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Formulation and Evaluation of Bilayer Tablet of Metformin and Vildagliptin

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ABSTRACT

The Bilayered tablets containing Metformin SR and Vildagliptin IR were successfully prepared by direct compression method respectively. Various formulations were prepared and evaluated with an aim of presenting Metformin as sustained release and Vildagliptin as immediate release for improving the patient's compliance. The prepared blend for IR layer tablets and SR layer tablets were also maintained the physiochemical properties of tablets such as thickness, hardness, weight variation, friability. The optimized formulation V6 in IR formulations contains the average thickness of 2.4mm, average hardness of 2.0 kg/cm 2 , average weight of 150mg, friability of 0.27%. The optimized formulation M5 in SR formulations contains the average thickness of 2.46mm, average hardness of 3.44kg/cm 2 , friability of 0.46%. The M5 formulation which releases the Metformin in sustained manner in 1 st hour it releases 18.26% but the remaining drug release was sustained up to 12 hours and Vildagliptin immediate release V6 formulation showed 98.3% drug release with in 60min.With the data of kinetic analysis, M5 formulation showed best linearity in Zero order plot indicating that the release of drug from matrix tablet follows Non Fickian diffusion. The dissolution study was carried out for optimized bilayer tablet and it correlates with the drug release of individual release layer formulations.

Keywords: Immediate release, SR layer, kinetic analysis, bilayer tablet

INTRODUCTION

1.1 BILAYER TABLETS

Bilayer tablets are tablets made by compressing several different granulations fed in to a die in succession, one on top of another, in layer. Each layer comes from a separate feed frame with individual weight control. Rotary tablet presses can be set up for 2 or 3 layers. More are possible but the design becomes very special. Ideally a slight compression of each layer and individual layer ejection permits weight checking for control purposes[1].

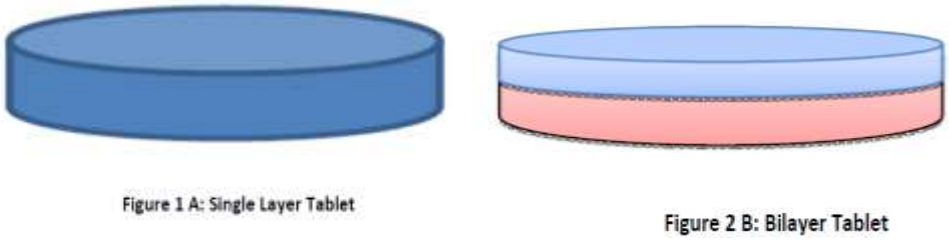

Figure 1 A: Single Layer Tablet

Figure 2 B: Bilayer Tablet

Figure 1: Bilayer tablet

Layer thickness

Layer thickness can be varied within reasonable proportions within the limitations of the tablet press. Thickness is dependent on the fineness of the granulation.

Sizes and shapes:

Size is limited by the capacity of the machine with the total thickness being the same as for a single layer tablet[2]. Many shapes other than spherical are possible and are limited only by the ingenuity of the die maker. However, deep concavities can cause distortion of the layers. Therefore standard concave and flat face beveled edge tooling make for the best appearance, especially when layers are of different colors.

Granulations

For good quality tablets with sharp definition between the layers, special care must be taken as follows,

1. Dust fines must be limited. Fines smaller than 100 meshes should be kept as a minimum.
2. Maximum granule size should be less than 16 meshes for a smooth, uniform scrap off at the dye.
3. Materials that smear, chalk or coat on the die table must be avoided to obtain clean scrape off and uncontaminated layers.
4. Low moisture is essential if incompatibilities are used.
5. Weak granules that break down easily must be avoided. Excessive amounts of lubrication, especially metallic stearates, should be avoided for better adhesion of the layers.

Formulation of the multilayer tablets is more demanding than that of single layer tablets for this reason, selection of additives is critical[3]

1.2 The Goal To Designing Bilayer Tablets:

- Controlling the delivery rate of either single or two different API'S.
- To separate incompatible API's with each other, to control the release of one layer by utilizing the functional property of the other layer (such as osmotic property).
- For the administration of fixed dose combinations of drugs, Prolong the drug product life cycle**,** buccal /mucoadhesive delivery systems, manufacture novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery systems.
- To adapt the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable/ erodible barriers for controlled release[4].
- 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. In which the one layer is formulated to obtain immediate release of the drug, with the aim of reaching a high serum concentration in a short period of time. The second layer is a controlled release, which is designed to maintain an effective plasma level for a prolonged period of time. The pharmacokinetic advantage relies on the fact that drug release from fast releasing layer leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining layer.

1.3 VARIOUS TECHNIQUES FOR PREPARATION OF BILAYER TABLETS[5]:

OROS® push pull technology

This system consist of mainly two or three layer among which the one or more layer are essential of the drug and other layer are consist of push layer. The drug layer mainly consists of drug along with two or more different agents. So this drug layer comprises of drug which is in poorly soluble form. There is

further addition of suspending agent and osmotic agent. A semi permeable membrane surrounds the tablet core.

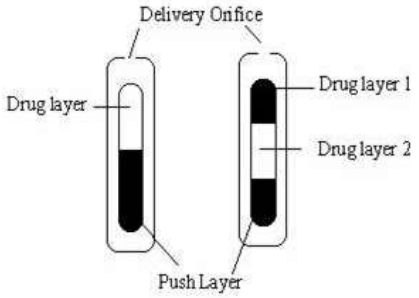

Figure 2: Bilayer and Trilayer oros push pull technology

L-OROS tm technology.

This system used for the solubility issue Alza developed the L-OROS system where a lipid soft gel product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, than osmotic push layer and than a semi permeable membrane, drilled with an exit orifice.

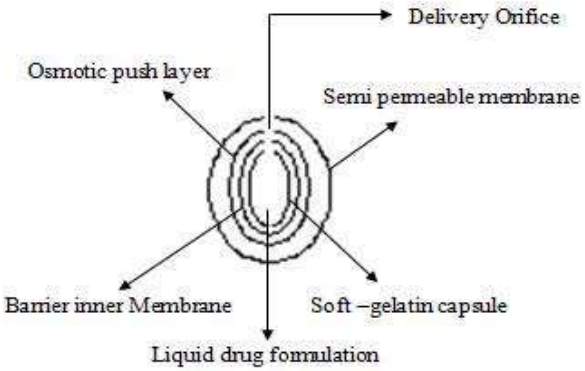

Figure 3: L-Oros TM Technology

EN SO TROL technology.

Solubility enhancement of an order of magnitude or to create optimized dosage form Shire laboratory use an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies.

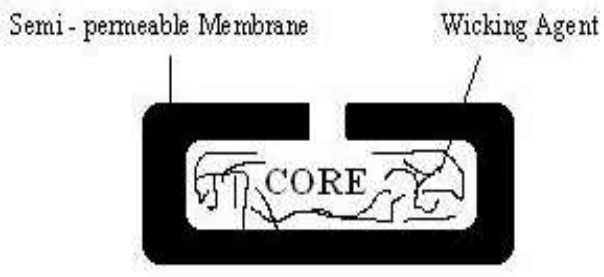

Figure 4: En So TROL TECHNOLOGY

iv) DUROS technology

The system consists from an outer cylindrical titanium alloy reservoir. This reservoir has high impact strength and protects the drug molecules from enzymes[13]. The DUROS technology is the miniature drug dispensing system that opposes like a miniature syringe and reglious minute quantity of concentrated form in continues and consistent from over months or year.

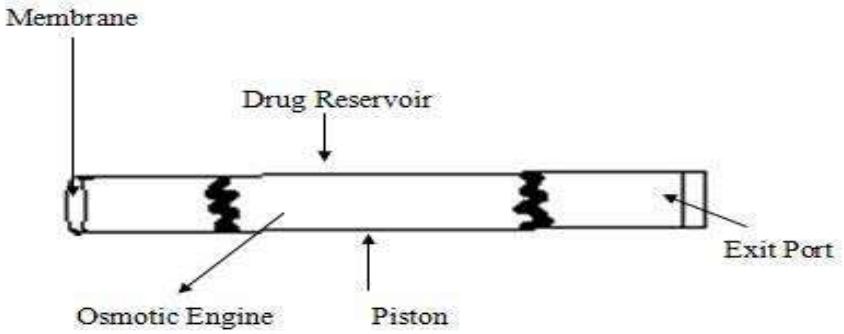

Figure 5: Duros Technology

Elan Drug Technologies' Dual Release Drug Delivery System

(DUREDAS™ Technology) is a bilayer tablet which can provide immediate or sustained release of two drugs or different release rates of the same drug in one dosage form. The tableting process can provide an immediate release granulate and a modified-release hydrophilic matrix complex as separate layers within the one tablet. The modified-release properties of the dosage form are provided by a combination of hydrophilic polymers.

Benefits offered by the DUREDAS™ technology includes:

1. Bilayer tabletting technology.
2. Tailored release rate of two drug components.
3. Capability of two different CR formulations combined.
4. Capability for immediate release and modified release components in one tablet
5. Unit dose tablet presentation.

Typically an immediate release granulate is first compressed followed by the addition of a controlled release element which is compressed onto the initial tablet. This gives the characteristic bilayer effect to the final dosage form. A further extension of the DUREDAS™ technology is the production of controlled release combination dosage forms whereby two different drugs are incorporated into the different layers and drug release of each is controlled to maximize the therapeutic effect of the combination. Again both immediate release and controlled release combinations of the two drugs are possible[14].

ROTAB BILAYER:

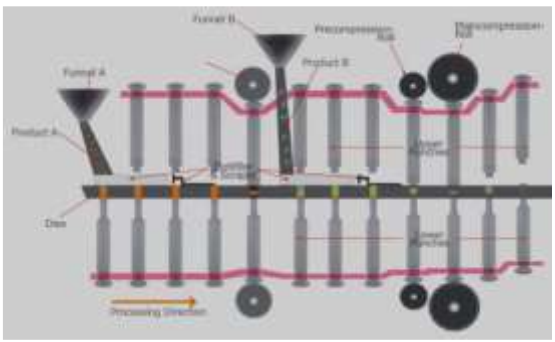

Figure 6: Rotab bilayer

SOFTWARE:

This software is modular designed and can be upgraded with additional functions at any time. An advanc

ed industrial PC-system with 15" touch-screen guarantees precise results and fast graphical evaluations. The wide range of instrumentations allows a nearly perfect simulation of production machines in laboratory scale. .

R&D.PLUS:

Contains all functions of Basic and R&D plus the possibility to evaluate and visualize the following special instrumentations on the 15" touch-screen display Punch tightness control, tablet scraper force and display of force displacement[15]. With R&D Plus the RoTab Bilayer sets new standards in tabletting technology.

1.4. Aim and objectives

- The Aim of of experiment is to formulate and evaluate a bilayer Tablet containing vildagliptin and metformin..
- To enhance rapid onset of action and also prolong release .
- **Objectives of the study**
- To finalize the deliberation of Polymer for sr layer, Metformin.
- To select and final disintegrant for IR layer vildagliptin
- To decide the appropriate filler to construct the largeness and preferred weight.
- To carry out the API – polymer compatibilities .
- Assessing formulation constraints such as weight variation, hardness, friability, disintegration, content homogeneity, and assay.
- To evaluate the in vitro research for the tablet in tablet preparation trials.

2.Methodology:

1. Construction of Standard Graph of Vildagliptin in 0.1N Hcl

Preparation of 0.1N Hcl

Take 8.5ml of Hcl in distilled water and make up to 1000ml with distilled Water to get 0.1N Hcl

Preparation of stock solution:

Accurately weighed amount of 50 mg was transferred into a 50ml volumetric flask. And the volume was made up with 0.1N Hcl. The resulted solution had the concentration of 1mg/ml (1000µg/ml) which was labeled as 'stock'.

Preparation of working standard solution:

From this stock solution 1ml was taken and diluted to 10 mL with 0.1N Hcl which has given the solution having the concentration of 100 mcg/mL.

Preparation of serial dilutions for standard calibration curve:

Necessary dilutions were made by using this second solution to give the different concentrations of Vildagliptin (2-10 mcg/mL) solutions. The absorbances of above solutions were recorded at λ_{max} (220nm) of the drug using double beam UV-Visible spectrophotometer. Standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis).

2. Construction Of Standard Graph Of Metformin (0.1N Hcl)

Preparation of standard stock solution:

Accurately weighed amount of 100 mg was transferred into a 100ml volumetric flask. Volume was made up to 100 mL with the 0.1N Hcl. The resulted solution had the concentration of 1mg/ml which was label

ed as 'stock'.

Preparation of working standard solution:

From this stock solution 10ml was taken and diluted to 100 mL with 0.1N Hcl which has given the solution having the concentration of 100mcg/mL.

Preparation of serial dilutions for standard calibration curve:

Necessary dilutions were made by using this second solution to give the different concentrations of metformin (5-25 mcg/mL) solutions.

The absorbances of above solutions were recorded at λ_{max} (218 nm) of the drug using double beam UV-Visible spectrophotometer. Standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis).

3. Construction of Standard Graph of Metformin (pH6.8 buffer)

Preparation of stock solution:

Accurately weighed amount of 100 mg was transferred into a 100ml volumetric flask. Few ml of water was added to dissolve the drug and volume was made up to 100 mL with pH6.8 buffer. The resulted solution had the concentration of 1mg/ml which was labeled as 'stock'.

Preparation of working standard solution:

From this stock solution 10ml was taken and diluted to 100 mL withpH6.8 buffer which has given the solution having the concentration of 100 mcg/mL.

Preparation of serial dilutions for standard calibration curve:

Necessary dilutions were made by using this second solution to give the different concentrations of metformin (5-25mcg/mL) solutions.

The absorbances of above solutions were recorded at λ_{max} of the drug using double beam UV-Visible spectrophotometer. Standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis).

3.1 FORMULATION DEVELOPMENT

3.1 Formulation of Bilayer Matrix Tablet (Sustained Release Layer)

The sustained release tablets containing 500mg metformin were prepared with a total tablet weight of 750mg were prepared.

***Manufacturing Procedure*:**

- Micro crystalline cellulose, Hydroxy propyl methyl cellulose K4M and Xanthan gum were weighed and sifted through 40 mesh.
- To the above blend metformin was added and sifted through 18 mesh.
- The sifted materials were mixed for 10min.
- PVPK30 was dissolved in IPA and this solution was added slowly to the above mixture to form a damp mass.
- The wet mass passed through 12 mesh and dried at room temperature.
- The dried granules were passed through 18 mesh.
- Magnesium Stearate was weighed and sifted through 40 mesh.
- To the dried granules lubricated blend was added and mixed properly.
- The lubricated blend was compressed using 9mm round punches.

COMPOSITION OF SUSTAINED RELEASE LAYER

Table 1: Formulation table for Sustained Release layer

Formulation	M_1	M_2	M_3	M_4	M5
Metformin	500mg	500mg	500mg	500mg	500mg
HPMC K4M	100mg	150mg			100mg
Xanthan gum			100mg	150mg	50mg
MCC	qs	qs	qs	qs	qs
Magnesium stearate	6mg	6mg	6mg	6mg	6mg
PVP K30	15mg	15mg	15mg	15mg	15mg
IPA	qs	qs	qs	qs	qs
Total weight	750mg	750mg	750mg	750mg	750mg

3.2) Formulation Of Bilayer Matrix Tablet (Immediate Layer)

The immediate release tablets containing 50mg Vildagliptin were prepared with a total tablet weight of 150mg.

Manufacturing Procedure:

- Lactose mono hydrate, super disintegrants like cross povidone, cross caramellose sodium, were weighed and sifted through 40 mesh.
- To the above blend Vildagliptin was added and sifted through 18 mesh.
- The sifted materials were mixed for 10min.
- PVP K-30 was dissolved in IPA and this solution was added slowly to the above mixture to form a damp mass.
- The wet mass passed through 12 mesh and dried at room temperature.
- The dried granules were passed through 18 mesh.
- Magnesium Stearate and talc were weighed and sifted through 40 mesh.
- To the dried granules lubricated blend was added and mixed properly.
- The lubricated blend was compressed using 8mm round punches.

Composition Of Immediate Release Layer

Table 2: Formulation table for Immediate release layer

Formulation	V_1	V_2	V_3	V_4	V_5	V_6
Vildagliptin	50mg	50mg	50mg	50mg	50mg	50mg
CP	7.5mg	11.25mg	-	-	-	-
CCS	-	-	7.5mg	11.25mg	-	-
SSG	-	-			7.5mg	11.25 mg
Lactose	qs	qs	qs	qs	qs	qs

Monohydrate						
Magnesium stearate	3 mg	3 mg	3 mg	3 mg	3 mg	3 mg
Talc	1.5%	1.5%	1.5%	1.5%	1.5%	1.5%
Total weight	150	150	150	150	150	**150**

EVALUATION OF BILAYERED TABLETS:

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, Friability and invitro-dissolution characters.

In vitro Dissolution Studies for immediate release layer of Vildagliptin

In vitro drug release studies were carried out using USP XXIV dissolution apparatus type II, with 900ml of dissolution medium maintained at 37±1°C for 1hr, at 50 rpm, 0.1 N HCl was used as a dissolution medium.5ml of sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn were filtered through 0.45µ membrane filter, and drug release in each sample was analyzed after suitable dilution by UV/Vis Spectrophotometer at 220nm.

BILAYERED TABLET PUNCH

After the batch was optimized in both immediate release layer (V6) and sustained release layer (M5).The optimized batch in both was compressed by using same ingredients.

STANDARD LINEARITY OF METFORMIN PREPARATION

Table 3: Std Linearity of Metformin in 0.1N Hydrochloric acid

Conc(ug/ml)	Abs at 218nm
0	0
5	0.127
10	0.262
15	0.381
20	0.548
25	0.672

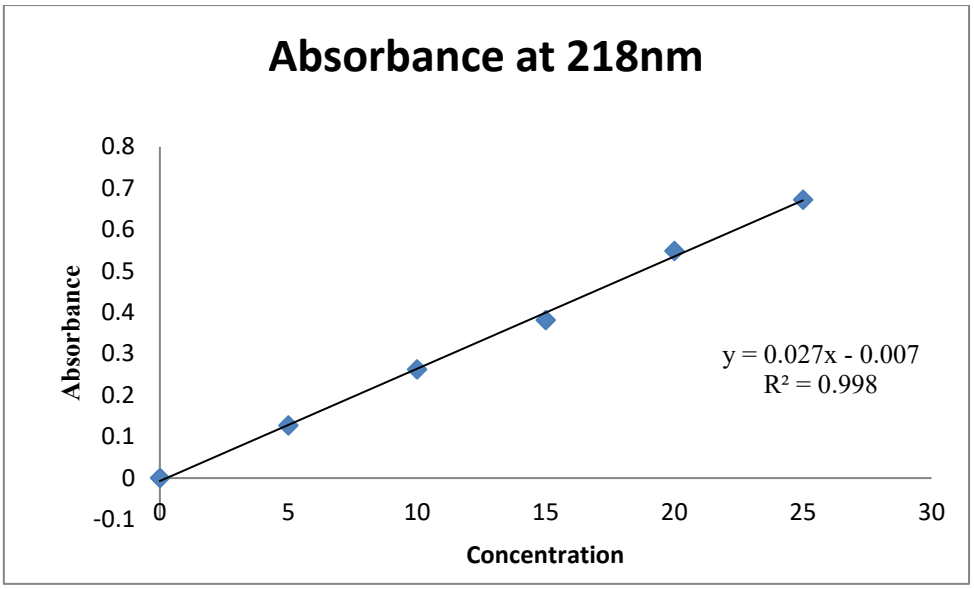

Figure 7: Linearity of Metformin IN 0.1N HCL

Standard Graph of Vildagliptin (0.1 N Hcl):

Std diagram of Vildagliptin has shown great linearity with R2 assessment 0.999 in 0.1 N Hydrochloric acid and which proposes that follows "Beer-Lambert's law"

Table 4: Standard linearity for Vildagliptin 0.1N Hcl

Concentration(µg/ml)	Absorbance
2	0.081
4	0.158
6	0.241
8	0.327
10	0.408

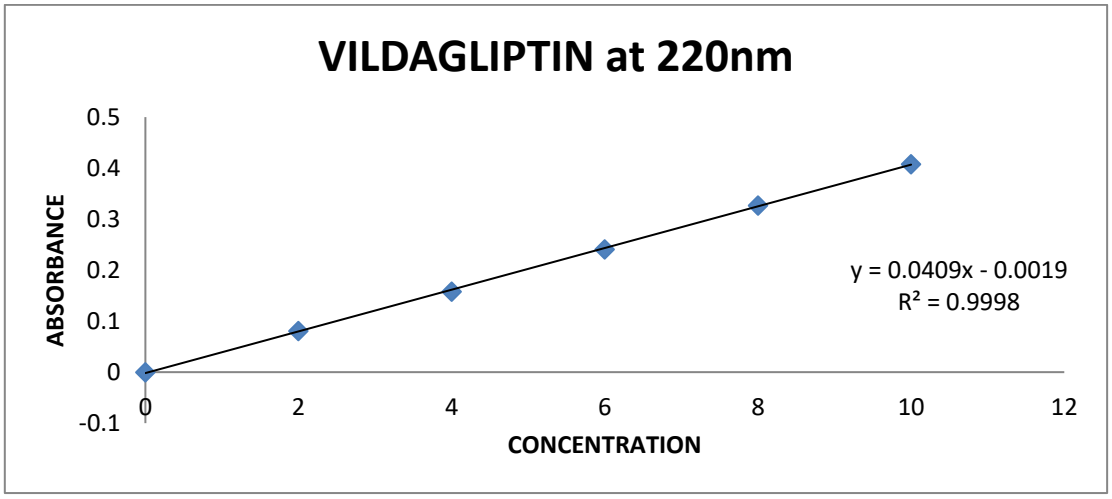

Figure 8: Linearity For Vildagliptin in 0.1 HCL at 220nm

FTIR COMPATIBILITIES

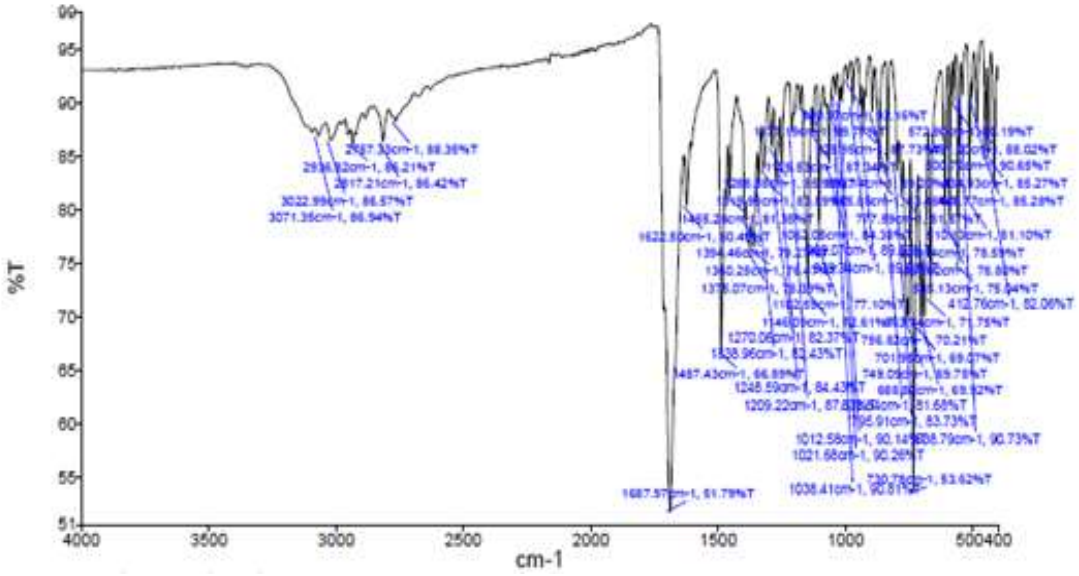

Figure 9: FTIR Spectrum of Metformin

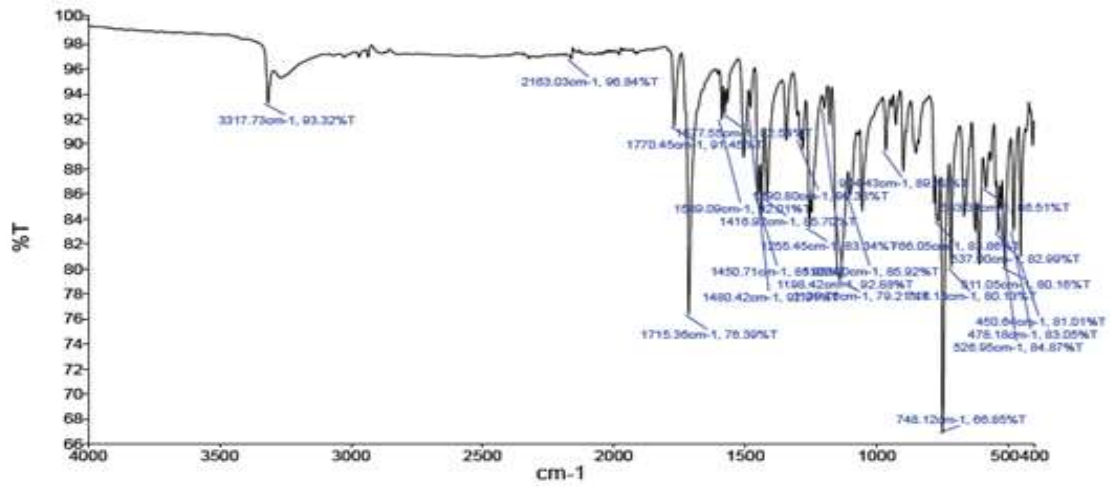

Figure 10: FTIR Spectrum of Metformin with Excipients

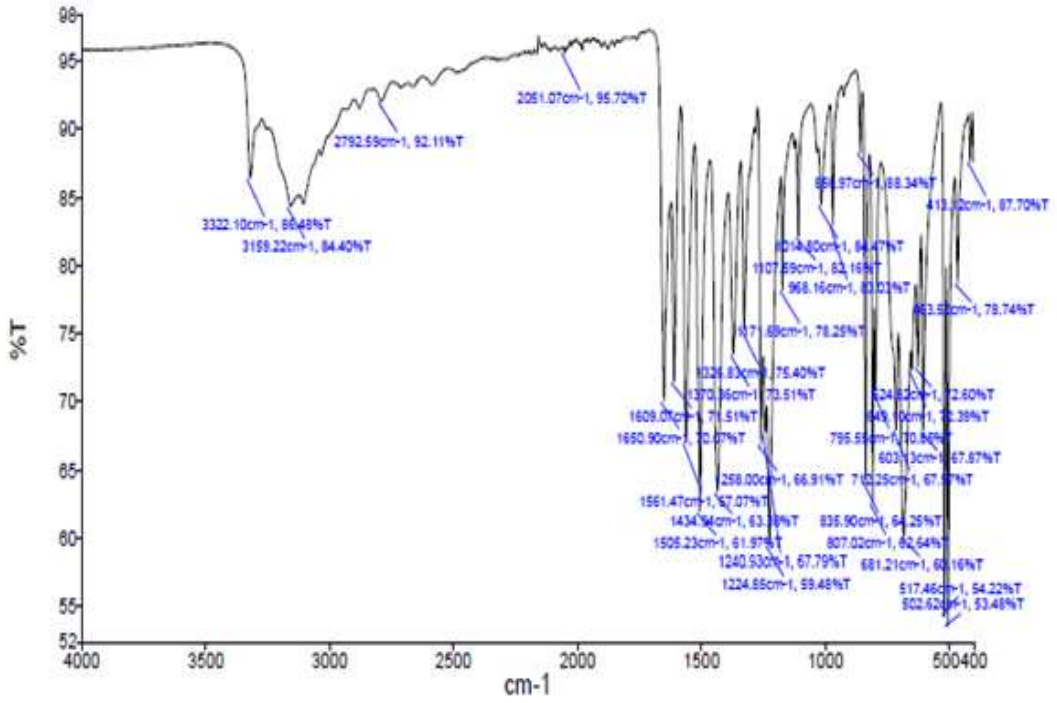

Figure 11 FTIR Spectrum of Vildagliptin

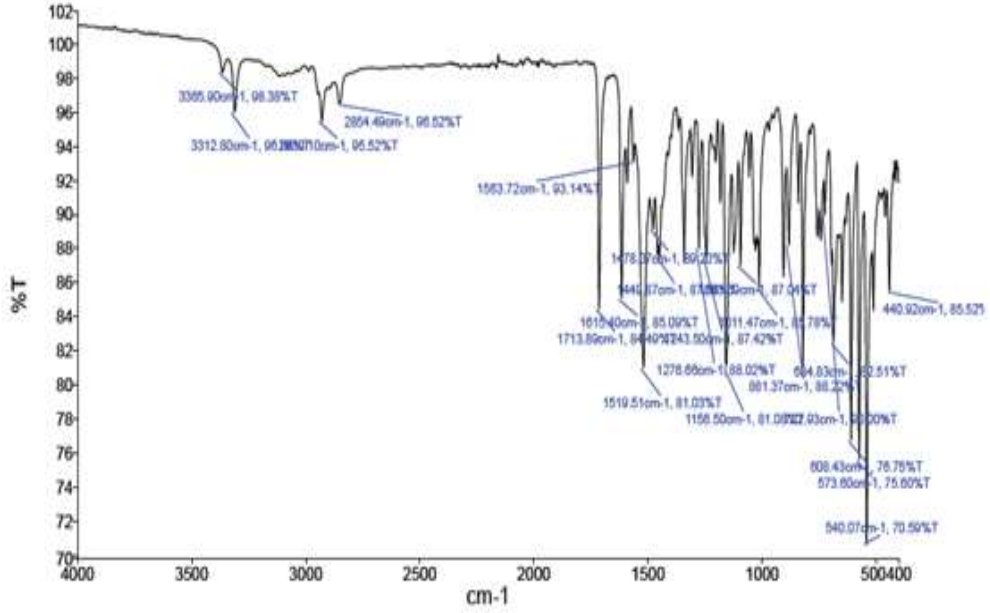

Figure 12: FTIR Spectrum of drug Vildagliptin with excipients

Table 5: Evaluation of Pre- Compression Limitations of SR Layer Of Metformin

Formulation	Angle of repose (°)	Bulk Density	Tapped density	Carr's Index (%)	Hausner's ratio
M1	28.14	0.32	0.38	15.78	1.18
M2	27.16	0.34	0.41	17.07	1.20
M3	26.37	0.31	0.37	16.21	1.19

M4	28.19	0.34	0.40	15.01	1.17
M5	25.17	0.32	0.37	13.51	1.15

Table 6: Post Compression limitations for SR Tablet

F.NO	Weight Variation(mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)
/M1	750	3.8	2.4	0.42
M//2	749	3.4	2.6	0.41
M3	749	3.4	2.5	0.49
M4	751	3.,NN.2	2.4	0.48
M5	750	3.4	2.4	0.51

***IN-VITRO* DISSOLUTION FOR METFORMIN -**

Acidic medium:

USP - II (paddle type) apparatus type; medium is 0.1N HCL at 50RPM . Up to the volume of 900 ml. It is 12 hours and the temperature is 37ºC±0.5.

Drug release studies of all formulation

Table 7: Cumulative percentage drug release of Sustained release layer

Time in hrs	M1	M2	M3	M4	M5
0.5	28.12	24.15	37.41	17.17	10.28
1	42.26	31.27	52.17	26.25	18.26
2	57.23	45.26	68.9	38.15	28.48
3	68.27	56.12	80.16	49.34	34.28
4	82.15	68.16	91.51	58.48	41.27
6	97.26	80.27	100.12	70.26	52.39
8	--	96.27	--	84.78	68.19
10	--	--	--	100.29	82.64
12	--	--	--	--	98.67

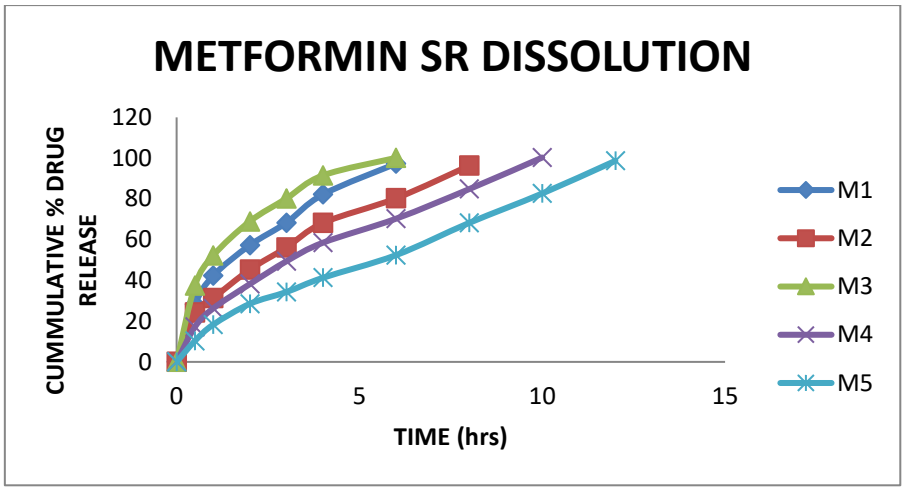

Figure 13: Dissolution fo Metformin

Drug release kinetics

Table 8: Drug Release Kinetics of Formulation M5

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	7.583	-0.117	28.02	0.972
Intercept	8.183	2.132	-9.123	0.963
R 2	0.986	0.770	0.964	0.615

Discussion for in-vitro release of Metformin tablet

The supported delivery hypothesis is not satisfied by the M1, M2, M3, and M4 definition of the supported discharge layer for a period of 12 hours, as confirmed by the chart. Furthermore, based on the chart, it was determined that the plan utilizing a mixer of Xanthium and HPMC (M5) showed the greatest drug release over a 12-hour period.

EVALUATION PARAMETERS FOR IMMEDIATE RELEASE LAYER OF VILDAGLIPTIN PRE-COMPRESSION LIMITATIONS

Table 9: Pre-compression parameters of Vildagliptin

F.NO	Angle of repose	Bulk Density (g/mL)	Tapped Density(g/mL)	Carr's Index (%)	Hausner's ratio
V1	22.41	0.31	0.36	13.88	1.16
V2	24.17	0.32	0.38	15.78	1.18
V3	25.31	0.28	0.33	15.15	1.17
V4	26.15	0.29	0.34	14.70	1.17
V5	27.42	0.30	0.34	12.07	1.13
V6	26.19	0.34	0.39	12.82	1.14

Table 10: Post compression limit for Immediate Release layer

F.No	Weight Variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)
V1	150	2.1	2.4	0.27
V2	149	2.0	2.5	0.24
V3	150	2.1	2.4	0.28
V4	152	2.2	2.6	0.34
V5	151	2.1	2.4	0.24
V6	148	2.0	2.1	0.28

Table 11: Dissolution for IR tablet of Vildagliptin

Minutes	V1	V2	V3	V4	V5	V6
5	11.77	14.45	14.71	26.77	18.29	22.18
10	21.42	24.75	26.42	42.41	31.37	36.47
15	28.18	33.75	32.85	54.18	42.24	47.26
30	40.29	46.2	54.61	76.29	59.26	65.37
45	52.77	60.07	76.15	92.26	74.41	81.5
60	58.15	65.75	86.75	96.3	89.27	98.3

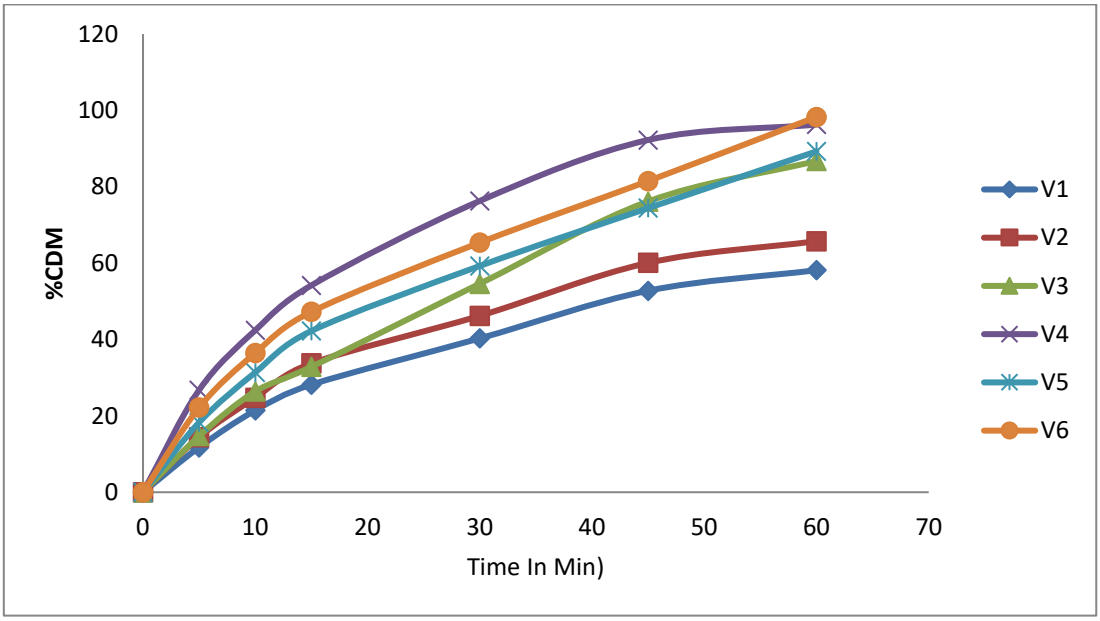

Figure 16: Dissolution for V1-V6 preparations

BI-LAYERED TABLET COMPRESSION

After the cluster was streamlined in both prompt delivery layer (V6) and Supported discharge layer(M5).The enhanced clump in both was compacted by utilizing same fixings.

DISSOLUTION (BILAYERED TABLETS) :

Table 12: Dissolution data for bilayer tablet

Time	Bilayertablet (Immediate Release + Sustained release)
Vildagliptin(150mg)	
Min	Dose
30min	64.28
60min	98.03
Metformin (750mg)	
hrs	dose
1hr	18.15
2hr	29.74
3hr	36.15
4hr	42.19
6 hr	51.48
8 hr	66.27
10 hr	81.49
12 hr	98.12

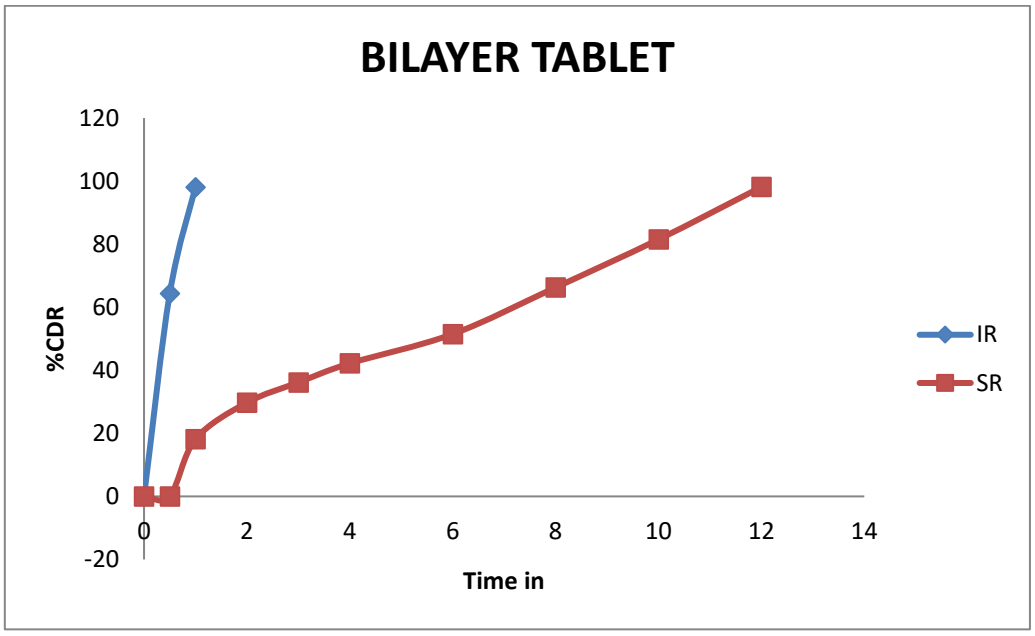

Figure 17: In-vitro drug release of bilayered tablets

STABILITY STUDIES

Stability studies were carried out according to ICH guidelines by exposing the Formulations in their final packing mode to the temperature 40±2°C and relative humidity 75±5 % in programmable environmental test chamber (CHM-10S, Remi Instruments Ltd., Mumbai, India). Aliquot were withdrawn at 30 and 60 days and analyzed for change in in-vitro dissolution profile.

Selected Formulation was subjected to stability studies as per ICH guidelines.
Following conditions were used for Stability Testing:

1. 21˚C/45% RH analyzed every month for period of three months.
2. 25˚C/60% RH analyzed every month for period of three months.
3. 30˚C/70% RH analyzed every month for period of three months.

CONCLUSION

- The bilayered tablets containing Vildagliptin and Metformin were efficiently arranged using a direct compression technique.
- The physiochemical properties of the tablets were also preserved in the equipped blend for SR and IR layer tablets.
- The advanced detailing V6 within IR plans carry the normal Thickness of 2.4mm, normal Hardness of 2.0 Kg/cm, normal load of 150mg, Friability of 0.27%.
- Enhanced definition M5 in the SR formulation has a normal hardness of 3.44 kg/cm2 and a friability of 0.46%. The typical thickness is 2.46 mm
- The M5 formulation which delivers the Metformin in supported way in first hour it discharges 18.26% however the leftover medication release was supported as long as 12 hours and Vildagliptin immediate release V6 formulation showed 98.3% medication release with in 60min.
- The M5 formulation showed the best linearity in the Zero request plot using the motor test data, suggesting that the distribution of drug release from the grid tablet is non-Fickian.

"Consequently it is summed up that the tablets arranged by direct compression technique for Sustained release layer and immediate release layer may be an ideal and powerful plan for the treatment of Diabetes".

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