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Formulation development and stability studies of bilayer tablets of linagliptin and metformin

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Abstract

In vitro release studies were carried out by USP type 2 paddle apparatus. The results showed that Eudragit's in a sustained layer can control the release of drugs. The in vitro release profile of the drug from the sustained-release layer could be expressed by Higuchi's equation as the pilot shows high linearity R2 =0.9911and diffusion was the dominant mechanism of drug release. The formulation (F6) having an immediate-release layer produces an immediate effect of 93.53 ± 0.30 within 45 minutes followed by a sustained release effect of 94.77 ± 0.37 up to 8 hours. The present study concluded that Bilayer tablets of Lingaptin and Metformin HCl can be a better alternative to conventional dosage forms for providing sustained drug delivery.

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Introduction

TheType 2 diabetes mellitus is a heterogeneous disorder characterized by an defiecinecy of insulin release. This insufficiency results from defective insulin utilization and can be corrected by administration of one or more of the currently available oral hypoglycemic agents [1,2]. Combination therapy have various advantages over monotherapy such as problem of dose-dependent side effects is minimized, a low dose combination of two different agents reduces the dose-related risk, the addition of one agent may counteract some deleterious effects of the other, using low dosage of two different agents minimize the clinical and metabolic effects that occur with maximal dosage of individual component of the combined tablet [3]. Metformin is an oral biguanidine first-line choice of drug. Metformin has an oral bioavailability of 50–60% under fasting conditions, and is absorbed slowly. The average elimination half-life in plasma is 6.2hours. Peak plasma concentrations (Cmax) are reached within 4 to 8 hours with extended-release formulations [4, 5]Linagliptin is a DPP-4 inhibitor developed by Boehringer Ingelheim for the treatment of type II diabetes. Two pharmacological characteristics that set linagliptin apart from other DPP-4 inhibitors is that it has a non-linear pharmacokinetic profile and is not primarily eliminated by the renal system.

Methods and Materials

Metformin HCl and Linagliptin were gift samples obtained from Abhilasha Pharma, Ankleshwar and Cadila Healthcare Limited, Ahmedabad respectively. MCC was purchased from FMC Biopolymer, India; Red Iron Oxide- Roha dye Chem., Mumbai Colorants; PVP K 30- Cadila Healthcare, Ahmedabad; Magnesium stearate, CCS- Astron Research Limited, Ahmedabad; Eudragits- Cadila Healthcare, Ahmedabad; Talc– Merck Specialties Private Limited, Mumbai. All the chemicals and reagents were of high quality analytical grade

Preparation of Bilayer tablets [6-9]

a) **Preparation of Immediate release layer:**

The Immediate release layer contains uniform mixture of Linagliptin Crospovidone, MCC were weighed. followed by shifting through 40# sieve and mixed well with binder solution as a PVP K-90 to made a damp mass . later the damp mass is passed through sieve 20# and dried. finally prepared granules are lubricated with magnesium stearate and the well mixed powder were used as upper layer.

b) Preparation of Sustained release layer:

All Formulations were prepared by direct compression. Metformin and excipients sifted through sieve no 40 # and thoroughly mixed in a blender approximately for 6min. This mixer was lubricated for 2 min. with Magnesium Stearate which was already passed through sieve 60. The lubricated granules were then compressed into tablets.

c) Preparation of Bilayer tablet:

Bilayer tablets were prepared by combining of fast release layer and various formulations of sustained release layer. After the compression upper punch was lifted and the blend of powder for immediate release layer was poured into the die, containing initially compressed matrix tablet on RIMEK multi station punching machine using flat punches, with the hardness of 6.5 kg/cm2.

Formulation of Bilayer tablet: 10

Table No. 1 Formulation of immediate release layer

S. No	Ingridients	F1	F2	F3	F4	F5	F6	F7	F8	F9
	IR release granules									
1	Linagliptin	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
2	Crosspovidone	7	7	7	7	7	7	7	7	7
3	Mannitol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
4	PVP K 90	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
5	Magnesium stearate	4	4	4	4	4	4	4	4	4
	SR release granules									
6	Metformin	500	500	500	500	500	500	500	500	500
7	HPMC K100M	125	170	215						
8	Gatti gum				135	180	225			
9	Sodium alginate							135	180	225
10	MCC	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
11	Aerosil	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
12	Mg.Stearate	2 2.5	2 2.5	2 2.5	2 2.5	2 2.5	2 2.5	2 2.5	2 2.5	2 2.5
	Total weight(mg)	1000	1000	1000	1000	1000	1000	1000	1000	1000

Compression method [11-12]

Final bilayer tablets were compressed by as one layer only for Metformin HCl and second layer for Linagliptin using 12 mm punch in rotary tablet compression machine. The tablet was compressed as bilayer tablets using both Metformin HCl granules and Linagliptin blend. In this Metformin HCl granules were introduced first into the die cavity and slight pre compression was made so the layer was uniformity distributed after that Linagliptin blends were added and final compression was made.

Evaluation [13-15]

All the formulations were evaluated for Appearance, Weight variation test, Hardness, Thickness, Friability and drug content.

In vitro dissolution studies for IR

Dissolution of the tablets was carried out on USP XXIII dissolution type II apparatus using paddle. The tablet was fixed to the paddle by hydration mechanism. 900 ml of pH 1.2 buffer (0.1N HCl) as dissolution medium was filled in a dissolution vessel and the temperature of the medium was set at 37 ± 0.50 C. The rotational speed of the paddle was set at 100 rpm. 1 ml of sample was withdrawn at predetermined time interval of 2 min upto 12 min and same volume of fresh medium was replaced. The withdrawn samples were diluted to 10 ml with 0.01N HCl, filtered and analyzed on UV spectrophotometer at 240 nm using 0.01N HCl as a blank. Percentage cumulative drug release was calculated.

In vitro dissolution studies for SR

Dissolution of the tablets was carried out on USP XXIII dissolution type II apparatus using paddle. The tablet was fixed to the paddle by hydration mechanism. 900 ml of pH 6.8 buffer as dissolution medium was filled in a dissolution vessel and the temperature of the medium was

set at 37 ± 0.50 C. The rotational speed of the paddle was set at 50 rpm. 5 ml of sample was withdrawn at predetermined time interval of 1 hr upto 12 hr and same volume of fresh medium was replaced. The withdrawn samples were analyzed on UV spectrophotometer at 232 nm using 0.01N HCl as a blank. Percentage cumulative drug release was calculated.

Table 02: Preformulation studies for all formulations of IR(Linagliptin)

Code	Angle of Repose ±SD	Bulk Density (g/ml)±SD	Tapped Density (g/ml)±SD	Carr's Index. (%)±SD	Hausner's ratio± SD
L1	27°54′±0.37	0.374±0.018	0.424±0.021	10.81±0.17	1.12±0.025
L2	25°58′±0.25	0.387±0.024	0.437±0.018	11.11±0.12	1.12±0.037
L3	24°32′±0.24	0.365±0.033	0.424±0.025	13.15±0.26	1.15±0.032
L4	26°42′±0.29	0.378±0.019	0.437±0.029	13.51±0.17	1.15±0.018

Table 03: Preformulation studies for all formulations of SR (METFORMIN) tablets

Code	Angle of Repose ±SD	Bulk Density (g/ml)±SD	Tapped Density (g/ml)±SD	Carr's Index. (%)±SD	Hausner's ratio± SD
F1	27°32′±0.27	0.319±0.031	0.413±0.032	11.12±0.11	1.15±0.010
F2	25°36′±0.26	0.354±0.029	0.432±0.019	13.32±0.17	1.12±0.028
F3	28°12′±0.12	0.370±0.012	0.413±0.034	10.46±0.36	1.16±0.019
F4	27°53′±0.37	0.372±0.018	0.423±0.021	10.48±0.17	1.11±0.025
F5	25°62′±0.25	0.384±0.024	0.434±0.018	11.79±0.12	1.13±0.037
F6	24°45′±0.24	0.362±0.033	0.423±0.025	13.63±0.26	1.12±0.032
F7	26°42′±0.29	0.377±0.019	0.436±0.029	13.03±0.17	1.15±0.018
F8	25°64′±0.22	0.369±0.012	0.423±0.024	10.32±0.26	1.16±0.029
F9	23°23′±0.23	0.379±0.010	0.436±0.019	13.63±0.12	1.12±0.031

Evaluation Parameters

Table 04: Evaluation parameters bilayer formulations

Formulation code	Mean Hardness Kg/cm2	Thickness (mm)	Friability % w/w	Average weight (mg)	Mean drug content %±SD	
					LINAGLIPTIN	METFORMIN
F1	6.34	2.9	0.63	997.5	98.18 ±0.90	99.45 ±0.20
F2	7.42	3	0.55	999.1	96.42 ±1.40	99.48 ±1.60
F3	7.3	3.4	0.5	1000.2	95.90 ±0.90	95.60 ±0.20
F4	7.52	2.8	0.6	999.0	98.77 ±0.10	98.97 ±0.80
F5	7.25	3.2	0.5	999.4	100.22±1.15	100.2 ±1.15
F6	7.36	2.5	0.52	997.9	95.44 ±0.70	95.97 ±0.60
F7	7.5	3	0.61	998.6	95.09 ±2.15	98.50 ±2.45
F8	7.41	2.8	0.66	1001.1	98.18 ±0.90	99.18 ±0.70
F9	7.3	2.2	0.6	998.5	101.14±1.45	99.14 ±1.97

Table 05: Cumulative Percent Drug Release of Linagliptin Tablets

S.No.	Time in minutes	L1	L2	L3	L4
1.	05	16.36±0.426	15.26±0.424	26.44±0.522	33.78±0.524
2.	10	33.78±0.524	37.78±0.621	42.07±0.423	56.39±0.324
3.	15	47.45±0.438	52.36±0.419	61.65±0.412	77.23±0.318
4.	20	56.39±0.324	62.22±0.248	72.00±0.321	90.28±0.421
5.	30	65.88±0.523	77.23±0.318	80.94±0.348	98.73±0.621
6.	40	67.67±0.491	79.25±0.312	90.13±0.129	
7.	50	76.64±0.483	83.57±0.429	97.48±0.246	
8.	60	80.88±0.394	94.65±0.326		

9.	75	92.09±0.429	98.28±0.421		
10.	90	99.65±0.248			

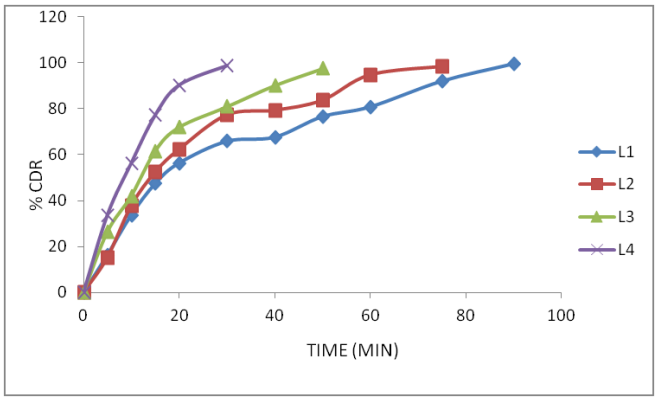

Fig 01: Cumulative Percent Drug Release versus Time Plots of Linagliptin Tablets

Table 06: Evaluation parameters of SR (METFORMIN) formulations

Formulation code	Mean Hardness Kg/cm2	Thickness (mm)	Friability % w/w	Average weight (mg)	Mean drug content %±SD
F1	6.21	3.12	0.62	298.5	97.07±2.15
F2	6.32	2.82	0.67	300.2	98.19±0.90
F3	6.41	2.22	0.63	298.6	101.13±1.45
F4	6.56	2.96	0.62	297.7	98.16±0.90
F5	6.01	3.65	0.54	199.3	96.26±1.40
F6	6.45	3.41	0.55	201.4	96.98±0.90
F7	6.52	2.80	0.63	299.2	98.97±0.10
F8	6.31	3.29	0.50	299.6	100.32±1.15
F9	6.43	2.55	0.52	297.8	95.26±0.70

Table 07: *In-vitro* drug release data of METFORMIN SR tablets

Time(hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	8	6.5	4	7	5	4	7	5	3
1	50.35	35.14	22.12	32.14	24.68	14.65	35.14	22.25	14.04
2	70.85	65.29	39.93	50.88	38.47	20.48	52.19	40.51	21.36
4	81.69	74.52	57.67	69.85	51.98	30.98	73.98	55.698	35.78
6	99.85	86.55	69.59	88.36	72.19	49.12	90.014	78.41	52.01
8		98.89	85.85	100	86.63	64.25	100.1	88.145	70.28
10			97.5		99.95	79.5		97.89	82.69
12						95.4			97.89

Table 8 In-vitro drug release data of bilayer tablets of Linagliptin(IR) best & Metformin (SR)

		F1		F2		F3		F4		F5		F6		F7		F8		F9
TIME (HRS)	L4 IR	F1	L4 IR	F2	L4 IR	F3	L4 IR	F4	L4 IR	F5	L4 IR	F6	L4 IR	F7	L4 IR	F8	L4 IR	F9
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	99.89	8	99.12	6.5	99.87	4	98.99	7	99.68	5	99.55	4	99.85	7	99.35	5	99.98	3
1		50.35		35.14		22.12		32.14		24.68		14.65		35.14		22.25		14.04
2		70.85		65.29		39.93		50.88		38.47		20.48		52.19		40.51		21.36
4		81.69		74.52		57.67		69.85		51.98		30.98		73.98		55.698		35.78
6		99.85		86.55		69.59		88.36		72.19		49.12		90.014		78.41		52.01
8				98.89		85.85		100		86.63		64.25		100.1		88.145		70.28
10						97.5				99.95		79.5				97.89		82.69
12												95.4						97.79

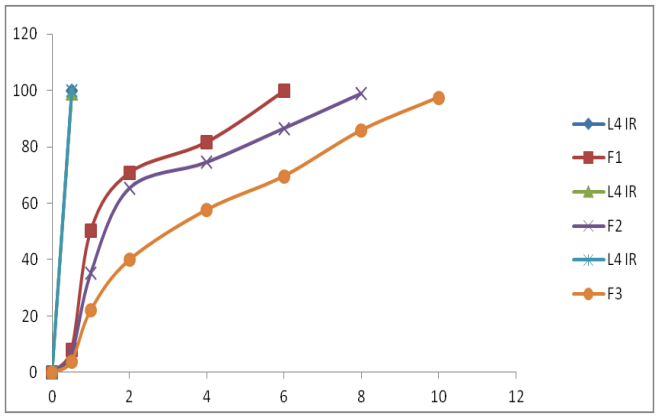

Fig 02: *In-vitro* drug release profile of bilayer tablets of batches F1 to F3

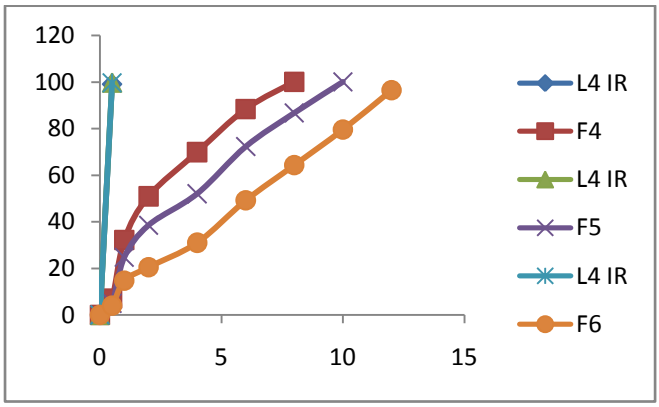

Fig 03: *In-vitro* drug release profile of bilayer tablets of batches F4 to F6

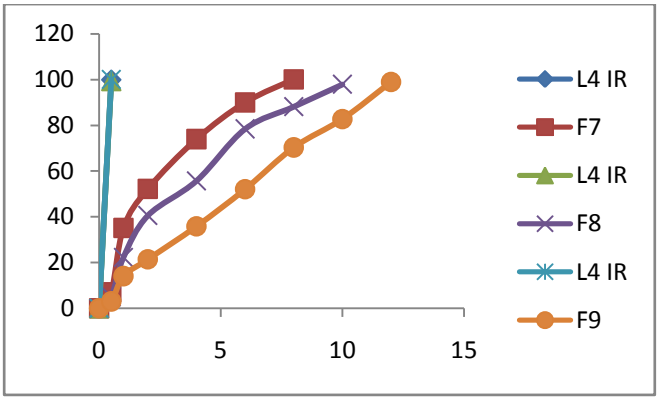

Fig 04: *In-vitro* drug release profile of Bilayer tablets of batches F7 to F9

Drug Release Kinetics of Bilayer Tablet

Zero Order Release Kinetics

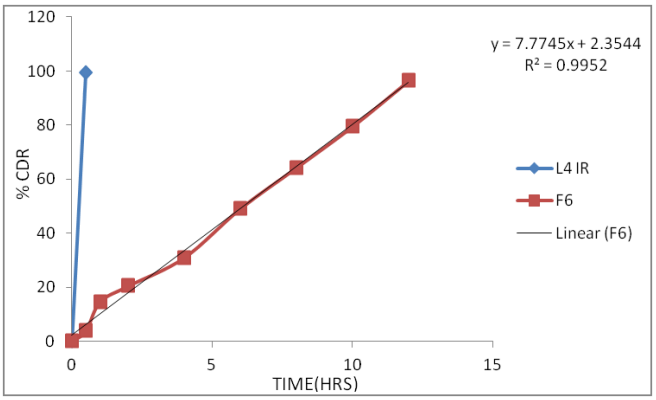

Fig 05: Zero order release profile of bilayer tablets of best formulation

First order release kinetics data of bilayer tablets

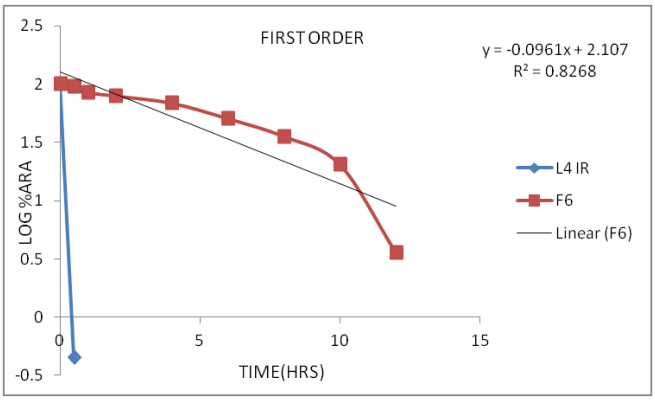

Fig 06: First order release profile of bilayer tablets of best formulation

Higuchi release kinetics data of bilayer tablets

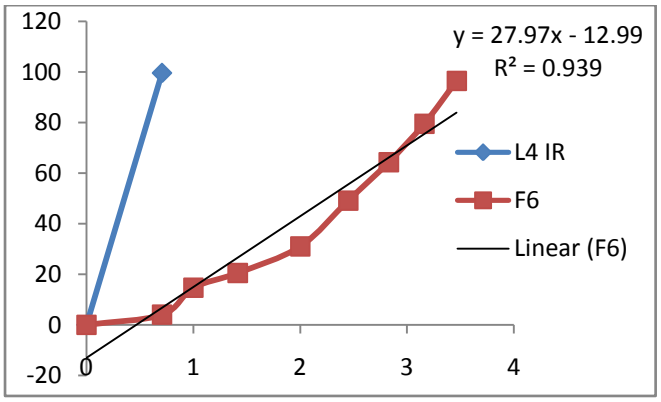

Fig 07: Higuchi release kinetics profile of bilayer tablets of best formulation

Peppas Release Kinetics Data of BILAYER Tablets

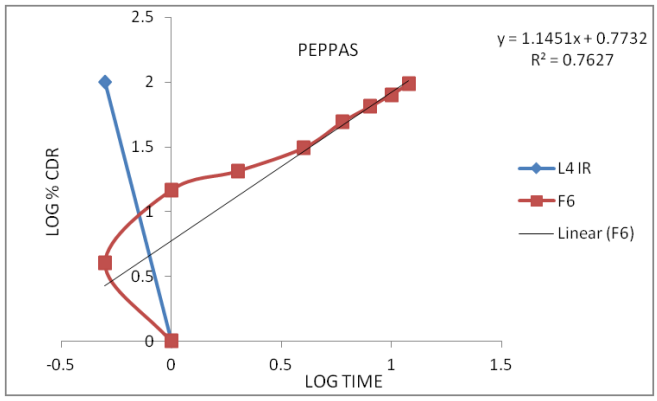

Fig 08: Peppas release kinetics profile of bilayer tablets of best formulation

Different Drug Release Kinetics Model For bilayer Tablets

Table 09: Regression coefficients fit to different drug release kinetics models for bilayer tablets

Formulation code Best	Zero order	First order	Higuchi	Peppas
	r^2	r^2	r^2	r^2
L4F6	0.9923	0.8568	0.959	0.8627

Table 10: Stability Studies for Formulation F6

Time	Evaluation parameters			
	Colour	Hardness (kg/cm^2)	Drug content Uniformity (%)	% CDR
0 Month	White	6.3	99.22	97.46
1 Month	White	6.3	98.06	96.11
2 Month	White	6.2	99.51	95.24
3 Month	White	6.2	98.97	97.12

Discussion

The purpose of the present study was to formulate and evaluate sustained release bilayer tablet of Metformin HCl and Lingaptin. develop bilayer tablets of Metformin as Sustained Release part using Hydroxylpropyl Methylcellulose as hydrophilic polymer and Linagliptin as Immediate Release part using Crospovidone. From the melting point determination it has been found that melting point of Metformin HCl was found in the range of 222°C-224°C and Lingaptin was in the range of 201°C-202°C. λmax was determined for both drugs, Lingaptin in 0.1 N HCl and for Metformin HCl in phosphate buffer pH 6.8. It was found to be 241 nm for glimepiride HCl and 232 nm for metformin HCl, which was exactly similar to the earlier reported λmax .From the standard curve of Linagliptin & Metformin, it obeys Beer's law in concentration range of 5–30 µg/ml in 0.01N HCl for linagliptin & 2-12 µg/ml in 0.01N HCl & 6.8 buffer for metformin. The linear regression equation generated was used for the calculation of amount of drug released.For floating drug delivery system, the polymers used must be highly swellable in shortest time. Hence HPMC K100M was preferred because it is widely used as low-density hydrocolloid system; upon contact with water, a hydrogel layer would be formed to act as a gel boundary for the release of drug, but it would fail to retard the release of drug through the matrix because of its solubility in stomach pH. Various grades of HPMC were

reported to have duration of buoyancy of more than 12 hours in the simulated meal medium, as well as in distilled water. The immediate release layer was formed by using Crospovidone as a disintegrant that was widely used in tablet formulation due to its effectiveness. Crospovidone gives the maximum disintegration and invitro dissolution release. The prepared tablets were subjected to preliminary characterization such as hardness, thickness, % weight variation, friability and drug content. The evaluated parameters were within acceptable range for all the ten formulations. Hardness (kg/cm^2) range from 6.24-7.42 , Thickness (mm) range 2.3-3.6, % Friability range 0.5-0.67, Drug content (%) range 95.09 - 101.14 In vitro drug release studies were carried out on dissolution test apparatus USP XXIII with paddles in 900ml of 0.1N HCl. These release studies revealed that, the order of release was found to be follows zero order release and higuchi mechanism for L4 formulation of immediate release and F6 formulation of sustained release which is selected as optimized formulation. Preformulation study was carried out using different concentration (level) of Crospovidone, gatti gum, to optimize formulations. All the formulation showed good tablet characteristics. Among the all formulation, L4 formulation of immediate release and F6 formulation of sustained release which contains Crospovidone, Gatti gum, Mg Stearate, and talc selected as optimized formulation.

Conclusion

Based on results it concluded that, among all the polymers used Crospovidone and Gatti gum shows maximum invitro drug release . MCC, magnesium stearate are used as lubricants. Bilayer tablet give good drug release ranges. In-vitro release rate studies showed that the maximum drug release was observed in L4 (IR), F6(SR) formulations upto 12 hrs. Formulations F6 found to be stable at room temperature for a period of 3 month. From the study it is evident that a promising Bilayer tablets of linagliptin and Metformin can be developed.

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