IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

FORMULATION AND EVALUATION OF BILAYER TABLET OF ANTIDIABETIC AGENTS

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Abstract

The objective of present study was to prepare and characterize Bilayer tablet formulation containing Metformin HCl in extended release matrix form and Sitagliptin HCL in immediate release form for the treatment of diabetes mellitus. Different formulations containing Metformin HCl were manufactured using 3^2 factorial designs. Influence of hydrophilic carrier, hydrophobic polymer on drug release was studied. Immediate release layer of Pioglitazone was optimized using different super disintegrants. All formulations were evaluated for percentage drug release. Optimization results indicated that release rate of Metformin is directly proportional to the levels of Eudragit S 100 and PEG 6000. Results confirmed that Bilayer tablet formulation containing extended release of Metformin HCl and immediate release of Pioglitazone HCl could be developed by using melt granulation technique..

Keywords: β-cell, metformin, monotherapy, hypoglycaemia, Sitagliptin HCL, Type II Diabetes

Introduction

Dual release tablet is a unit comprdqaswessed tablet dosage form intended for oral application. It contains two parts in which one part is conventional or immediaterelease part another one is sustained or controlled release part.

Advantages of Bilayer Tablets:

- Bilayer tablets can be designed in such a manner as to modify the release as either of the layers can be kept as extended and the other as immediate release.
- Provide prolonged-action products.
- Separation of physically or chemically incompatible ingredients.
- Better therapeutic efficacy.
- Provide good treatment efficacy.
- Better patient compliance due to increased dosing intervals.
- Reduce number of doses and number of dosage forms.

Applications:

- Used in the combination therapy.
- Used to deliver the loading dose and sustained dose of the same or different drugs.
- Used for bilayer floating tablet in which one layer is floating layer another one is release layer of the drug.
- Used to deliver two different drugs having different release profile.

Disadvantages of Bilayer tablets:

- Layer separation.
- Insufficient hardness.
- Inaccurate individual layer weight control.
- Cross contamination between layers.
- Reduced yield.
- Bilayer rotary presses are expensive.

Manufacturing of Bilayer Tablets:

Bilayer tablets were manufactured by removal of upper punch after the initial layer decompression and refilling the die for the final compaction. After the second compression and decompression the lower punch was removed and the tablet was ejected by the application of a force to the upper punch driving the tablet out of the die.

Ideal Properties for Bilayer Tablet Press [3]

- To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the selected press is capable of:

- Preventing capping and separation of the two individual layers that constitute the bi-layer tablet.
- Providing sufficient tablet hardness.
- Preventing cross-contamination between the two layers.
- Producing a clear visual separation between the two layers.
- High yield.
- Accurate and individual weight control of the two layers.

Types of Bilayer Tablet Press:

· Single sided tablet press

· Double sided tablet press

(a) Single Sided Tablet Press:

The simplest design is the single sided press with both chambers of the double feeder separated from each other. Each chamber is gravity or forced fed with different powder, thus producing the two individual layers of the tablets. When the die passes under the feeder, it is first loaded with the first layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two steps.

Limitations of the Single Sided Press:

- No weight monitoring / control of the individual layers.
- No distinct visual separation between the two layers.
- Very short first layer dwell time due to the small compression roller, possibly resulting in poor de-aeration, capping and hardness problems.

Dwell Time: Dwell time is defined as the time during which compression force is above 90% of its peak value. Longer dwell times are a major factor in producing a quality tablet, especially when compressing a difficult formulation.

(b) Double Sided Tablet Press:

- A double sided press offers an individual fill station, pre-compression and main compression for each layer. In fact the bilayer tablet will go through four compression stages before being ejected from the press.
- Most double sided tablet presses with automated production control use compression force to monitor and control tablet weight.
- The effective peak compression force exerted on each individual tablet or layer is measured by the control system at main compression of the layer.

This measured peak compression force is the signal used by the control system to reject out of tolerance tablet and correct the die fill depth when required

Materials and methods:

Drug Metformin was obtained as a gift sample from Mylan Laboratories and Drud Sitagliptin was obtained from Mehta API PVT LTD and other excipients were obtained from Loba Chemicals Gujarat.

Preformulation Studies:

Pre-formulation Studies

Preformulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms.

Organoleptic properties:

Metformin & Sitagliptin

Colour:

A small quantity of pure Metformin hydrochloride and sitagliptin powder was taken in a butter paper and viewed in well illuminated place.

Taste and Odour:

Very less quantity was used to get taste with the help of tongue as well as smelled to get the odour.

Solubility analysis[37]:

Solubility is important pre-formulation parameter because it affects the dissolution of drug bio availability of drug. Solubility of metformin hydrochloride and Sitagliptin was determined in ethanol, Acetone, Ether and Chloroform. Solubility studies were performed by taking excess amount of metformin hydrochloride and sitagliptin in different beakers containing the solvent.

Melting point[38]:

The melting point of Metformin hydrochloride and Sitagliptin was determined by capillary method, using small quantity of metformin hydrochloride and Sitagliptin were taken and placed in apparatus and determined the melting point and matched with standards.

Loss on drying[39]:

It is determined on 1 g by drying in an oven at 100℃ to 105℃ for 3 hours. Mixed and accurately weighed the substance to be tested. Take a glass stopper, shallow weighing bottle that has been dried for 30 minutes under the same conditions to be employed in the determination. Weigh the empty bottle (W_1). Put the sample in bottle, replace the cover, and accurately weighed the empty bottle with contents (W_2).

By gentle, sidewise shaking, distributed the sample as evenly as practicable to a depth of about 5 mm. Place the loaded bottle in the drying chamber. Dry the sample at the specified temperature in desiccator before weighing. Weigh the bottle (W3). The difference between successive weights should not less than 0.3%.

The loss on drying is calculated by the formula:

$$\% \text{ LOD} = \frac{(W_2 - W_3)}{(W_2 - W_1)} \times 100$$

Where,

W_1 = Weight of empty weighing bottle W_2 = Weight of weighing bottle + sample

W_3 = Weight of weighing bottle + dried sample

Drug powder characterization:

Angle of repose:

Angle of repose is the maximum angle of a stable slope determined by friction, cohesion and the shapes of the particles. The internal angle between the surface of the pile and horizontal surface is known as the angle of repose and is related to the density, surface area and co-efficient of friction of the raw material[40,41.]

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

Where,

h = height of heap, r = radius of heap, Θ = angle of repose. Formulation Study

Table:5 :Limits

Angle of repose Flow property	Angle of repose Flow property
<25° Excellent	<25° Excellent
25-30° Good	25-30° Good
30-40° Passable	30-40° Passable
>40° Very poor	>40° Very poor

Bulk density:

Bulk density is defined as the mass of the powder divided by the bulk volume. Bulk density largely depends on particle shape, as the particle become more spherical in shape, bulk density was increased. In addition as the granule size increases bulk density decreases[42].

A quantity of 5 gm of powder weighed and transferred to a measuring cylinder and observed the volume occupied by the sample. The initial volume was calculated. Bulk density was calculated using the formula[43].

Bulk density = Bulk mass / Bulk volume

Tapped density:

Tapped density is achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder is mechanically tapped and volume readings are taken until little further volume changes is observed the mechanical tapping is achieved by raising the cylinder and allowing it to drop under its own weigh a specific distance device that rotates device during tapping may be preferred to minimize any possible separation of the mass during tapping down[44,45].

The powder in the measuring cylinder was tapped for specific times at a height of 2.5 cm at a interval of 2 seconds. The powder in the graduated cylinder was tapped for specific times at a height of 2.5 cm at an interval of 2 seconds. The final volume occupied by the sample was noted and tapped density was calculated by using the formula:

$$\text{Tapped density} = \frac{m}{V_f}$$

Where, m = initial weight of material in gm, V_f = volume of material after tapping.

Generally replicate determinations are desirable for the determination of this Property.

Measurement of powder compressibility[46]:

Based on the apparent bulk and the tapped density, the percentage compressibility of bulk was determined by the following formula.

Compressibility index: $=100\ \frac{(V_0-V_f)}{V_0}$

Where,

V_f = final tapped volume,

V_o = initial un tapped volume

Table-6: Limits:

S. No	Compressibility index	Flow
1	5-12	Free flow
2	12-16	Good Flow
3	18-21	Fair
4	23-25	Poor
5	33-38	Very Poor
6	>40	Extremely poor

Table-7: Limits:

S.No	Hausner' ratio	Flow
1	1-1.2	Free flowing
2	1.2-1.6	Cohesive powder

6.1.6. Construction of standard curve for Sitagliptin and metformin

λ max determination test:

UV Spectra: The spectra of Metformin in 0.01 N HCL suggest that maximum absorption occurs at 232 nm

Preparation of standard calibration curve of Metformin

Principle: The Metformin exhibits peak absorbance at 232 nm 0.01 NHCL

Procedure:

- **Preparation of standard solution(0.01N HCL):**

Standard stock solution of Metformin was prepared in 0.01N HCL. 100 mg of Metformin was accurately weighed into 100ml volumetric flask and dissolved in small quantity of HCL The volume was made up with 0.01N HCL to get a concentration of 1000µg/ml (SS-I).

From this 25ml solution was withdrawn and diluted to 100ml to get a concentration of 250µg/ml (SS-II).

- **Preparation of standard solution (6.8 Phosphate buffer):**

Standard stock solution of Metformin was prepared in 6.8 Phosphate buffer. 100 mg of metformin was accurately weighed into 100ml volumetric flask and dissolved in small quantity of buffer solution. The volume was made up with 6.8 Phosphate buffer to get a concentration of 1000µg/ml (SS-I).From this 25ml solution was withdrawn and diluted to 100ml to get a concentration of 250µg/ml (SS-II).

- **Preparation of working standard solutions(0.01N HCL):**

Further, from (SS-II) aliquots of 0.2ml, 0.4ml, 0.6ml, 0.8ml, 1.0ml, & 1.2ml were pipetted into 25ml volumetric flasks. The volume was made up with 0.01 N HCL to get the final concentrations of 2,4,6,8,10 and 12µg/ml respectively. The absorbance of each concentration was measured at 232 nm.

- **Preparation of working standard solutions(6.8 Phosphate buffer):**

Further, from (SS-II) aliquots of 0.2ml, 0.4ml, 0.6ml, 0.8ml, 1.0ml, & 1.2ml were pipetted into 25ml volumetric flasks. The volume was made up with 6.8 Phosphate buffer to get the final concentrations of 2,4,6,8,10 and 12µg/ml respectively. The absorbance of each concentration was measured at 232 nm.

λ Max : 232nm.

Preparation of standard calibration curve of Sitagliptin

Principle: The Sitagliptin exhibits peak absorbance at 267 nm in 0.01 N HCL.

Procedure:

- **Preparation of standard solution:**

Standard stock solution of Sitagliptin was prepared in 0.01N HCL. 100 mg of Sitagliptin was accurately weighed into 100ml volumetric flask and dissolved in small quantity of 0.01N HCL. The volume was made up with 0 . 01 N HCL to get a concentration of 1000µg/ml (SS-I). From this 25ml solution was withdrawn and diluted to 100ml to get a concentration of 250µg/ml (SS-II).

- **Preparation of working standard solutions:**

Further, from (SS-II) aliquots of 0.5ml, 1.0ml, 1.5ml, 2.0ml, 2.5ml, and 3.0ml were pipetted into 25ml volumetric flasks. The volume was made up with 0.01 N HCL to get the final concentrations of 5, 10, 15, 20, 25 and 30 µg/ml respectively. The absorbance of each concentration was measured at 241nm.

λ Max : 267nm

6.1.7 Drug excipient compatibility study

Prior to the development of Sitagliptin, metformin dosage forms, infrared spectra of the physical mixture of the polymers individually and the mixture of drug and polymer were taken.

6.1 Formulation of bilayer tablet:

Table 8 Formulation of immediate release tablet

S.NO	INGRIDIENTS	L1	L2	L3	L4
1	Sitagliptin	2.5	2.5	2.5	2.5
2	Cros povidone	0	2	4	6
3	Mannitol	q.s	q.s	q.s	q.s
4	PVP K 90	3	3	3	3
5	Magnesium stearate	4	4	4	4

Table 9 Formulation of bilayer tablet

S.NO	INGRIDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
IR release granules (L4)										
1	Sitagliptin	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	.5
2	Cros povidone	6	6	6	6	6	6	6	6	
3	Mannitol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	.s
4	PVP K 90	3	3	3	3	3	3	3	3	
5	Magnesium stearate	4	4	4	4	4	4	4	4	
SR release granules										
6	Metformin	500	500	500	500	500	500	500	500	00
7	HPMC K100M	135	180	225						
8	Gatti gum				135	180	225			
9	Sodium alginate							135	180	25
10	MCC	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	.s
11	Aerosil	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	.5
12	Mg.Stearate	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	2.5
	Total weight(mg)	1000	1000	1000	1000	1000	1000	1000	1000	1000

Preparation of Bilayer tablets

a) Preparation of Immediate release layer:

The Immediate release layer contains uniform mixture of Sitagliptin cros povidone, 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 was passed through sieve 20# and dried. Finally prepared granules were lubricated with magnesium stearate and the well mixed powder was 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 5 min. 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 multi station punching machine using flat punches, with the hardness of 6.5 kg/cm^2.

6.2 Evaluation of Bilayer Tablets:

All the prepared bilayer tablets were evaluated for following parameters.

6.2.1 Appearance:

The bilayer tablets were identified visually by checking the difference in colour.

6.2.2 Thickness:

Thickness was measured using a calibrated dial caliper. Five tablets of the formulation were picked randomly and thickness was measured individually.

6.2.3 Hardness:

Hardness was measured using Monsanto hardness tester. For each batch three tablets were tested.

6.2.4 Friability: Twenty tablets were weighed and placed in the roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions, the tablets were weighed again. The percentage friability was measured using formula,

$$\% F = \{1-(W_t/W)\} \times 100$$

Where, % F = Friability in percentage

W = Initial weight of tablets

W_t = Weight of tablets after revolution

6.2.5 Weight variation:

Ten tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviate from the average weight.

6.2.6 *In-vitro* dissolution studies for IR:

Dissolution of the tablets was carried out on USP 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 ± 0.5^0 C. The rotational speed of the paddle was set at 100 rpm. 1 ml of sample was withdrawn at predetermined time interval up to 90 minutes 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 241 nm using 0.01N HCL as a blank. Percentage cumulative drug release was calculated.

6.2.7 *In-vitro* dissolution studies for SR:

Dissolution of the tablets was carried out on USP 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 ± 0.5^0 C. The rotational speed of the paddle was set at 50 rpm. 5 ml of sample was withdrawn at predetermined time interval up to 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.

Details of dissolution test:

Dissolution test apparatus : USP XX III

Speed : 50 rpm

Stirrer : Paddle type

Volume of medium : 900 ml

Volume withdrawn : 5 ml

Medium used : 0.1N HCL, pH 6.8 buffer

Buffer temperature : 37 ± 0.5^0 C

6.2.8 Stability studies of the optimized formulation:

Stability of a pharmaceutical preparation can be defined as "the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life."

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf-lives to be established.

ICH specifications for stability study:

Long term testing: 25^{0}C ± 2^{0}C /60% RH ± 5% RH for 12 months. Accelerated testing: 40^{0}C ± 2^{0}C /75% RH ± 5% RH for 6 months.

Procedure:

In the present study, stability studies were carried out at 40 ^{0}C and 75% RH for a specific time period up to 3 months for selected formulation. For stability study, the tablets were sealed in aluminium packaging coated inside with polyethylene. These sample containers were placed in desiccator maintained at 75% RH.

Evaluation of samples:

The samples were analyzed for the following parameters:

I. Physical evaluation:

Appearance: The samples were checked for any change in colour at an interval of 1 month upto 3 month

Hardness: The samples were tested for hardness at an interval of 1 month upto 3 month.

II. Chemical evaluation:

Drug content: The samples were checked for drug content at an interval of 1 month upto 3 month

Drug release: The samples were subjected to drug release studies at an interval of 1 month upto 3 month

Results and discussion:

PREFORMULATION STUDY

These tests were performed as per procedure. The results were illustrated in below.

Organoleptic properties:

Table-10: Observation of organoleptic properties: Metformin

Test	Specification	Observation
Colour	White hygroscopic crystalline Powder	White hygroscopic crystalline Powder
Odour	Odourless	Odourless
Taste	Bitter Taste	Bitter taste

Table 11 Observation of organoleptic properties: Sitagliptin

Test	Specification	Observation
Colour	Pale yellow	Pale Yellow
Odour	Odour less	Odourless
Taste	Tasteless	Tasteless

Solubility analysis:

Metformin:

Samples are examined and it was found to be freely soluble in water and slightly soluble ethanol, but almost insoluble in Acetone, Ether chloroform.

Sitagliptin:

Samples are examined and it was found to be soluble in water.

Melting point

Metformin:

The melting point was determined by capillary method, melting point of metformin hydrochloride was found to be 222. 5°C.Melting point compared with USP standards that showed that drug is pure.

Sitagliptin:

The melting point was determined by capillary method, melting point of Sitagliptin was found to be 206°C.Melting point compared with USP standards that showed that drug is pure.

Loss on Drying:

It was determined as per procedure. The results were given in table no.12.

Table-12: Observations for loss on drying Metformin

Test	Loss on Drying	Observation
Loss on Drying	Not more than 0.5%	0.40%

Observations for loss on drying Sitagliptin

Test	Loss on Drying	Observation
Loss on Drying	Not more than 0.5%	0.42%

The loss drying of drug was founded as 0.42 which is within the limit.

Drug powder characterization: Angle of repose

It was determined as per procedure. The results were given in table no.13

Table-13: Angle of Repose

Material	Angle of repose
Metformin	26°32’
Sitagliptin	26°54’

The results indicating that the raw material had good flow property.

Flow properties

It was determined as per procedure given under methods. The results were given in table no.14

Table-14: Flow properties of drugs

Material	Bulk Density	Tapped Density	Carr’s index	Hausner Ratio
Metformin	0.219	0.313	10.12	1.05
Sitagliptin	0.274	0.324	11.81	1.02

7.1.6. Construction of standard curve for Sitagliptin and metformin

Table 15: Standard calibration curve of Sitagliptin in 0.01N HCL

S. No	Concentration(µg/ml)	Absorbance
1	5	0.1523
2	10	0.3119
3	15	0.4789
4	20	0.6368
5	25	0.7943
6	30	0.8575

Fig 4 Standard calibration curve of Sitagliptin at 267nm

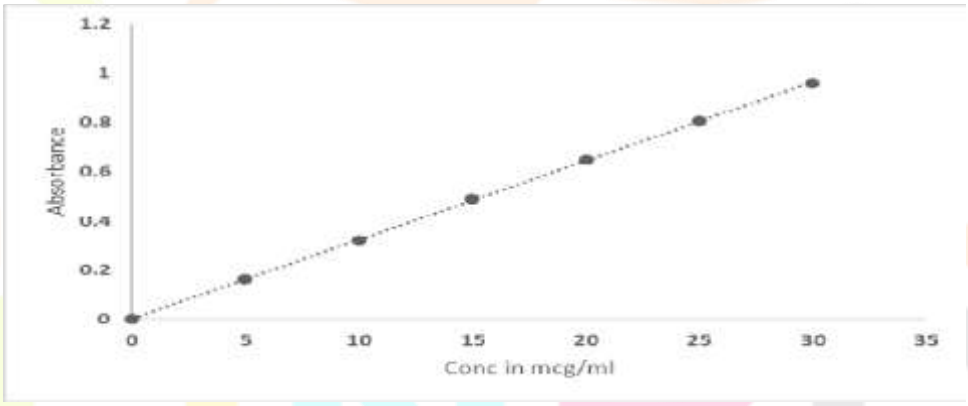


Table 16: Standard calibration curve of Metformin in 0.01N HCL

S. No.	Concentration(µg/ml)	Absorbance
1	0	0
2	2	0.041
3	4	0.201
4	6	0.35

5	8	0.51
6	10	0.767
7	12	0.72

Fig 5 **Standard calibration curve of Metformin at 232nm**

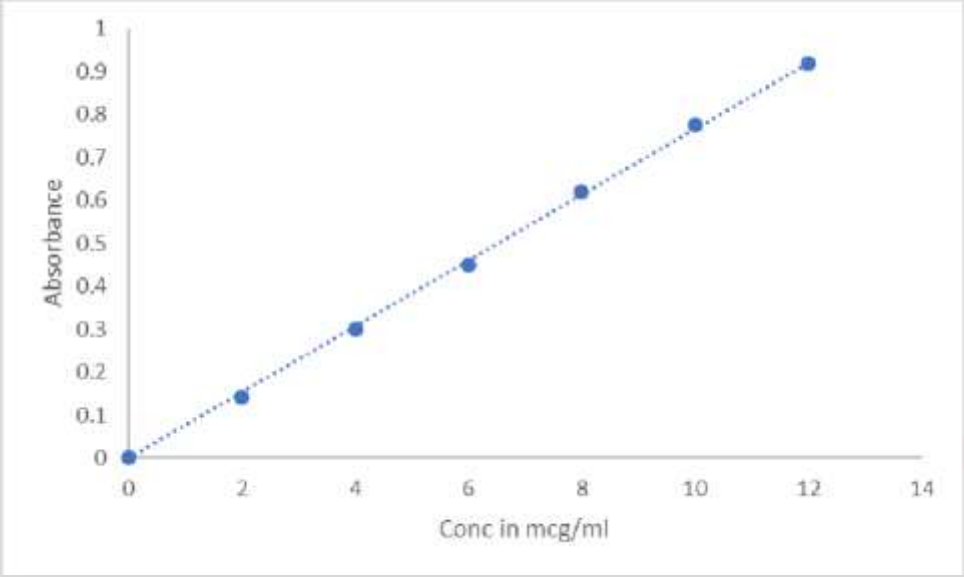
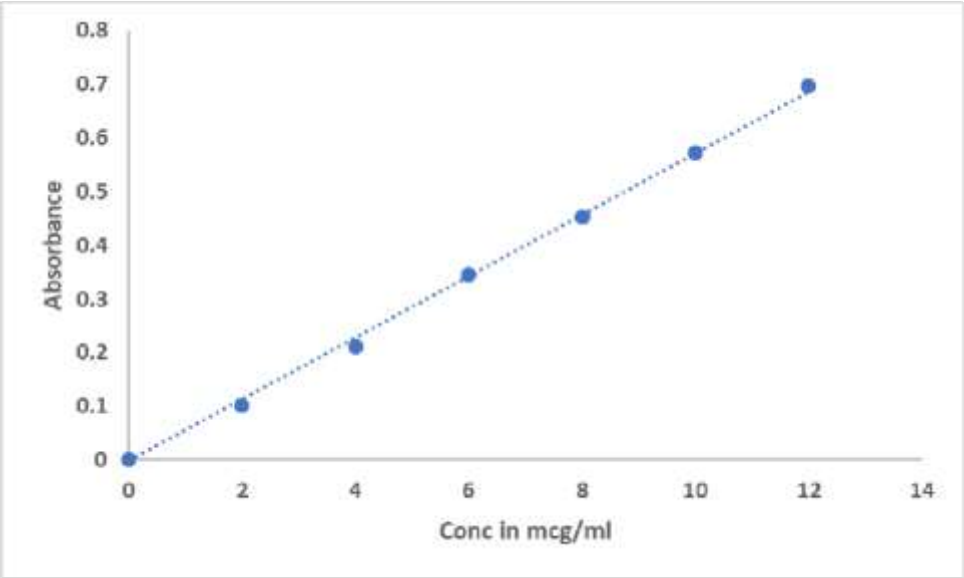


Table 17: Standard calibration curve of Metformin in Phosphate Buffer pH 6.8

S. No	Concentration(µg/ml)	Absorbance
1	0	0
2	2	0.102
3	4	0.212
4	6	0.346
5	8	0.453
6	10	0.571
7	12	0.697

Fig 6 **Standard calibration curve of Metformin at 232nm**



7.1.7 Drug excipient compatibility study

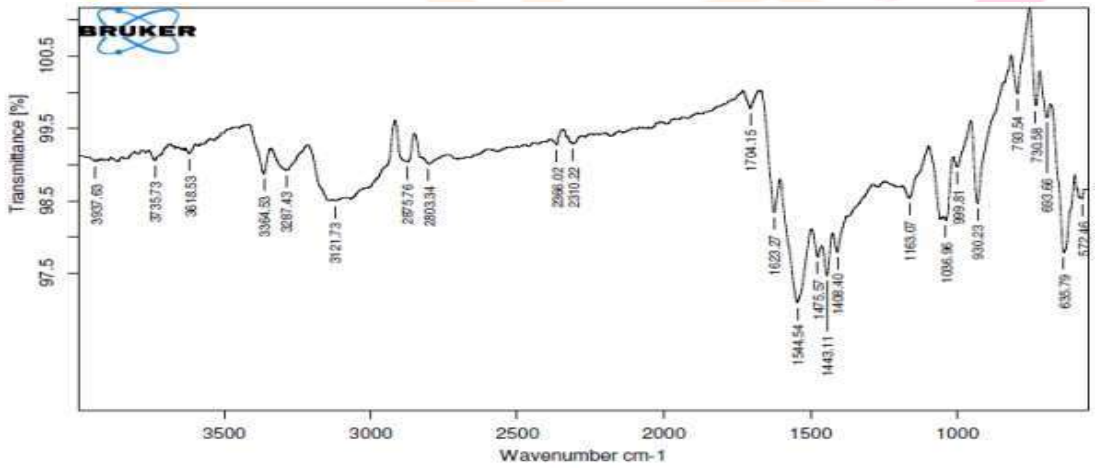


Fig 7 Spectra IR Spectra of Metformin

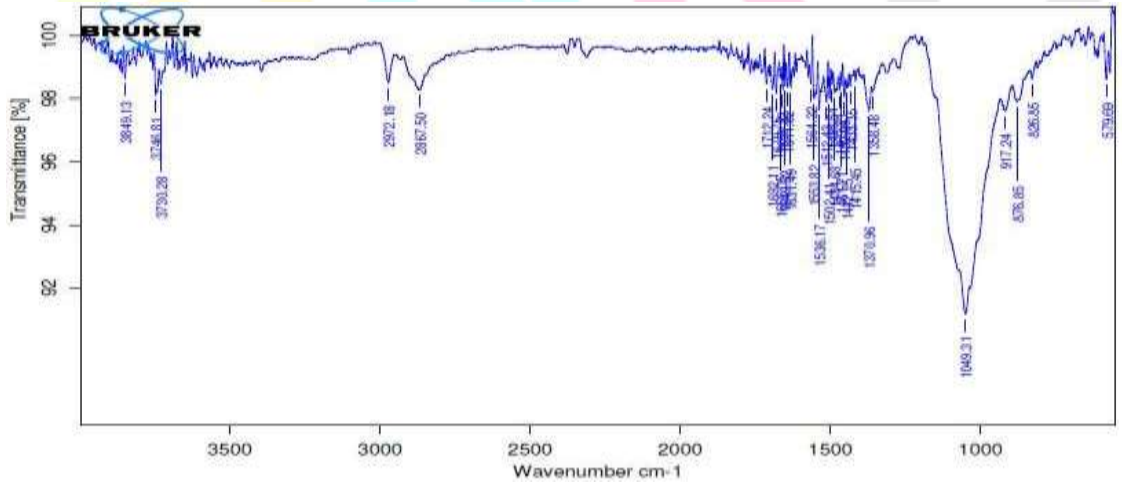


Fig 11 IR spectra of Sitagliptin

7.1 Formulation of bilayer tablet:

Pre-compression parameters of Sitagliptin and metformin were carried out and reported in table no 18 & 19.

Table 18 . Pre-compression parameters for all formulations of IR (Sitagliptin)

Code	Angle of Repose ±SD	Bulk Density (g/ml)±SD	Tapped Density (g/ml)±SD	Carr's Index. (%)±SD	Hausner's ratio±SD
L1	26°54'±0.37	0.364±0.018	0.414±0.021	10.81±0.17	1.12±0.025
L2	26°58'±0.25	0.377±0.024	0.427±0.018	11.11±0.12	1.12±0.037
L3	24°32'±0.24	0.355±0.033	0.414±0.025	13.15±0.25	1.15±0.032
L4	25°42'±0.29	0.368±0.019	0.417±0.029	13.51±0.15	1.15±0.018

Table :19. Pre-compression parameters 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	26°32'±0.27	0.319±0.031	0.413±0.032	11.12±0.11	1.15±0.010
F2	24°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

7.2 Physicochemical evaluation:

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 formulations.

Table No. 20: Range for value of preliminary characterization of formulations

Parameters	Range
Hardness (kg/cm^2)	6.34-7.52
Thickness (mm)	2.2-3.4
% Friability	0.5-0.66
Drug content (%)	95.09 - 101.14

7.2.1 *In-vitro* dissolution studies

Table 21 Cumulative percent drug release of Sitagliptin 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	99.73±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			

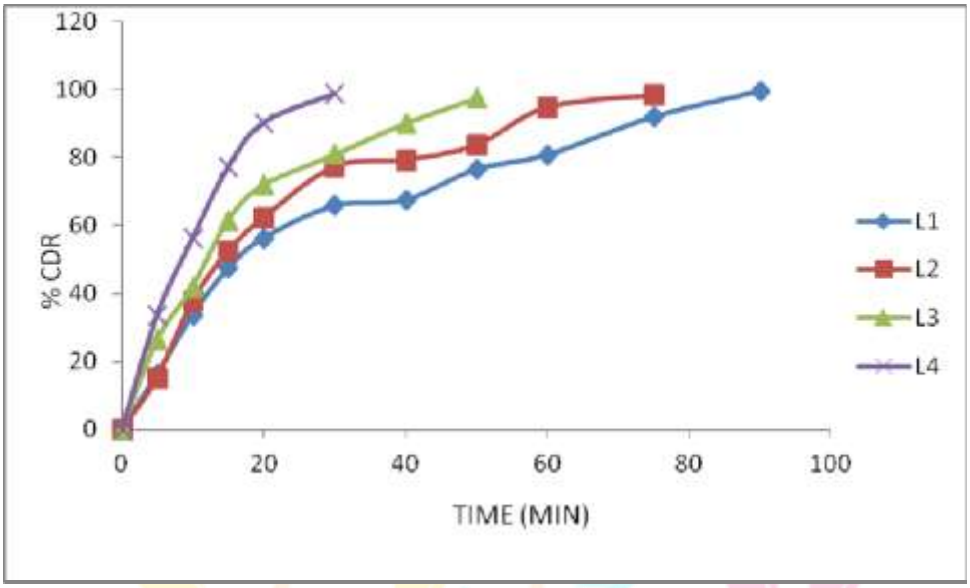


Fig 14. Cumulative percent drug release versus time plots of Sitagliptin tablets

Table No. 22: Evaluation parameters bilayer formulations.

Formulation code	Mean Hardness Kg/cm2	Thickness (mm)	Friability % w/w	Average Weight (mg)	Mean drug content %±SD	
					Sitagliptin	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

7.2 Evaluation parameter

Table No. 23: Evaluation parameters of SR 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 24 *In-vitro* drug release data of metformin SR tablets metformin

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	47.58	21.36
4	81.69	74.52	57.67	69.85	51.98	30.98	73.98	72.54	35.78
6	99.85	86.55	69.59	88.36	72.19	49.12	90.014	88.40	52.01
8		98.89	85.85	99.94	86.63	64.25	100.1	99.80	88.14
10			97.5		99.95	87.42			98.94
12						99.84			

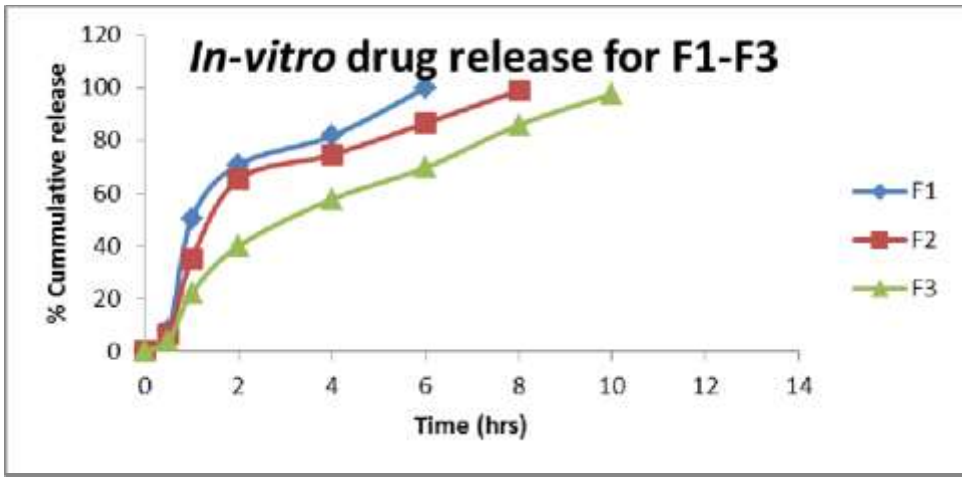


Fig 15 *In-vitro* drug release profile of bilayer tablets of batches F1 to F3.

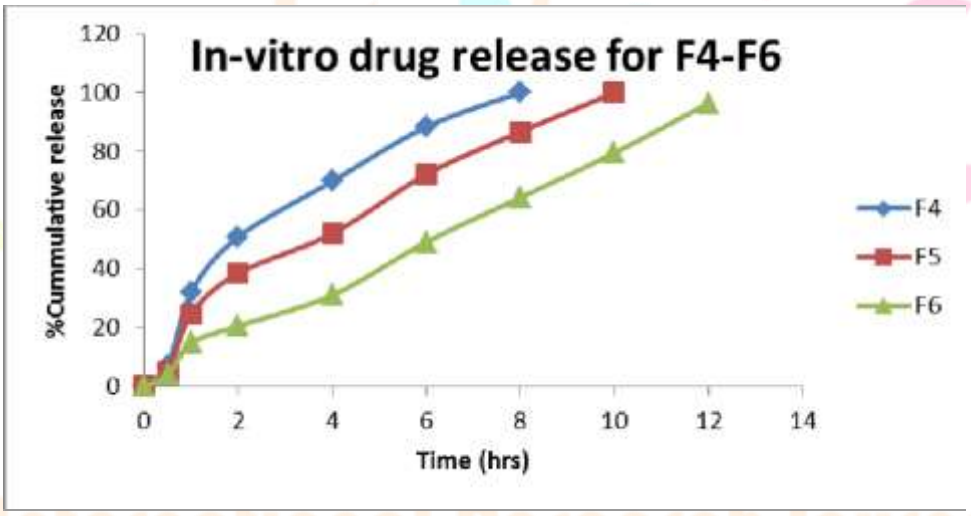


Fig 16 *In-vitro* drug release profile of bilayer tablets of batches F4 to F6.

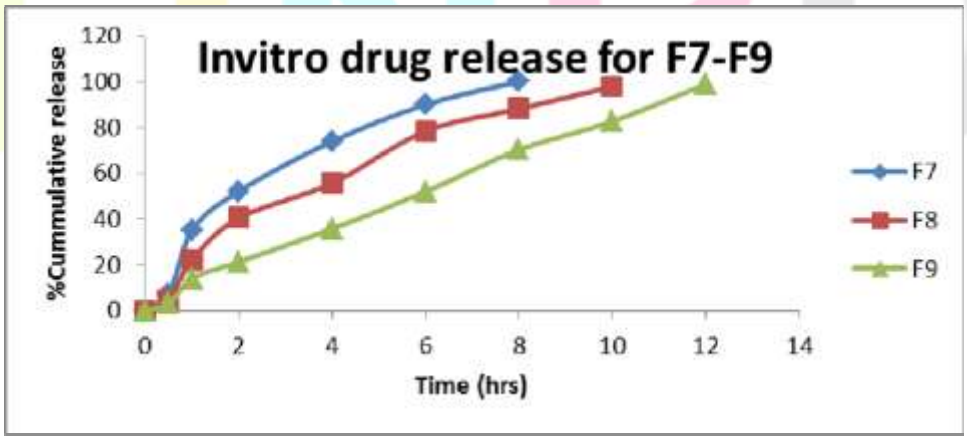


Fig 17 *In-vitro* drug release profile of Bilayer tablets of batches F7 to F9

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 a s optimized formulation.

7.2.2 Stability studies of the optimized formulation:

Table 27: Stability Studies for Formulation F6

Time	Evaluation parameters			
	Colour	Hardness (kg/cm2)	Drug content Uniformity	% CDR
0 Month	White	6.3	99.22	97.96
1 Month	White	6.3	98.06	96.21
2 Month	White	6.2	99.51	95.64
3 Month	White	6.2	98.97	97.42

Summary

Summary and Conclusion

Metformin completely absorbed in gastric pH but rapidly hydrolyzed in intestinal mucosa. Thus reducing its oral bioavailability. Therefore an attempt was made to increase oral bioavailability of Metformin by retaining the dosage form in stomach for longer period of time. These tablets mainly prepared for reduction of lag time and may also increase the bioavailability of the drugs by utilizing the drug to full extent avoiding frequency of dosing and subsequently degradation of drug in intestine.

For the formulation of bilayered tablets different concentrations of crospovidone, was used as disintegrating agents, HPMC K100, gattigum and sodium alginate were used as sustained release polymer. Other excipients used are, MCC, Mg stearate, (lubricating agent) aerosol, mannitol. Fourier transform Infrared spectroscopy confirmed the absence of any drug/polymers/excipients interactions.

The prepared bilayered tablets were evaluated for hardness, weight variation, thickness, friability, drug content uniformity, and *in-vitro* dissolution studies.

It was observed that Formulations F6 gave maximum drug release upto 99.84% within 12 hrs for SR and L4 gave maximum drug release upto 99.85% within 30 minutes for IR. F6 was subjected for drug release kinetics studies viz. Zero order, First order, Higuchi matrix, Peppas model equations and it followed zero order release kinetics.

Based on various evaluation parameters formulation F6 was selected as optimized formulation for (SR) and L4 for (IR) was further subjected for stability study. The formulation showed good stability and values were within limit.

Thus conclusion can be made that stable dosage form can be developed for metformin for the sustained release and Sitagliptin for immediate release by bilayered tablets.

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