metformin HCl and at λ_{max} 210 nm of Vildagliptin, against blank reference and reported.

***In vitro* Drug Release Study**

In vitro drug release study of the samples was carried out using USP type 1 apparatus at 100 rpm using 1000 ml of buffer solution pH 1.2 and phosphate buffer pH 6.8 as a dissolution medium. Temperature of the dissolution medium was maintained at 37 ± 0.50°C, aliquots of 10 ml of sample was withdrawn at specified time interval.

The concentration of both drugs was determined by standard calibration curves and simultaneous estimation.

Theoretical dissolution profile of Metformin HCl sustained release layer

The theoretical dissolution profile for Metformin HCl sustained release was calculated using formula and cumulative percentage drug release was considered as target for Metformin HCl SR layer.

Table 1: Composition of Vildagliptin immediate release layer

Ingredients (mg)	A1	A2	A3	A4	A5	A6	A7	A8	A9
Vildagliptin	50	50	50	50	50	50	50	50	50
Microcrystalline cellulose	144	141	138	142.5	141	139.5	142.5	139.5	136.5
Croscarmellose Sodium	1.5	4.5	7.5	-	-	-	-	-	-
Cross Povidone	-	-	-	3	4.5	6	--	--	--
Sodium Starch Glycolate	-	-	-	--	--	--	3	6	9
Magnesium stearate	3	3	3	3	3	3	3	3	3
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total Weight (mg)	200	200	200	200	200	200	200	200	200

Table 2: Composition of Metformin HCl Sustained Release Layer

Ingredients	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12
Metformin HCl	500	500	500	500	500	500	500	500	500	500	500	500
HPMC K100M CR	80	120	160	200	250	350	40	80	120	40	80	120
HPMC K4M	-	-	-	-	-	-	40	60	80	-	-	-
Carbolpol 934P	-	-	-	-	-	-	-	-	-	40	60	80
Lactose monohydrate	160	120	80	125	100	50	157.6	97.6	37.6	157.6	97.6	37.6
Microcrystalline cellulose	-	-	-	125	100	50	-	-	-	-	-	-
Povidone K30	50	50	50	30	30	30	50	50	50	50	50	50
Water:IPA (1:1)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Aerosil	-	-	-	-	-	-	2.4	2.4	2.4	2.4	2.4	2.4
Magnesium stearate	10	10	10	20	20	20	10	10	10	10	10	10

Table 3: Blend properties of Vildagliptin IR layer

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (θ)	Carr's index (%)	Hausner's ratio
A1	1.12 ± 0.02	1.33 ± 0.01	28.19 ± 1.06	15.78 ± 1.12	1.19 ± 0.01
A2	1.06 ± 0.01	1.14 ± 0.01	27.29 ± 0.21	7.01 ± 0.14	1.08 ± 0.01
A3	1.17 ± 0.02	1.33 ± 0.04	28.17 ± 0.04	12.04 ± 0.05	1.13 ± 0.02
A4	1.08 ± 0.03	1.20 ± 0.02	27.43 ± 0.30	10.35 ± 0.13	1.11 ± 0.01
A5	1.09 ± 0.04	1.18 ± 0.02	23.62 ± 0.06	11.36 ± 0.15	1.08 ± 0.01
A6	1.10 ± 0.02	1.26 ± 0.02	29.43 ± 0.49	12.69 ± 0.11	1.14 ± 0.02
A7	1.07 ± 0.01	1.19 ± 0.49	28.52 ± 0.20	10.08 ± 0.42	1.11 ± 0.01
A8	1.15 ± 0.03	1.39 ± 0.02	26.84 ± 0.05	17.26 ± 0.07	1.22 ± 0.02
A9	1.13 ± 0.03	1.25 ± 0.04	27.51 ± 0.05	9.84 ± 0.06	1.11 ± 0.02
C1	0.248 ± 0.01	0.285 ± 0.02	26.71 ± 0.07	12.98 ± 0.05	1.14 ± 0.03
C2	0.254 ± 0.03	0.294 ± 0.08	25.31 ± 0.04	13.60 ± 0.07	1.17 ± 0.02
C3	0.253 ± 0.02	0.285 ± 0.05	27.64 ± 0.33	11.22 ± 0.05	1.20 ± 0.03
C4	0.247 ± 0.03	0.281 ± 0.05	28.14 ± 0.08	12.09 ± 0.04	1.18 ± 0.03
C5	0.246 ± 0.01	0.296 ± 0.04	26.97 ± 0.36	16.89 ± 0.08	1.20 ± 0.03
C6	0.245 ± 0.08	0.292 ± 0.09	27.64 ± 0.07	16.09 ± 0.03	1.19 ± 0.04
C7	0.251 ± 0.07	0.290 ± 0.07	29.26 ± 0.05	13.44 ± 0.17	1.15 ± 0.02
C8	0.255 ± 0.08	0.280 ± 0.03	26.08 ± 0.07	8.92 ± 0.19	1.09 ± 0.03
C9	0.237 ± 0.003	0.274 ± 0.007	27.77 ± 0.23	13.50 ± 1.41	1.15 ± 0.02
C10	0.250 ± 0.08	0.287 ± 0.03	26.08 ± 0.07	12.89 ± 0.19	1.14 ± 0.03
C11	0.252 ± 0.08	0.285 ± 0.03	26.08 ± 0.07	11.57 ± 0.19	1.13 ± 0.03
C12	0.248 ± 0.08	0.276 ± 0.03	26.08 ± 0.07	10.14 ± 0.19	1.11 ± 0.03

*Data in table represented as mean ± Std. Dev. With n = 3, Where, n= Number of replicates

Table 4: Post-compression parameters of Vildagliptin IR Layer and Metformin HCl SR Layer Tablet

Batch code	Weight variation (mg)	Hardness (Kg/cm^2)	Diameter (mm)	Friability (%)	Drug content (%)
A1	198.93 ± 0.41	2.46 ± 0.25	15.7 ± 0.25	0.606 ± 0.014	97.89 ± 0.41
A2	200.31 ± 0.71	2.71 ± 0.36	15.9 ± 0.11	0.361 ± 0.033	98.53 ± 0.31
A3	200.63 ± 0.97	2.81 ± 0.11	15.7 ± 0.44	0.316 ± 0.031	97.93 ± 0.12
A4	199.5 ± 0.02	2.96 ± 0.05	16.1 ± 0.08	0.381 ± 0.093	98.80 ± 0.96
A5	200.74 ± 0.24	2.71 ± 0.26	15.91 ± 0.21	0.475 ± 0.032	99.65 ± 0.89
A6	199.30 ± 0.91	2.61 ± 0.11	15.8 ± 0.11	0.463 ± 0.036	98.62 ± 0.21
A7	197.69 ± 0.55	2.76 ± 0.25	16.1 ± 0.68	0.581 ± 0.077	97.91 ± 0.76
A8	198.89 ± 0.17	2.81 ± 0.22	15.8 ± 0.21	0.458 ± 0.035	98.10 ± 0.11
A9	198.21 ± 0.15	2.06 ± 0.11	15.9 ± 0.41	0.534 ± 0.074	98.73 ± 0.89
C1	797.22 ± 0.105	5.23 ± 0.25	15.51 ± 0.89	0.586 ± 0.020	98.40 ± 0.31
C2	798.82 ± 0.026	5.31 ± 0.26	16.10 ± 0.74	0.592 ± 0.004	98.10 ± 0.91
C3	798.37 ± 0.046	5.33 ± 0.05	15.58 ± 0.61	0.586 ± 0.035	97.98 ± 0.85
C4	798.92 ± 0.032	5.53 ± 0.05	15.90 ± 0.21	0.555 ± 0.006	97.50 ± 0.86
C5	799.15 ± 0.054	5.33 ± 0.05	16.09 ± 0.12	0.547 ± 0.054	98.40 ± 0.70
C6	799.18 ± 0.330	5.36 ± 0.15	15.87 ± 0.01	0.614 ± 0.007	99.30 ± 0.98
C7	799.59 ± 0.602	5.56 ± 0.05	15.70 ± 0.98	0.492 ± 0.004	98.75 ± 0.32
C8	799.81 ± 0.261	5.60 ± 0.26	15.90 ± 0.90	0.659 ± 0.013	98.30 ± 0.70
C9	799.74 ± 0.365	5.50 ± 0.26	15.95 ± 0.97	0.561 ± 0.015	98.38 ± 0.01
C10	798.92 ± 0.72	5.16 ± 0.05	15.97 ± 0.04	0.626 ± 0.005	99.45 ± 0.01
C11	799.46 ± 0.45	5.36 ± 0.11	15.99 ± 0.01	0.518 ± 0.012	99.35 ± 0.01
C12	799.10 ± 0.54	5.72 ± 0.11	15.86 ± 0.07	0.567 ± 0.022	98.60 ± 0.06

Table 5: Dissolution profile of Vildagliptin IR layer Tablets

Time (min)	A1	A2	A3	A4	A5	A6	A7	A8	A9
5	36.13 ± 0.25	39.61 ± 0.24	48.05 ± 0.77	45.76 ± 0.32	48.91 ± 0.24	44.19 ± 0.35	46.23 ± 0.76	47.14 ± 0.17	47.34 ± 0.77
10	46.58 ± 0.23	58.46 ± 0.44	59.96 ± 0.22	59.55 ± 0.57	61.29 ± 0.16	57.44 ± 0.56	69.17 ± 0.86	67.79 ± 0.51	66.69 ± 0.96
15	65.50 ± 0.55	73.88 ± 0.62	75.69 ± 0.42	75.27 ± 0.33	79.67 ± .09	68.40 ± 0.65	79.57 ± 0.45	83.02 ± 0.17	79.30 ± 0.41
20	72.05 ± 0.25	80.51 ± 0.43	91.79 ± 0.04	90.64 ± 0.12	93.19 ± 0.09	90.26 ± 0.09	89.29 ± 0.25	91.47 ± 0.50	89.59 ± 0.19
30	91.51 ± 0.77	90.72 ± 0.24	97.90 ± 0.02	96.31 ± 0.09	**98.85 ± 0.07**	98.75 ± 0.09	97.65 ± 0.07	97.26 ± 0.33	95.82 ± 0.48

Table 6: Dissolution profile of Metformin HCl SR layer Tablets

Time (Hr.)	Theoretical drug release	C1	C2	C3	C4	C5	C6
0	0	0.00	0.00	0.00	0.00	0.00	0.00
1	42.71	57.14 ± 0.10	54.40 ± 0.20	53.10 ± 0.12	46.67 ± 0.27	50.12 ± 0.16	55.17 ± 0.18
2	47.92	69.45 ± 0.13	66.85 ± 0.16	62.50 ± 0.23	60.14 ± 0.18	64.34 ± 0.19	68.58 ± 0.15
4	58.34	82.32 ± 0.07	79.50 ± 0.10	75.83 ± 0.34	74.25 ± 0.16	78.54 ± 0.25	79.12 ± 0.22
6	68.75	95.65 ± 0.16	88.35 ± 0.14	86.45 ± 0.08	84.65 ± 0.31	89.43 ± 0.34	86.91 ± 0.28
8	79.17	98.78 ± 0.23	97.80 ± 0.19	91.64 ± 0.19	90.15 ± 0.24	93.76 ± 0.09	90.53 ± 0.17
10	89.58	-	-	95.30 ± 0.15	95.71 ± 0.14	95.67 ± 0.13	93.12 ± 0.37
12	100.00	-	-	98.20 ± 0.13	98.10 ± 0.34	98.25 ± 0.27	97.20 ± 0.26
F2		13.39	13.76	44.72	48.02	42.32	41.72
F1		60.85	57.47	16.48	13.77	17.91	18.45
Time (Hr.)	**Theoretical drug release**	**C7**	**C8**	**C9**	**C10**	**C11**	**C12**
0	0	0.00	0.00	0.00	0.00	0.00	0.00
1	42.71	52.44 ± 0.31	48.23 ± 0.17	47.14 ± 0.14	48.40 ± 0.09	35.78 ± 0.08	28.34 ± 0.13
2	47.92	63.24 ± 0.14	60.77 ± 0.23	58.81 ± 0.27	62.13 ± 0.12	44.63 ± 0.13	37.85 ± 0.08
4	58.34	75.32 ± 0.18	77.31 ± 0.29	74.27 ± 0.13	73.32 ± 0.29	61.27 ± 0.18	49.21 ± 0.31
6	68.75	84.48 ± 0.24	85.43 ± 0.38	86.65 ± 0.18	86.73 ± 0.37	75.19 ± 0.16	60.26 ± 0.23
8	79.17	91.74 ± 0.36	89.34 ± 0.35	90.12 ± 0.32	92.44 ± 0.18	87.33 ± 0.26	74.31 ± 0.26
10	89.58	94.56 ± 0.23	94.50 ± 0.11	94.34 ± 0.25	94.52 ± 0.23	91.62 ± 0.38	86.93 ± 0.32
12	100.00	96.38 ± 0.29	97.15 ± 0.24	98.25 ± 0.21	98.19 ± 0.27	98.73 ± 0.27	94.42 ± 0.27
F2		45.41	46.39	47.7	46.21	**64.26**	52.98
F1		16.23	14.79	13.69	14.98	**6.39**	11.34

*Values of f1 (<15) and f2 (>50) indicate that the curves can be considered similar.

Determination of Drug Release Kinetics

To understand the rate and mechanism of drug release from the prepared formulation, the dissolution data was fitted to Zero order, First order, Higuchi, Hixon-Crowell and Krosmeyer Peppas equations. Regression coefficient values were calculated and used to find the fitness of the data.

Stability Study

Short term stability study was carried out for optimized bilayer tablets of batch A5C11. The study was carried out according to ICH guidelines by storing the samples at 40 ± 2°C and 75 ± 5% RH for 1 month. The tablets were evaluated for hardness, drug content, and dissolution study and compared with tablets which were evaluated immediately after manufacturing.

RESULTS AND DISCUSSION

Identification of Drugs by Melting Point

Melting point of Vildagliptin and Metformin HCl was found to be 153° C and 225° C respectively, using capillary tube method. Both values were same as reported in literature.

Identification of Drugs and Compatibility Study by FTIR Spectroscopy

The FTIR spectra of both drugs showed peaks at wave numbers (cm^{-1}), which corresponds to the standard range of functional groups present in the structure of drug and data for the same are shown in Table 1. The FTIR spectrum of the powdered drugs and their mixture with excipients as well as mixture of both drugs showed no interaction between drugs-excipients and both drugs. Hence, it was concluded that, the studied excipients and drugs combination were compatible.

Evaluation of Powder Blends

Powder and flow characteristics of the blend can affect the formulation of tablets. The results shown in Table 3 indicated that, the all blends possessed good flow properties.

Evaluation of Tablets

The prepared tablets were characterized for different parameters such as hardness, friability, thickness, diameter, weight variation and drug content, which are summarized in Table 3, Table 4. For all formulations hardness, thickness and average weight of tablets were found with in proper range as mentioned in table. Friability was found to be less than 1.0%. The disintegration time for Viladaglitpin layer was in range 1.25 to 3.92 min and percentage drug content of the prepared tablets was in the range of 97.89 % to 99.65 %. The percentage drug content of the tablets containing Metformin HCl layer was in the range of 97.50% to 99.45 %. Post compression parameters of Bilayer tablet was also found satisfactory.

In vitro Drug Release Study

In vitro drug release studies were carried out as mentioned in methodology for all formulations and results are as shown in Table 5 and Table 6. *In vitro* drug release profiles for Vildagliptin IR tablets and Metformin HCl SR tablets, Figure and Figure 2 respectively. Formulation A5 containing Vildagliptin showed satisfactory cumulative percentage release up to 98.85% within 30 min. Cumulative % drug release of the formulations C1 to C6, which contained HPMC K100M CR in different ratios, were not satisfactory. Initial bursting effect and fast dissolution profile was observed. Cumulative % drug release of the formulations C7 to C9 which contained HPMC K100M CR and HPMC K4M in different ratios, also showed initial bursting effect and rapid drug release. From another three formulations C10 to C12, which contained HPMC K100M CR and Carbopol 934P in different ratios, the formulation C11 showed drug release up to 98.73 % for Metformin HCl in 12 hrs. Results of similarity factor (F2) and difference factor (F1) of the formulation C11 was found more satisfactory and dissolution profile was considered to be similar with theoretical dissolution profile. Bilayer tablet formulation A5C11 also showed identical release profile to that of individual layers and drug release was achieved for prolonged period of time.

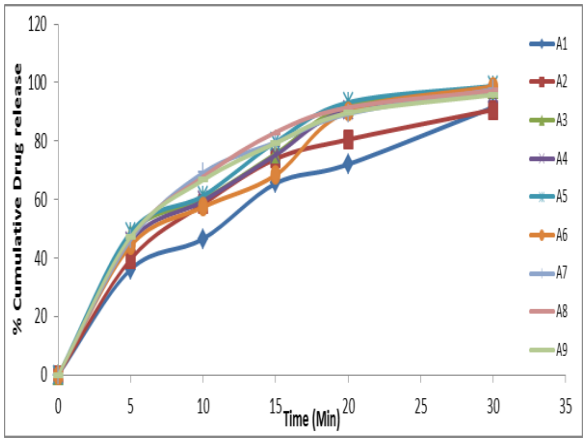

Figure 1: Dissolution profile of formulations A1 to A9

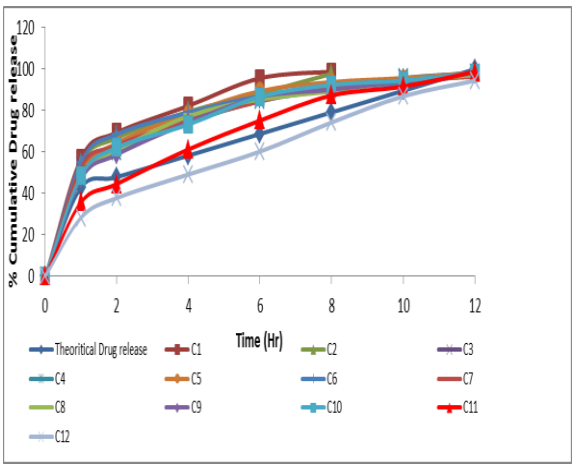

Figure 2: Dissolution Profile of formulations C1 to C12 along with Theoretical profile

Drug Release Kinetics

To determine the release model, which best describes the pattern of drug release, *in vitro* drug release data of Metformin HCl layer from bilayer tablet was fitted to zero order, first order, Hixon-Crowell, Krosmeyer Peppas and Higuchi models. Regression coefficient values were found to be 0.8949, 0.9280, 0.9918, 0.9633 and 0.8794 respectively.

The Highest regression coefficient R^2 value was obtained for Higuchi model and was found to be 0.9918. Hence, diffusion was considered as predominant release mechanism for tablet.

Stability Study

Bilayer tablet was placed in the modified stability chamber for accelerated stability study at 40 ± 2°C and 75 ± 5 % RH for 1 month.

After a period of one month, the samples were observed for any change in physical appearance. Tablets were analyzed for percentage drug content and *in vitro* drug release studies. It was observed that surface was devoid of any change in colour or appearance of any kind of odour in it. Results also revealed that, there were no significant changes in percentage drug content or *In vitro* drug release.

CONCLUSION

The study conducted on formulation development and evaluation of bilayer tablet of Vildagliptin and Metformin HCl for the effective management of type 2 diabetes mellitus revealed that, the bilayer tablets contains Vildagliptin as immediate release and Metformin HCl as sustained release. The pre compression parameters of the powder blends used for the preparation of immediate releasing layer and sustained layer were in acceptable range of pharmacopieal specification with good flow and good compressibility. Vildagliptin was formulated as immediate releasing layer using crosspovidone by direct compression technique. The *in vitro* release of Vildagliptin was rapid from tablet and showed highest drug release 98.85% within 30 minutes and hence, formulation A5 was selected for preparation of bilayer tablet. Metformin HCl was prepared as sustained release layer using HPMC K100M CR and Carbopol 934P in combination by wet granulation technique. The *in vitro* release was prolonged up to 12 hours as a 98.73%, which was comprised of using mixture of polymers HPMC K100M CR and Carbopol 934P in different proportions. Formulation C11 prolonged the drug release up to 12 hours with highest drug content and hence, it was selected for preparation of bilayer tablet. Bilayer tablets were prepared by using optimized batch of Vildagliptin immediate release layer and optimized batch of Metformin HCl sustained release layer. Hence, bilayer tablet of Vildagliptin immediate release layer and Metformin HCl sustained release layer could be used to improve patient compliance towards the effective management of type 2 diabetes mellitus with improved dosing frequency and bioavailability.

REFERENCES

1. Nagappa AN. Novel strategies for the therapeutic management of type-II diabetes, Health administrator, 20, 2008, 58-68.
2. U.K Prospective Diabetes study group, Intensive blood-glucose control with sulphonylurea or insulin compared with type-II diabetes, UKPDS 33, Lancet, 352, 1998, 837-859.
3. U.K Prospective Diabetes study group, Intensive blood-glucose control with Metformin on complications in over weight patients with type-II diabetes, UKPDS 34, Lancet 352, 1998, 854-865.
4. Panchal HA and Tiwary A. A novel approach of bilayer tablet technology review, International Journal of Scientific Review and Research, 5, 2012, 44-49.
5. Bristol Myers Squibb. Package inserts, Glucophage/Glucophage XR, June 2001.
6. Zouboulis ChC. Retinoids: Which dermatological indications will benefit in the near future? Skin Pharmacology and Applied Skin Physiology, 14, 2001, 303-315.
7. Mandal A. What Is Diabetes? Available from: <http://www.news-medical.net/health/What-is-Diabetes.aspx>. [Accessed on: April 2009]
8. Raghuram RK, Srinivas M and Srinivas R. Once daily sustained Release matrix tablets of Nicorandril: Formulation and *In vitro* Evaluation, AAPS PharmSciTech, 4(4), 2003, 1-9.
9. Savavanan S, Nataraj KS, Verampalayam K and Ganesh S. Hydroxy propyl methyl cellulose based cephalexin extended release tablet: influence of tablet formulation: Hardness and storage on *In vitro* release kinetics, Chemical and Pharmaceutical Bulletin, 51(8), 2003, 978-983.
10. Nagoji K, Srinivas RS and Bhanoji Rao ME. Release studies of nimesulide from ethyl cellulose and hydroxyl propyl methyl cellulose matrices, Indian Journal of Pharmaceutical Sciences, 62(5), 2000, 482–484.
11. Rao KR, Senapti P and Das MK. Formulation and *in vivo* evaluation of ethyl cellulose microspheres containing Zidovudine, Journal of Microencapsulation, 22(8), 2005, 863-876.
12. Ray S, Ghosh PK, Das B, Gosh LK and Gupta BK. Statistical optimization supported product development of antiasthamatic multiparticulate drug delivery system, Indian Journal of Pharmaceutical Sciences, 62(3), 2000, 175-180.

Source of Support: Nil, **Conflict of Interest:** None.