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Original Research Article

FORMULATION AND EVALUATION OF BILAYER TABLETS OF SITAGLIPTIN PHOSPHATE AND METFORMIN HYDROCHLORIDE

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ABSTRACT

The purpose of this research work is to establish Metformin Hydrochloride (500mg) as sustained release layer and Sitagliptin Phosphate (50mg) as immediate release layer in the form of bilayer tablets. Sustained release layer is prepared by direct compression method using combination of different polymers like Sodium alginate, HPMC K4M, Carbomer, and Xanthum gum. Immediate release layer is prepared by Wet granulation method by using combination of Superdisintegrants like Crosspovidone, Crosscarmellose intragranularly and extragranularly. Finally both the layers were compressed by direct compression. Tablets were evaluated for different parameters like friability, weight variation, hardness, drug content, dissolution studies, stability studies, ft-ir studies for compatability purpose. The release of one drug remain unaffected in presence of other drug. The optimized formulation gave an Immediate release effect followed by Sustained release effect. The release pattern of Metformin Hydrochloride was fitted to different models based on coefficient of correlation. The present study concluded that bilayer tablets can effectively be formulated to deliver more than one drug so as to have improved patience compliance and better disease management.

Key words: Metformin Hydrochloride, Sitagliptin Phosphate, UV Visisble spectrophotometer.

INTRODUCTION

Diabetes is one of the most prevailing and advancing diseases in the world. Diabetes mellitus is a chronic metabolic disorder characterised by a high blood glucose concentration-hyperglycaemia caused by insulin deficiency, often combined with insulin resistance.

Metformin hydrochloride is the most widely used oral Anti Diabetic drug. The absolute bioavailability of Metformin hydrochloride is 50–60% and is having short biological half-life. Metformin lowers both basal and postprandial plasma glucose. Metformin decreases blood glucose levels by decreasing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity by increasing peripheral glucose uptake and utilization.Frequent dosing schedule leading to high GI side effects and high daily dose makes its use unsuccessful, thus it is reasonable to formulate sustained release Metformin tablets to prolong its duration of action and to reduce total dose of drug administered as well as the incidence of adverse side effects.[14]

Sitagliptin Phosphate is an Anti-diabetic drug, belonging to class of Dipeptidyl peptidase 4 (DPP-4) inhibitor. Sitagliptin is a selective inhibitor of the enzyme dipeptidyl peptidase-4 (DPP-4), which metabolizes the naturally occurring incretin hormones glucagon-like peptide-1(GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) resulting in enhanced glucose-dependent insulin secretion from the pancreas and decreased hepatic glucose production.[15]

The combination of a DPP-4 Inhibitor (Sitagliptin Phosphate) with Biguanide class drug (Metformin Hydrochloride) allows a broad and complementary spectrum of anti diabetic actions. This combination of two drugs does not increase the risk of hypoglycemia, do not promote weight gain, and do not cause adverse effect caused by various other oral anti diabetic combinations. Both the drugs have a complimentary and possibly additive effect on glycemic control and reduced glycosylated haemoglobin (HbA(1c)) levels.

In this study combination of polymers like Sodium alginate, HPMC K4M, Carbomer, Xanthum gum were used for sustaining action of Metformin Hydrochloride layer.

Superdisintegrants are the agents that promote fast disintegration of the tablets by increasing water penetration and dispersion of the matrix. Here, in this study cross povidone, croscarmellose sodium were used as intragranularly and extragranularly superdisintegrants for the Immediate release Sitagliptin Phosphate layer.

Bilayer tablets offer definite advantages over conventional release formulation of the same drug. Several pharmaceutical companies are currently developing bi-layer tablets. For a variety of reasons: patent extension, therapeutic, marketing, to reduce capital investment etc. 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 maintenance dose, reducing the dose frequency or providing uniform drug delivery, promoting patient convenience and compliance.[1,2]

MATERIALS AND METHODS

Materials :

Drugs Sitagliptin phosphate and Metformin hydrochloride was received as gift sample from Vijilak pharma, India. Sodium alginate, HPMC K4M, Carbomer, Xanthan gum,Cross povidone, Crosscarmellose, Magnesium sterate , talc were obtained from Qualitech Pharma Hyderabad, India. All other ingredients, reagents and solvents were of analytical grade.

Methods: [2]

The bilayer tablets of Sitagliptin Phosphate and Metformin Hydrochloride were developed in two stages. Blends of immediate release layer of Sitagliptin Phosphate and sustained release layer of metformin Hcl were prepared separately. The individual layers were optimized based on the in vitro dissolution data and bilayer tablets were prepared by using the optimized formula

Preparation of immediate release layer of Sitagliptin Phosphate

The Immediate release layer was prepared by Wet Granulation method. Drug, diluents, one of super disintegrants(as intragranular part) were mixed properly in a mortar according to compositions with a granulating liquid to form dough mass. The resulting blend was passed through sieve # 60 which forms granules and the granules are dried in an oven. The formed granules are passed through sieve which gives uniform size of particles. Then lubricants and other superdisintegrant is added to the granules as extragranular part.

Preparation of Sustained release layer of Metformin Hcl

The Sustained release layer was prepared by direct compression method. Drug and various concentrations of polymer were mixed properly in a mortar. Later, MCC and PVPK-30 were added. The resulting blend was passed through sieve #60. Then Lubricants are added.

Steps involved in the formulation of bilayered tablet [2]

a. Filling IR powder into dies
b. Compression of IR layer.
c. Ejection of upper punch.
d. Addition of Sustained release blend over IR powder.
e. Compression of both layers.
f. Ejection of bilayered tablet.

EVALUATION PARAMETERS

Compatability studies : Compatability of the drug with its excipients was evaluated by using FT-IR Studies.

Precompression parameters : The blend was evaluated for different parameters like Organoleptic properties (colour, taste, smell, solubility, melting point) bulk denity, tapped density, compressibility index, Hausner's ratio, Angle of repose.

Bulk density : Density is a term obtained by dividing weight of powder by volume of powder. It was given as g/cm3. Apparent bulk density was determined by pouring presieved drug excipients blend into a graduated cylinder and measuring the volume and weight. It was determined by following equation.[9]

$$\rho b = m / vb$$

Where, ρb = Bulk density, m = Mass of powder,

vb = Volume of powder

Tapped density

It was determined by placing a graduated cylinder containing a known mass of drug and excipients blend on mechanical tapping apparatus, which was operated for a fixed numbers of taps until the powder bed volume has reached a minimum using the weight of a blend in a cylinder and from this minimum volume, the tapped density was computed. It was determined by following equation.

$$\rho t = m / vt$$

Where, ρt = Tapped density, m = Mass of powder,

vt = Tapped volume.

Compressibility Index

Compressibility was indirectly related to the relative flow rate, cohesiveness and particle size distribution of the powder. Powders with compressibility values lesser than about 20% have been found to exhibit good flow properties.Tapped (ρt) and apparent (ρb) bulk density measurements can be used to estimate the compressibility of a material11.

$$CI (\%) = (\rho t - \rho b) / \rho t * 100$$

Where, ρb = Bulk density, ρt = Tapped density

Hausner's ratio It was the ratio of bulk volume to tapped volume or tapped density to bulk density. It was a measure used to describe compressibility of powder89.

$$\text{Hausner's ratio} = \rho t / \rho b$$

Where, ρt = Tapped density, ρb = Bulk density

Angle of repose

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. Angle of repose is maximum angle possible

between pile of powder and horizontal plane.[10]

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

Where, h = Height of pile of powder,

r = The radius of the base of conical pile.

Post compression parameters :

The prepared tablets were evaluated for different parameters like Hardness, Friability, weight variation, thickness, Drug content, Sweeling Index for sustained release layer, Disintegration time for immediate release layer and In vitro dissolution studies.

Hardness:

Hardness is defined as the force required breaking a tablet in a diametric compression test. The devices operating in this manner are the Monsanto tester, the Strong- cobb tester, the Pfizer tester, the Erweka tester and the Schleuniger tester. Monsanto tester was used to measure the hardness of ten tablets. Mean and standard deviation were computed and reported. It is expressed in kg/cm^2.

Thickness

Thickness of the tablets was measured using a calibrated Vernier Caliper. Three tablets of each formulation were picked randomly and thickness was measured individually.

Friability:

Thermionic friabilator was used to determine the friability of the tablets. It is expressed in percentage (%). Initially ten tablets were weighed and transferred into the friabilator. It was operated at 25 rpm for 4 minutes. The tablets were weighed again after 4 minutes the % friability was then calculated by using the formula.

$$\% \text{ Friability} = \frac{\text{initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

Weight Variation:

Randomly twenty tablets were selected and the average weight of the tablets was determined. Then the weight of individual tablets was compared to the average weight.

Determination of swelling index:

Matrix tablet was introduced into basket type dissolution apparatus containing 900mL of 0.1N HCl (pH 1.2 at 37^0C) at 50 rpm. The tablets were removed at definite time intervals and swollen weight of each tablet was determined. Swelling (%) is calculated according to the following formula

$$\text{Swelling index} = (S-T)/T \times 100$$

where S is the weight of the floating matrix tablets after swelling; R is the weight of the eroded matrix tablet and T is the initial weight of the matrix tablets.

Disintegration Time : The test was carried out on 6 tablets using tablet disintegration tester. Distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in seconds taken for complete disintegration of the Tablets with no palable mass remaining in the apparatus was measured.

Drug Content Uniformity:

Metformin Hydrochloride : Twenty tablets were weighed and its average weight was taken which was crushed in motor and pestle. The powder weight equivalent to single tablets i.e. 500 mg was dissolved in 10 mL water in a 100 mL volumetric flask and allowed to stand for 10 min. To that 75 mL of methanol was added initially followed by addition of sufficient methanol to produce 100 mL which was then filtered through whatmann filter paper. 5 mL of this resulting solution was further diluted to 50 mL with 6.8 pH phosphate buffer: methanol (1 : 1). Again 5 mL was diluted to 50 mL by the same solvent. The absorbance of the solution was taken in UV-visible spectrophotometer at 233 nm using equal volumes of 6.8 pH phosphate buffer and methanol as blank.

Sitagliptin Phosphate: The powder equivalent to one tablet weight of Sitagliptin Phosphate was weighed and dissolved in 5ml of water and 60ml of methanol in 200 ml standard flask Shake for 30min and then make up with 0.1N HCL and then centrifuge it from that take 5ml of solution in 50 ml standard flask make up with 0.1N HCL. The absorbance of the solution was taken in UV-visible spectrophotometer at 265 nm.

In Vitro Dissolution Studies:

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 sustained release layer buffer was taken as 0.1 N Hcl for 2hrs then P^h 6.8 phosphate buffer for next 10hrs. For Immediate release layer 0.1N HCL was taken as dissolution medium. Sample was with drawn at pre-determined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn were filtered through 0.45µ membrane filter, and concentration of drug in each sample was analyzed by UV spectrophotometer and cumulative percent drug release was calculated. The study was performed in triplicate .

RESULTS

Table.1.Different formulations of Metformin Hydrochloride tablets

Ingredients	**FM_1**	**FM_2**	**FM_3**	**FM_4**	**FM_5**	**FM_6**	**FM_7**	**FM_8**	**FM_9**	**FM_{10}**	**FM_{11}**	**FM_{12}**
Metformin	500	500	500	500	500	500	500	500	500	500	500	500
Microcrystalline Cellulose	171.5	129	86.5	171.5	129	86.5	171.5	129	86.5	171.5	129	86.5
Sodium Alginate	-	-	-	42.5	85	127.5	42.5	85	127.5	42.5	85	127.5
HPMC K_4 M	85	85	85	-	-	-	-	-	-	85	85	85
Carbomer	42.5	85	127.5	-	-	-	85	85	85	-	-	-
Xanthum Gum	-	-	-	85	85	85	-	-	-	-	-	-
PVP K-30	25.5	25.5	25.5	25.5	25.5	25.5	25.5	25.5	25.5	25.5	25.5	25.5
Magnesium Sterate	17	17	17	17	17	17	17	17	17	17	17	17
Talc	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5

*** Quantities were taken in milligrams**

Table.2.Different formulations of Sitagliptin Phosphate tablets

Ingredients	**FS_1**	**FS_2**	**FS_3**	**FS_4**	**FS_5**	**FS_6**	**FS_7**	**FS_8**	**FS_9**
Sitagliptin	50	50	50	50	50	50	50	50	50
Microcrystalline Cellulose	78	-	39	75	-	37.5	72	-	36
Starch	-	78	39	-	75	37.5	-	72	36
PVP K-30	11	11	11	11	11	11	11	11	11
Isopropyl Alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Cross Povidone	03	03	03	4.5	4.5	4.5	06	06	06
Talc	03	03	03	03	03	03	03	03	03
Cross Caramellose	03	03	03	4.5	4.5	4.5	06	06	06
Magnesium Sterate	02	02	02	02	02	02	02	02	02

*** Quantities were taken in milligrams**

Table.3.Pre compression parameters of Metformin Hydrochloride blend

Formulations	Bulk density	Tapped density	Carr's index	Angle of repose	Hausner's ratio
FM_1	0.37 ± 0.20	0.41 ± 0.08	12.06 ± 0.71	20.68 ± 0.09	1.10 ± 0.13
FM_2	0.38 ± 0.20	0.45 ± 0.02	14.42 ± 0.5	22.16 ± 0.11	1.18 ± 0.07
FM_3	0.37 ± 0.91	0.46 ± 0.24	18.45 ± 0.64	21.83 ± 0.12	1.24 ± 0.21
FM_4	0.36 ± 0.13	0.42 ± 0.02	14.29 ± 0.80	21.62 ± 0.09	1.16 ± 0.27
FM_5	0.38 ± 0.17	0.48 ± 0.04	20.63 ± 0.77	21.75 ± 0.13	1.26 ± 0.34
FM_6	0.39 ± 0.23	0.47 ± 0.18	17.88 ± 0.33	20.85 ± 0.13	1.20 ± 0.76
FM_7	0.35 ± 0.12	0.44 ± 0.06	20.45 ± 0.19	21.39 ± 0.09	1.25 ± 0.12
FM_8	0.37 ± 0.14	0.46 ± 0.14	19.3 ± 0.49	20.80 ± 0.11	1.24 ± 0.19
FM_9	0.39 ± 0.22	0.46 ± 0.12	15.22 ± 0.78	22.97 ± 0.12	1.17 ± 0.31
FM_{10}	0.37 ± 0.14	0.43 ± 0.17	13.95 ± 0.09	22.33± 0.16	1.38 ± 0.13
FM_{11}	0.37 ± 0.19	0.44 ± 0.09	15.90 ± 0.16	23.12 ± 0.12	1.10 ± 0.09
FM_{12}	0.38 ± 0.14	0.45 ± 0.02	14.42 ± 0.5	20.06 ± 0.08	1.18 ± 0.12

Table.4.Pre compression parameters of Sitagliptin Phosphate blend

Formulations	Bulk density	Tapped density	Carr's index	Angle of repose	Hausner's ratio
FS_1	0.88 ± 0.021	0.98 ± 0.01	12.54 ± 0.42	20.58 ± 0.45	1.12 ± 0.05
FS_2	0.88 ± 0.047	0.98 ± 0.04	13.84 ± 0.90	23.67 ± 0.31	1.12 ± 0.01
FS_3	0.87 ± 0.098	0.99 ± 0.04	11.49 ± 0.53	22.49 ± 0.08	1.13 ± 0.06
FS_4	0.74 ± 0.01	0.99 ± 0.02	17.64 ± 1.2	24.29 ± 0.17	1.40 ± 0.02
FS_5	0.78 ± 0.08	0.98 ± 0.01	16.21 ± 1.62	26.13 ± 0.13	1.32 ± 0.02
FS_6	0.85 ± 0.047	0.98 ± 0.04	13.31 ± 0.78	22.29 ±0.17	1.15 ± 0.01
FS_7	0.78 ± 0.06	0.96 ± 0.08	16.66 ± 0.79	23.72 ± 0.23	1.15 ± 0.01
FS_8	0.86 ± 0.047	0.99 ± 0.04	12.5 ± 0.44	24.47 ± 0.21	1.14 ± 0.05
FS_9	0.86 ± 0.022	0.97 ± 0.04	11.38 ± 1.20	22.77 ± 0.15	1.13 ± 0.01

Table.5.Post compression parameters- Metformin Hydrochloride tablets

Formulations	Weight Variation mg (n=10)	Thickness	Hardness Kg/cm2 (n=3)	Friability % (n=10)	Drug Content (%)
FM_1	850 ± 1.06	3.86 ± 0.15	6.2 ± 0.3	0.40 ± 0.03	98.92 ±0.70
FM_2	850 ± 1.61	3.96 ± 0.14	6.5 ± 0.4	0.51 ± 0.09	96.43 ± 0.42
FM_3	850 ± 1.02	3.94 ± 0.12	6.4 ± 0.2	0.58 ± 0.15	95.38 ± 1.02
FM_4	849 ± 1.05	3.92 ± 0.33	6.0 ± 0.4	0.48 ± 0.04	99.83 ± 0.73
FM_5	850 ± 2.05	3.89 ± 0.43	6.5 ± 0.4	0.39 ±0.12	101.02 ±0.71
FM_6	850 ± 1.91	3.91 ± 0.32	6.3 ± 0.2	0.54 ±0.08	95.03 ± 0.32
FM_7	850 ± 2.12	3.87 ± 0.24	6.4 ± 0.3	0.48 ±0.11	98.17 ± 0.41
FM_8	848 ± 0.09	3.93 ± 0.62	6.5 ± 0.6	0.36 ±0.08	100.21 ±0.73
FM_9	850 ± 0.06	3.90 ± 0.85	6.4 ± 0.5	0.29 ±0.04	96.73 ± 1.13
FM_{10}	850 ± 1.32	3.68 ± 0.30	6.3 ± 0.7	0.46 ±0.05	98.67 ± 1.67
FM_{11}	850 ± 1.12	3.75 ± 0.50	6.5 ± 0.2	0.57 ±0.16	95.34 ± 0.79
FM_{12}	850 ± 0.08	3.90 ± 0.10	6.5 ± 0.3	0.38 ±0.07	100.74 ± 0.13

Table.6.Post compression parameters- Sitagliptin Phosphate tablets

Formulations	Weight Variation mg (n=10)	Thickness (n=3)	Hardness Kg/cm2 (n=3)	Friability % (n=10)	Drug Content (%)
FS_1	150 ± 1.61	2.0 ± 0.15	3.3 ± 0.6	0.51 ± 0.04	98.92 ±0.70
FS_2	147 ± 1.60	2.1± 0.14	3.4 ± 0.2	0.39 ± 0.06	100.43 ± 0.42
FS_3	150 ± 1.93	2.3± 0.12	3.2 ± 0.5	0.48 ± 0.11	97.38 ± 1.02
FS_4	148 ± 1.87	2.7 ± 0.33	3.5 ± 0.4	0.52 ± 0.04	96.87 ± 0.73
FS_5	149 ± 1.02	2.5± 0.43	3.0 ± 0.2	0.37 ±0.19	95.02 ± 0.71
FS_6	150 ± 0.19	2.4± 0.32	3.5 ± 0.2	0.39 ±0.08	99.03 ± 0.32
FS_7	150 ± 1.23	2.5 ± 0.24	3.6 ± 0.3	0.58 ±0.09	98.17 ± 0.41
FS_8	150 ± 1.07	2.3± 0.62	3.5 ± 0.2	0.42 ±0.06	96.21 ± 0.73
FS_9	151 ± 0.09	2.2± 0.85	3.1 ± 0.4	0.57 ±0.04	98.73 ± 1.13

Table.7.Swelling Index of Metformin Hydrochloride

Time (hrs)	FM_1	FM_2	FM_3	FM_4	FM_5	FM_6	FM_7	FM_8	FM_9	FM_{10}	FM_{11}	FM_{12}
1	3.92 ±0.16	4.81 ±0.05	7.68 ±0.09	12.35 ±0.01	18.23 ±0.05	21.38 ±0.12	0.92 ±0.08	9.45 ±0.6	4.81 ±0.05	19.40 ±0.15	12.35 ±0.01	23.10 ±0.12
2	6.9 ±0.60	7.21 ±0.09	12.68 ±0.03	26.67 ±0.15	29.05 ±0.16	30.17 ±0.09	1.38 ±0.19	14.11 ±0.06	7.21 ±0.09	34.97 ±0.07	26.67 ±0.15	38.42 ±0.04
4	11.20 ±0.11	12.68 ±0.03	22.38 ±0.16	35.96 ±0.17	38.64 ±0.5	42.86 ±0.21	3.95 ±0.15	25.96 ±0.05	12.68 ±0.03	43.05 ±0.02	35.96 ±0.17	53.62 ±0.21
6	19.25 ±0.02	23.09 ±0.01	32.79 ±0.60	47.28 ±0.16	48.89 ±0.07	49.13 ±0.16	6.83 ±0.12	36.04 ±0.09	23.09 ±0.11	56.12 ±0.11	47.28 ±0.16	62.13 ±0.09
8	33.36 ±0.08	34.29 ±0.07	42.19 ±0.16	52.51 ±0.13	56.90 ±0.01	51.17 ±0.23	6.06 ±0.01	45.83 ±0.29	34.29 ±0.09	64.24 ±0.19	52.51 ±0.13	86.42 ±0.02
10	30.72 ±0.09	32.46 ±0.03	43.52 ±0.19	50.07 ±0.05	54.49 ±0.12	53.89 ±0.01	6.53 ±0.06	44.39 ±0.03	31.26 ±0.03	62.88 ±0.09	50.07 ±0.05	81.14 ±0.01
12	25.29 ±0.08	29.53 ±0.01	38.39 ±0.11	46.14 ±0.07	50.03 ±0.17	52.16 ±0.05	6.44 ±0.02	39.20 ±0.03	29.53 ±0.01	61.37 ±0.05	46.14 ±0.07	80.12 ±0.06

Table.8.Dissolution profile of Metformin formulations

Time (hrs)	FM_1	FM_2	FM_3	FM_4	FM_5	FM_6	FM_7	FM_8	FM_9	FM_{10}	FM_{11}	FM_{12}
0.5	10.89 ±0.16	15.01 ±0.70	13.98 ±0.16	11.42 ±0.39	10.28 ±0.41	12.49 ±0.19	14.73 ±0.31	17.48 ±0.48	14.87 ±0.96	12.98 ±0.53	10.21 ±0.41	15.14 ±0.12
1	19.67 ±0.71	26.34 ±0.28	29 ±0.23	27.83 ±0.76	23.71 ±0.37	28.16 ±0.38	23.98 ±0.29	24.13 ±0.39	22.64 ±0.38	21.34 ±0.76	21.67 ±0.78	21.20 ±0.09
2	28.43 ±0.84	33.81 ±0.34	34.7 ±0.37	31.47 ±0.43	28.39 ±0.96	33.87 ±0.47	36.47 ±0.84	30.89 ±0.71	33.73 ±0.73	29.83 ±0.46	30.48 ±0.46	32.64 ±0.38
3	35.67 ±0.23	40.42 ±0.76	42.6 ±0.71	43.79 ±0.26	35.17 ±0.36	42.08 ±0.76	48.74 ±0.76	37.94 ±0.24	40.31 ±0.17	36.79 ±0.98	39.23 ±0.19	44.31 ±0.61
4	44.92 ±0.46	49.83 ±0.29	51.3 ±0.43	50.34 ±0.19	46.41 ±0.73	48.39 ±0.93	53.93 ±0.16	43.88 ±0.16	48.26 ±0.28	44.23 ±0.16	42.62 ±0.31	51.87 ±0.78
5	53.88 ±0.38	57.67 ±0.53	57.7 ±0.53	58.16 ±0.38	50.87 ±0.42	54.71 ±0.51	62.18 ±0.53	56.71 ±0.34	53.87 ±0.74	57.84 ±0.79	48.98 ±0.49	58.34 ±0.34
6	67.82 ±0.72	65.74 ±0.67	63.4 ±0.29	65.17 ±0.93	57.41 ±0.36	63.83 ±0.59	77.46 ±0.78	62.47 ±0.18	65.73 ±0.63	60.21 ±0.38	50.24 ±0.78	61.97 ±0.24
7	75.43 ±0.23	70.34 ±0.41	69.9 ±0.79	70.97 ±0.90	65.97 ±0.97	69.72 ±0.63	87.31 ±0.17	77.83 ±0.30	72.19 ±0.12	67.32 ±0.46	58.47 ±0.34	68.43 ±0.89
8	84.67 ±0.79	79.15 ±0.34	74.6 ±0.94	78.31 ±0.84	72.43 ±0.47	72.02 ±0.71	94.71 ±0.73	84.36 ±0.57	85.31 ±0.23	74.35 ±0.19	62.34 ±0.51	75.16 ±0.58
9	91.03 ±0.34	86.34 ±0.83	79.73 ±0.34	83.12 ±0.19	79.38 ±0.93	78.74 ±0.83	-	97.19 ±0.09	92.79 ±0.31	80.29 ±0.27	70.11 ±0.78	81.03 ±0.79
10	96.21 ±0.83	94.38 ±0.31	91.97 ±0.62	96.83 ±0.46	86.19 ±0.78	82.13 ±0.31	-	-	-	85.21 ±0.24	79.38 ±0.62	88.39 ±0.46
11	-	-	-	-	97.61 ±0.18	94.97 ±0.24	-	-	-	94.49 ±0.18	83.48 ±0.53	92.76 ±0.23
12	-	-	-	-	-	-	-	-	-	-	92.36 ±0.48	98.95 ±0.11

Table.9. Dissolution profile of Sitagliptin Phosphate formulations

Time (mins)	FS_1	FS_2	FS_3	FS_4	FS_5	FS_6	FS_7	FS_8	FS_9
5	30.48 ±0.19	33.86 ±0.79	39.54 ±0.83	35.89 ±0.63	28.76 ±0.22	39.54 ±0.75	35.12 ±0.34	32.17 ±0.16	32.47 ±0.38
10	59.82 ±0.67	48.17 ±0.36	58.37 ±0.17	60.23 ±0.42	42.13 ±0.31	58.37 ±0.38	51.78 ±0.24	53.78 ±0.38	59.21 ±0.21
15	63.13 ±0.23	65.37 ±0.08	78.64 ±0.39	74.12 ±0.13	60.45 ±0.05	78.64 ±0.19	63.46 ±0.18	66.42 ±0.42	64.36 ±0.19
20	73.51 ±0.81	77.42 ±0.16	84.86 ±0.51	83.96 ±0.95	73.98 ±0.92	99.12 ±0.42	75.39 ±0.09	73.86 ±0.53	67.82 ±0.08
30	83.46 ±0.53	86.94 ±0.23	95.12 ±0.19	93.78 ±0.12	90.11 ±0.46	-	84.1 0.56	86.49 ±0.74	96.27 ±0.52
40	95.74 ±0.72	97.41 ±0.45	-	-	-	-	94.16 ±0.32	92.68 ±0.96	-
50	-	-	-	-	-	-	-	-	-
60	-	-	-	-	-	-	-	-	-

Table.10.Disintegration Profile of Sitagliptin Phosphate

Formulations	Disintegration time (sec)
FS_1	65 ± 2.52
FS_2	90 ± 3.61
FS_3	73 ± 1.13
FS_4	62 ± 2.64
FS_5	88 ± 1.02
FS_6	55 ± 1.96
FS_7	65 ± 1.75
FS_8	75 ± 2.85
FS_9	93 ± 1.92

Table.11.Regression values of the Metformin formulations

Formulations	ZERO ORDER	FIRST ORDER	HIGUCHI	PEPPAS	HIXSON & CROWELL
FM_1	0.989	0.651	0.957	0.643	0.981
FM_2	0.973	0.566	0.984	0.547	0.950
FM_3	0.952	0.541	0.987	0.535	0.937
FM_4	0.966	0.578	0.981	0.581	0.954
FM_5	0.982	0.611	0.969	0.630	0.965
FM_6	0.953	0.548	0.986	0.570	0.940
FM_7	0.979	0.602	0.973	0.533	0.969
FM_8	0.981	0.595	0.945	0.521	0.953
FM_9	0.980	0.593	0.967	0.544	0.960
FM_{10}	0.976	0.596	0.981	0.607	0.962
FM_{11}	0.968	0.584	0.974	0.627	0.952
FM_{12}	0.964	0.561	0.992	0.596	0.951

Table.12.Post Compression parameters of Bilayer tablet

Formulation	Weight Variation	Hardness	Friability	Drug Content	
				Metformin	Sitagliptin
Bilayer Tablets	998 ± 1.38	6.5 ± 0.5	0.54 ± 0.08	99.13 ± 0.26	100.08± 0.13

Table.13.In-Vitro Drug Release Profile of Bilayer optimized Tablet

Time	% CDR	
	Sitagliptin	**Metformin**
0 min	0	-
5 min	30.14 ± 0.43	-
10 min	61.86 ± 0.12	-
15 min	79.13 ± 0.62	-
20 min	99.76 ± 0.29	-
30 min	-	16.02 ± 0.22
1 hr	-	23.86 ± 0.19
2 hr	-	30.42 ± 0.61
3 hr	-	44.98 ± 0.57
4 hr	-	52.34 ± 0.48
5 hr	-	59.06 ± 0.35
6 hr	-	63.19 ± 0.57
7 hr	-	69.23 ± 0.14
8 hr	-	74.08 ± 0.26
9 hr	-	81.23 ± 0.97
10 hr	-	88.17 ± 0.74
11 hr	-	93.16 ± 0.65
12 hr	-	98.03 ± 0.12

Table.14. Stability data of optimized formulation physico-chemical parameters

Parameter		Initial		After 4 weeks at 40°C /75%RH	
Weight Variation		998 ± 1.38		998 ± 1.37	
%Friability		0.54 ± 0.08		0.54 ±0.10	
Hardness(kg/cm^2)		6.5 ± 0.5		6.5 ± 0.4	
% Drug content		Metformin Hcl	Sitagliptin Phosphate	Metformin Hcl	Sitagliptin Phosphate
Drug 1	Drug 2	99.13 ± 0.26	100.08 ± 0.13	99.16 ± 0.22	101.04 ± 0.08

Table.15.Stability data of optimized formulation in-vitro dissolution

Time	% CDR - Initially		After 4 weeks at 40°C /75%RH	
	Sitagliptin Phosphate	Metformin Hcl	Sitagliptin Phosphate	Metformin Hcl
0 min	0	-	0	-
5 min	30.14 ± 0.16	-	29.56 ± 0.25	-
10 min	61.86 ± 0.69	-	63.21 ± 0.12	-
15 min	79.13 ± 0.32	-	78.32 ± 0.67	-
20 min	99.76 ± 0.06	-	99.59 ± 0.19	-
30 min	-	16.02 ± 0.12	-	15.97 ± 0.13
1 hr	-	23.86 ± 0.68	-	23.29 ± 0.23
2 hr	-	30.42 ± 0.91	-	30.96 ± 0.48
3 hr	-	44.98 ± 0.77	-	46.23 ± 0.85
4 hr	-	52.34 ± 0.86	-	53.36 ± 0.08
5 hr	-	59.06 ± 0.24	-	58.09 ± 0.86
6 hr	-	63.19 ± 0.95	-	62.86 ± 0.42
7 hr	-	69.23 ± 0.05	-	70.06 ± 0.58
8 hr	-	74.08 ± 0.16	-	73.15 ± 0.16
9 hr	-	81.23 ± 0.37	-	81.69 ± 0.45
10 hr	-	88.17 ± 0.28	-	87.59 ± 0.32
11 hr	-	93.16 ± 0.64	-	93.58 ± 0.86
12 hr	-	98.03 ± 0.19	-	98.94± 0.26

Graphical representation of drug release profiles of the formulations.

METFORMIN HYDROCHLORIDE

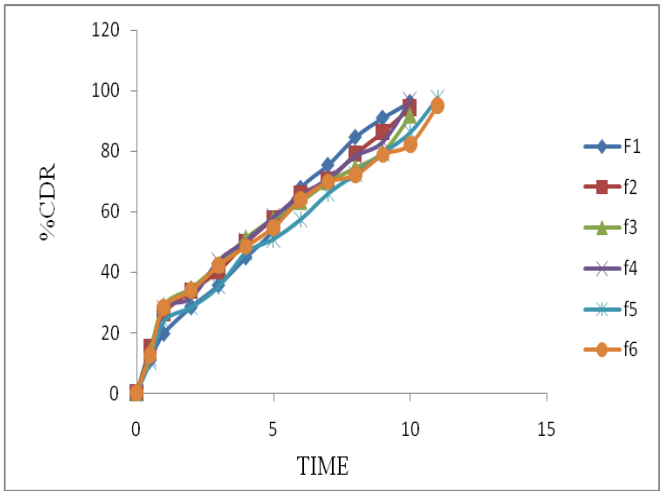

Fig.1.In vitro dissolution profile of FM_1 –FM_6

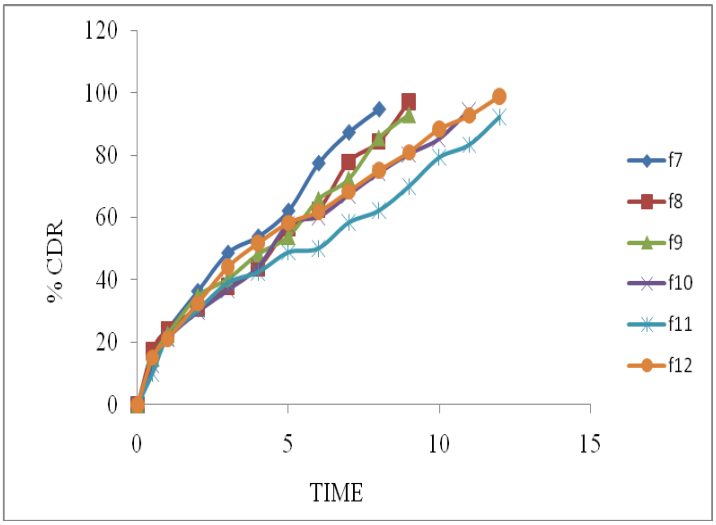

Fig.2.In vitro dissolution profile of FM_7 –FM_{12}

SITAGLIPTIN PHOSPHATE

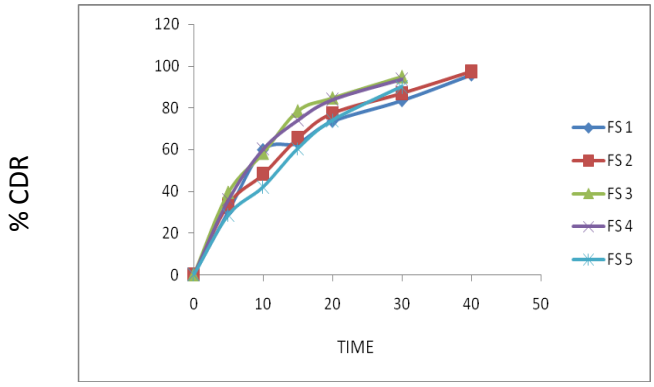

Fig.3.In vitro dissolution profile of FS_1 –FS_5

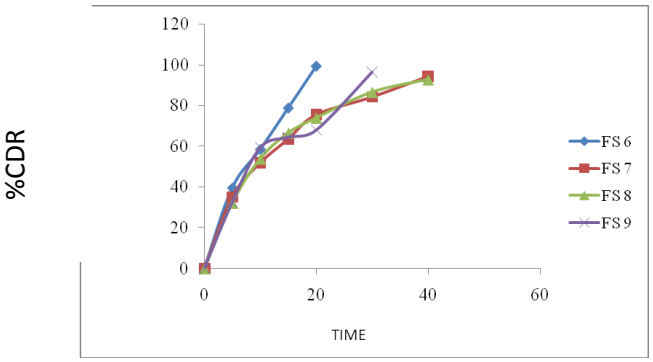

Fig.4.In vitro dissolution profile of FS_6 –FS_9

Graphical representation of Best formulation in Metformin layer (FM_{12})

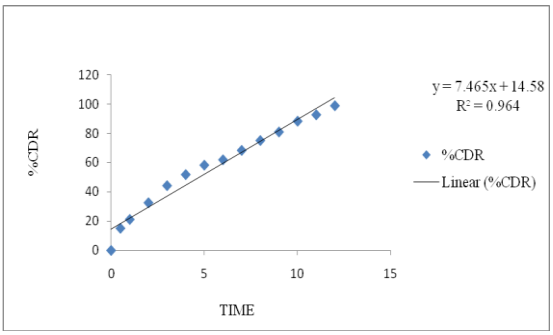

Fig.5.Zero Order Release Graph

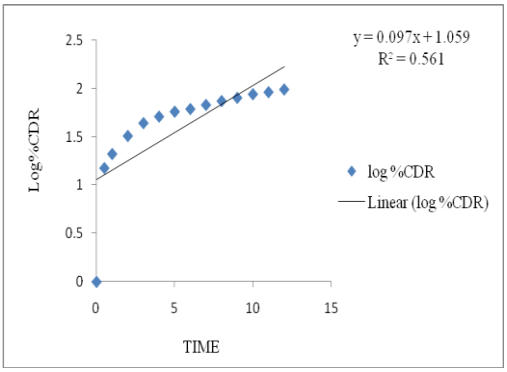

Fig.6.First Order Release Graph

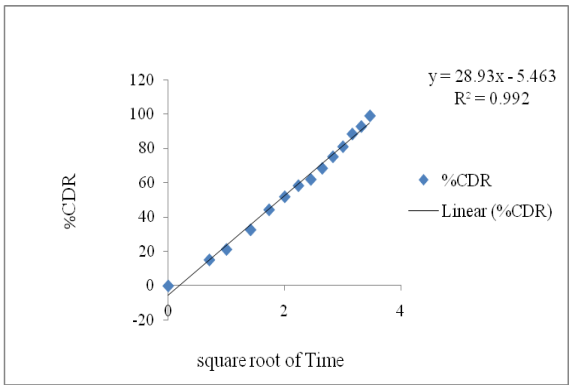

Fig.7.HIGUCHI Model graph

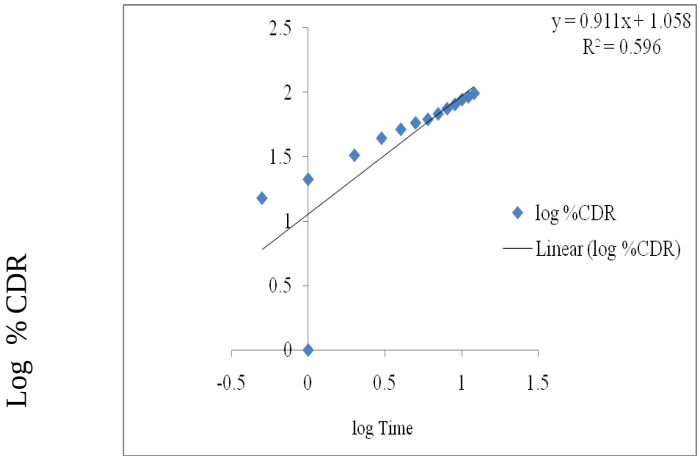

Fig.8.PEPPAS Model graph

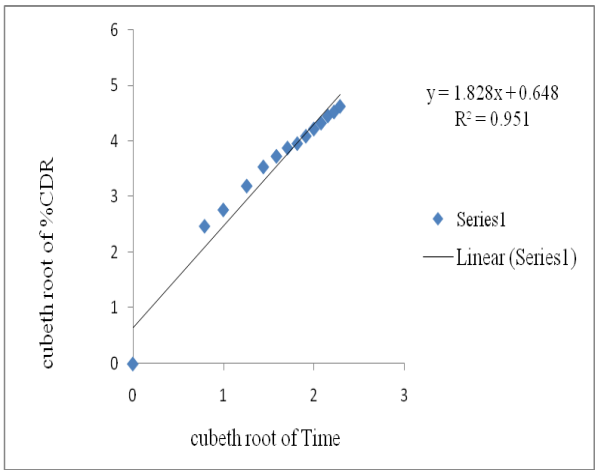

Fig.9.HIXSON-CROWELL Model

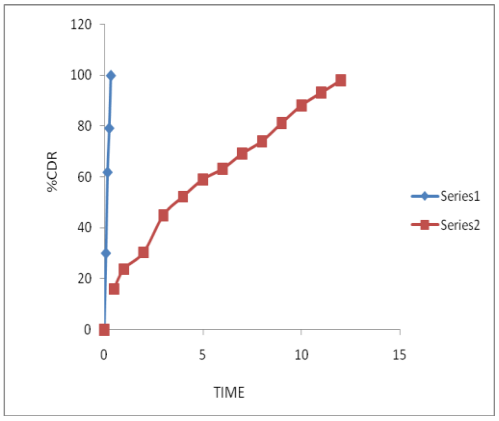

Fig.10.In-Vitro Drug Release Profile of Bilayer Tablet (FM_{12} + FS_6)

Series1 = Sitagliptin phosphate drug release in bilayer tablet
Series2 = Metformin hydrochloride drug release in bilayer tablet

DISCUSSION

Drug excipient compatibility studies

Drug excipients interaction was checked out by comparing the FTIR spectra of pure drugs and FTIR spectra of the physical mixture of drug and excipients.

Pre-compression parameters:

The bulk density and tapped bulk density for all the formulation varied in range of 0.35 to 0.39gm/cm3 and 0.41 to 0.48 gm/cm3 for Metformin hydrochloride, of 0.74 to 0.88gm/cm3 and 0.96 to 0.99 gm/cm3 for Sitagliptin phosphate. The values obtained lies within the acceptable range and with not much difference found between loose bulk density and tapped bulk density.

The percent compressibility and Hausner's ratio for all formulation was found within the range of

12-20% (Metformin hydrochloride),

11-18% (Sitagliptin phosphate)

1.10 -1.38 for metformin hydrochloride, 1.12-1.40 for Sitagliptin phosphate respectively. All the formulation showed acceptable compressibility and flow property .

Post compression parameters:

Post compression parameters were evaluated. The hardness varied from 6 to 6.5 kg\cm^2 for metformin hydrochloride & 3-3.6 kg/cm^2 found satisfactory. The friability test was passed for two layer formulations. Weight variation values for all the formulations of two layers found to be satisfactory.

Disintegration Studies : The best formulation of Sitagliptin layer (FS_3) has disintegration time of 55seconds.

Dissolution Studies

By following dissolution studies it has been observed that the FM_{12} (Metformin Hydrochloride) formulation showed best drug release profile of 98.95% in 12hrs having polymer combination of HPMC K_4 M (10%) and Sodium alginate (15%). FS_6 (Sitagliptin Phosphate) formulation showed best drug release profile of 99.12% in 20mins having Superdisintegrants CP and CCS in concentration of 4% and diluents MCC and Starch in equal ratio's of 25%. In kinetic data formulation FM_{12} (98.95%) followed Zero order release describing the systems where the drug release rate is independent of its concentration of the dissolved substance.

CONCLUSION

In the present study an attempt was made to design a combination bi layer tablet containing Metformin Hcl Sustained release layer and Sitagliptin Phosphate as an Immediate release layer .Bilayer tablet was formulated from optimized formulations of two individual layers.FM_{12} formulation of Metformin layer and FS_6 formulation of sitagliptin layer were optimized and thus bilayer tablet was formulated by these two

optimized layers. From this study by preparing bilayer tablets, it was concluded that we could reduce the total dose, dosage frequency, dose related side effects, and improve the bioavailability of Metformin, Sustained immediate release layer serves as loading dose and metformin sustained release layer serves as maintenance dose. In addition the combination of two drugs doesnot produce hypoglycaemic effect, which is most common problem with other Anti-diabetic drugs. Hence, this optimized bi-layer tablet dosage form (a fixed dose combination tablet of Metformin and Sitagliptin) could be a potential formulation for delivery of two drugs from a single dosage form which could improve patient compliance and give better disease management.

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