FOMULATION AND EVALUATION OF METFORMIN AND VILDAGLIPTIN BILAYER TABLETS

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ABSTRACT

The objective of present research work is formulation and evaluation of metformin and vildagliptin bilayer tablets. The bulk density and the tapped density for all the formulations varied from 0.352 to 0.374gm/cm^3 and 0.452 to 0.485gm/cm^3 respectively. The values obtained lies within the acceptable range. The result of Hausner's ratio of all formulations ranges from 1.238 to 1.321. The results of the Compressibility index of all the formulations ranges from 19.248% to 24.301%. The thickness depends on the size of the punches (8 mm) and the weight of one tablet (350mg). The value of thickness ranges between 2.3±0.2 to 2.5±0.1mm. The friability for all the formulations was below 1% indicating that the friability was within the prescribed limits. The friability value ranges from 0.622±0.035 to 0.775±0.042. The hardness value ranges from 3.4±0.1 to 3.6±0.1kg/cm^2. The values of tablets average weight ranging from 348±4 to 355±4mg. All the tablets passed weight variation test as the % weight variation was within the USP Pharmacopoeia's limits of ±5% of the weight. The % drug content of all the formulated tablets were found within the limit. % drug content value of vildagliptin was within 98.85±0.45% to 99.78±0.32%. The disintegration time of instant layer of vildagliptin IF1, IF2, IF3, IF4, IF5, IF6, IF6, IF7, IF8 and IF9 was found to be 120 ± 5, 110 ± 4, 98 ± 3, 125 ± 4, 115 ± 4, 99 ± 5, 110 ± 6, 83 ± 4 and 98 ± 6 respectively. The minimum disintegration time was found in formulation IF7 (83 ± 4), select as optimized formulation. Eight different formulations (F1, F2, F3, F4, F5, F6, F7, & F8) were prepared by direct compression. Formulation F7 showed release from formulation 33.21, 40.23, 60.32, 71.12, 78.89, 82.23, 89.98, 95.59 and 99.12% after 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0 and 12 Hrs. Optimized formulation IF-7 of Instant release layer and optimized formulation of F-7 for control release used for formulation of Bi-layer tablet. The Instant layer of vildagliptin release approx 98.85 percent drug within 1.5 Hrs. and controllayer metformin shows release up to 12 Hours Approx 99.85 percent of drug release in 12 hours.

KEYWORDS: *Drug, Evaluation, Hardness, Thickness, Excipients.*

INTRODUCTION

A tablet s a mixture of active substance and excipients usually in powder form pressed or compacted into a solid. The excipients includes binders, glidents (flow- aids), and lubricants to ensure efficient tableting, disintigrants to ensure that the tablet breaks up in the digestive tract; sweeteners or flavours to mask the taste of the bad tasting active ingredients and pigments to make uncoated tablets visually attractive. A coating may be applied to hide the taste of tablets components, to make the tablet smoother and easier to swallow and to make it more resistant to environment extending its self life. The compressed tablet s most popular dosage form in use today. About two third prescriptions are dispensed as sold dosage forms and half of these are compressed tablets.

Advantages of tablet dosage form

- Tablet is intact dosage form and offers the best capabilities of all oral dosageforms for accuracy in size and content of the lowest variability.
- tablet dosage form which is the lowest cost of manufacture (if it is calculatedper dose).
- Tablets is an oral dosage form of the lightest, most compact, easiest and mostinexpensive way to packed and shipped.
- The product identification on the tablets the most easy and inexpensive,requiring no additional work steps when using the printer surface that monogram or arising accessories.
- Tablet can be used as a product of specific release profiles, such as therelease in the intestine or slow release products.
- Tablets is an oral dosage form of the most easy to be produced in bulk (largescale).

Disadvantages of tablet dosage form

- Some drugs cannot be compressed into solid and compact, depending on its amorphous state, flocculation, or low density.
- Drugs moistened difficult, slow dissolves, moderate or high dose, high optimum absorption via the gastrointestinal tract or any combination of the properties above, it would be difficult or impossible to be formulated and fabricated in the form of tablets that produce sufficient drug bioavaibility.
- Medicine that tastes bitter, a drug with the smell was terrible and cannot be eliminated, or drugs that are sensitive to oxygen or air humidity needs to encapsulation or compression cloaking before (if possible) or require coating first. In this case, the capsule is a cheaper way out.

Bilayer tablet is new era for successful development of controlled release formulation along with various features to provide successful drug delivery system. Bilayer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles. The manufacture of bi-layer tablets, produced by sequential compaction of loose powder layers has become of increased interest within the pharmaceutical industry due to the tailored release profiles of active ingredients that may be obtained. Bilayer 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 loading dose and second layer is maintenance dose. In case of bilayered tablets drug release can be rendered almost unidirectional if drug can be incorporated in the upper non adhesive layer its delivery occurs into the whole oral cavity. The immediate release layer of bilayer tablet has worked as the loading dose and the sustained release layer has maintained therapeutic plasma drug concentration for prolonged time. This article explains why development and production of quality bi-layer tablets needs to be carried out on purpose-built tablet presses to overcome common bilayer problems, such as layer-separation, insufficient hardness, inaccurate individual layer weight control, cross-contamination between the layers, reduced yield, etc. Using a modified tablet press may therefore not be the best approach in producing a quality bilayer tablet under GMP-conditions, especially when high production output is required.

Ideal characteristics of bilayer tablet:

- A bi-layer tablet should have elegant product identity while free of defects like chips, cracks, discoloration and contamination.
- It should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
- It should have the chemical and physical stability to maintain its physical attributes over time. The bi-layer tablet must be able to release the medicinal agents in apredictable and reproducible manner.
- It must have a chemical stability shelf-life, so asnot to follow alteration of the medicinal agents.

Objectives behind designing bilayer tablet:

- To control the delivery rate of either single or two different active pharmaceutical ingredient.
- To separate incompatible active pharmaceutical ingredient (APIs) from each other, to control the release of API from one layer by utilizing the functional property of the other layer (such as, osmotic property).
- To modify 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 modified release.
- To administer fixed dose combinations of different APIs, prolong the drug product life cycle, fabricate novel drug delivery systems such as chewing device buccal/ mucoadhesive delivery systemsand floating tablets for gastro-retentive drug delivery.

Advantages of the bilayer tablet:

• It is the dosage form and offers the greatest capabilities of all oral dosage form forthe greatest dose precision and the least content variability.
• Cost is lower compared to all other oral dosage form.
• Lighter and compact.
• Easiest and cheapest to pack and strip.
• Easy to swallow with least tendency for hangup.
• Suitable for large scale production.

MATERIALS AND METHODS

Materials used for formulation

Table 1: Materials used for formulation development of Bilayer tablets

Sr. No.	Chemicals	Supplier
1.	Metformin and vildagliptin	(Gift sample from Bioplus Life Science, Bangalore)
2.	PVP (Polyvinylpyrrolidone)	S. D. Fine Chem. Ltd., Mumbai
3.	Citric acid	Qualigens fine chemicals, Mumbai
4.	HPMC (Hydroxypropyl Methyl Cellulose)	Ozone International, Mumbai

5.	Sodium bicarbonate	Chem pure Pvt. Ltd
6.	Magnesium stearate	Jiangsu Huaxi International

Instruments Used in Investigation

Table 2: Instruments used for the preparation and evaluation of Bilayertablets

Sr. No.	Instrument / Apparatus	Supplier
1.	UV -Visible Spectrophotometer	Labindia 3000+ Mumbai
2.	Fourier Transform Infra-Red Spectroscopy	Brucker, Alpha, Germany
3.	pH Meter	Electronic India
4.	Electronic Balance	Winsor, India
5.	Melting Point Apparatus	Chemline CL-725
6.	Hot Air Oven	Electronic India

METHODS

Formulation development

Preparation of instant layer of Vildagliptin (Phase-1)

Fast dissolving (Instant Layer) tablets of vildagliptin were prepared by direct compression method after incorporating different super disintegrants such as, crosscarmellose sodium (Ac-Di-Sol), crospovidone and sodium starch glycolate in different concentrations. The ingredients given below were weighed and mixed in geometric progression in a dry and clean mortar. Then the ingredients were passed through mesh #60. Magnesium stearate as lubricant and talc as glidant were added in a final step and mixed, this blend was subjected to analysis of pre-compression parameters which included Angle of repose, Bulk density, Tap density, Carr's index and Hausner's ratio. The Blend was compressed on 8 mm (diameter) fat punches on a 'Rimek mini press16 station rotary compression machine. Nine different formulations of vildagliptin were prepared and each formulation contained one of the three disintegrant in different concentration[41]. Each tablets weighing 350mg, were obtained. Composition of tablets is mentioned in Table 3

Table 3: Composition of Vildagliptin fast dissolving tablets

Ingredients (mg)	Formulation code								
	IF1	IF 2	IF 3	IF 4	IF 5	IF 6	IF 7	IF 8	IF 9
Vildagliptin	50	50	50	50	50	50	50	50	50
Sodium Starch glycolate	10	15	20	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	10	15	20	-	-	-
Crospovidone	-	-	-	-	-	-	10	15	20
Microcrystalline Cellulose	25	20	15	25	20	15	25	20	15
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	10	10	10	10	10	10	10	10	10
Total weight	100	100	100	100	100	100	100	100	100

Evaluation of Precompression Parameter

Table 4: Results of pre-compressional parameters of vildagliptin

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
IF1	0.365	0.452	19.248	1.238
IF2	0.358	0.465	23.011	1.299
IF3	0.362	0.472	23.305	1.304
IF4	0.374	0.482	22.407	1.289
IF5	0.369	0.476	22.479	1.290
IF6	0.347	0.456	23.904	1.314
IF7	0.356	0.462	22.944	1.298
IF8	0.374	0.485	22.887	1.297
IF9	0.352	0.465	24.301	1.321

Evaluation of post compression Parameter

Table 5: Results of post-compression parameters of all formulations

F. Code	Hardness test (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)
IF1	3.4±0.1	0.658±0.014	355±4	2.4±0.2	98.85±0.45
IF2	3.5±0.2	0.652±0.021	352±6	2.3±0.2	98.87±0.65
IF3	3.6±0.1	0.612±0.032	354±5	2.3±0.1	99.12±0.25
IF4	3.5±0.1	0.715±0.025	348±4	2.4±0.3	99.45±0.36
IF5	3.5±0.1	0.689±0.015	352±2	2.5±0.1	99.65±0.41
IF6	3.5±0.2	0.775±0.042	349±3	2.4±0.2	99.78±0.32
IF7	3.6±0.1	0.645±0.032	353±2	2.5±0.1	99.74±0.26
IF8	3.5±0.2	0.658±0.022	354±1	2.4±0.3	99.18±0.41
IF9	3.5±0.1	0.622±0.035	352±2	2.5±0.1	99.25±0.33

Table 6: Results of Disintegration time of instant layer of vildagliptin

Formulation code	Disintegration time (sec.) (n=3) Mean ± SD
IF1	120 ± 5
IF2	110 ± 4
IF3	98 ± 3
IF4	125 ± 4
IF5	115 ± 4
IF6	99 ± 5
IF7	110 ± 6
IF8	83 ± 4
IF9	98 ± 6

Method for Preparation of Metformin Gastroretentive tablets

Direct compression was followed to manufacture the floating tablets of Metformin. Eight different formulations (F1, F2, F3, F4, F5, F6, F7, & F8) were prepared by direct compression. All the polymers selected, drug and excipients were passed through sieve no. 40 before using into formulation.

Optimization of gastro retentive tablets of Metformin

Table 7: various formulations of Metformin gastro retentive tablets

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Metformin	500	500	500	500	500	500	500	500
HPMC K4	90	120	-	-	-	-	30	40
HPMC K15	-	-	90	120	-	-	30	40
Xanthan gum	-	-	-	-	90	120	30	40
PVP K30	15	15	15	15	15	15	15	15
Talc	5	5	5	5	5	5	5	5
Magnesium Stearate	10	10	10	10	10	10	10	10
Lactose	80	50	80	50	80	50	80	50
Total Weight	700	700	700	700	700	700	700	700

Table 8: Result of pre-compression properties of Metformin tablets

F. Code	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
F1	0.452	0.562	19.573	1.243
F2	0.465	0.574	18.990	1.234
F3	0.454	0.565	19.646	1.244
F4	0.474	0.579	18.135	1.222
F5	0.465	0.572	18.706	1.230
F6	0.472	0.582	18.900	1.233
F7	0.458	0.571	19.790	1.247

F8	0.465	0.577	19.411	1.241

Evaluation of tablets:

All the tablets were evaluated for following different parameters which includes;

Table 9: Results of post compression properties of Metformin tablets

F. code	Thickness (mm)	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)
F1	3.5	5.2	498	0.858	98.89
F2	3.4	5.3	495	0.658	99.85
F3	3.5	5.1	498	0.489	98.89
F4	3.6	5.4	502	0.558	99.56
F5	5.5	5.3	505	0.658	99.28
F6	3.4	5.4	504	0.856	99.56
F7	3.4	5.2	503	0.658	99.23
F8	3.4	5.1	502	0.758	99.12

Dissolution rate studies: *In vitro* drug release of the sample was carried out using USP- type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was placed into the dissolution flask maintaining the temperature of 37±0.50ºc and rpm of 75. One Metformin tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 10 hours. Sample measuring 5 ml were withdrawn after every1 hour up to 10 hours using 10ml pipette. The fresh dissolution medium (37^0C) was replaced every time with the same quantity of the sample. From this take 0.5 ml and dilute up to 10 ml with 0.1 N HCl and take the absorbance at 233 nm using spectroscopy.

In vitro drug release study of Gastro retentive tablet

Table 10: *In-vitro* drug release study of tablets

Time	% Cumulative Drug Release							
(hr)	F1	F2	F3	F4	F5	F6	F7	F8
0.5	55.56	45.54	43.23	40.23	38.89	35.56	33.21	30.12
1	75.56	58.89	55.56	52.32	45.65	42.23	40.23	38.89
1.5	85.56	88.89	80.25	75.65	68.89	65.65	60.32	55.65

2	99.89	98.29	89.98	85.65	78.38	73.25	71.12	65.65
3	-	-	98.89	92.25	85.56	80.32	78.89	70.23
4	-	-	-	98.65	90.23	86.69	82.23	78.32
6	-	-	-	-	99.52	92.23	89.98	85.56
8	-	-	-	-	-	99.85	95.59	90.23
12	-	-	-	-	-	-	99.12	93.32

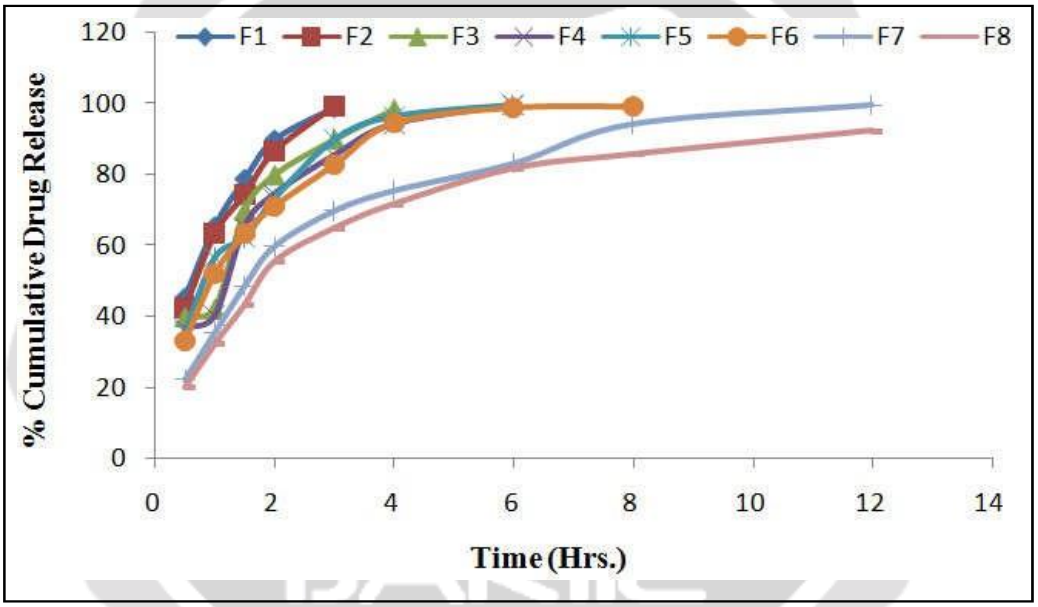

Figure 1: Graph of *in-vitro* drug release study of control layer

Formulation development of bilayer tablet

Optimized formulation IF-7 of Instant release layer and optimized formulation of F-7 for control release used for formulation of Bi-layer tablet.

Evaluation of bilayer tablets

All the tablets were evaluated for following different parameters which includes;

Table 11: Post-compression parameters of optimized formulation

Formulation	Hardness test (kg/cm^2)	Friability (%)	Weight variation	Thickness (mm)
1.	6.5	0.754	Passes	5.23

Table 12: Results of Drug content analysis

Formulation	Vildagliptin (% Label Claim)	Metformin (% Label Claim)
In-house Bilayer tablet	99.45	99.12

Table 13: Results of Dissolution rate studies of bilayer tablets

Time (Hour)	% Drug Release	
	Vildagliptin	Metformin
0.5	36.65	15.65
1	55.65	25.65
1.5	98.85	36.65
2	-	55.65
4	-	65.58
6	-	73.32
8	-	85.65
10	-	92.32
12	-	99.85

Graph of release of bilayer tablets

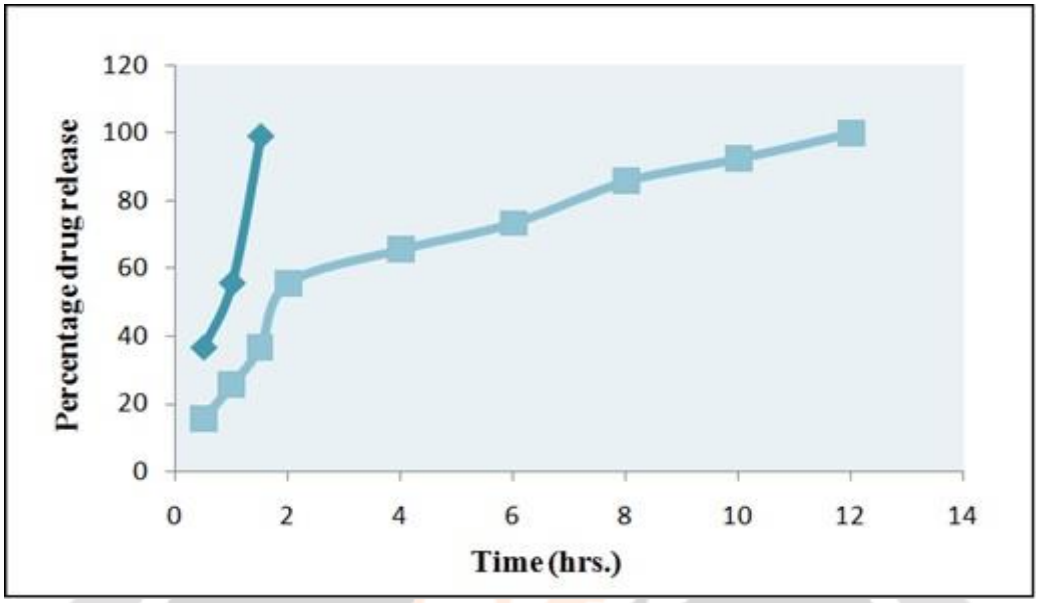

Figure 2: Graph of Release of Bilayer tablets

A dissolution study shows the release of vildagliptin and metformin. The Instant layer of vildagliptin release approx 98.85 percent drug within 1.5 Hrs. and controllayer metformin shows release up to 12 Hours Approx 99.85 percent of drug release in 12 hours.

SUMMARY AND CONCLUSION

Fast dissolving (Instant Layer) tablets of vildagliptin were prepared by direct compression method after incorporating different super disintegrants such as, crosscarmellose sodium (Ac-Di-Sol), crospovidone and sodium starch glycolate in different concentrations. The prepared tablets were evaluated for pre-compressionand post compression parameters. The loose bulk density (LBD) and Tapped bulk density (TBD) of the powders of Instant layer formulations were evaluated before the compression of powders in to tablets. The bulk density and the tapped density for all the formulations varied from 0.352 to 0.374gm/cm^3 and 0.452 to 0.485gm/cm^3 respectively. The values obtained lies within the acceptable range. The difference exists betweenthe bulk density and tapped density found to be very few. This result helps in calculating the % compressibility of the powder. The result of Hausner's ratio of all formulations ranges from 1.238 to 1.321. Results of Hausner's ratio of all formulations which indicates that the flow ability of all the formulation. The results of the Compressibility index of all the formulations ranges from 19.248% to 24.301%. Results clearly showed that the flow ability of all the formulations was good and also the powder had good compressibility.

The thickness of the tablets was reported in the micrometer (mm).The thickness of tablet indicates that, die fill was uniform. The thickness depends on the size of the punches (8 mm) and the weight of one tablet (350mg). The value of thickness ranges between 2.3±0.2 to 2.5±0.1mm. Friability determines the strength of the tablets. The friability for all the formulations was below 1% indicating that the friability was within the prescribed limits. The results of friability test indicate that the tablet possesses good mechanical strength. The friability value ranges from 0.622±0.035 to 0.775±0.042. The mean hardness values were measured for all the formulation using Monsanto hardness tester. The hardness value ranges from 3.4±0.1 to 3.6±0.1kg/cm^2. Twenty tablets were randomly selected from each formulation and evaluated. The average weight of each formulation was recorded. The obtained data were almost uniform. The values of tablets average weight ranging from 348±4 to 355±4mg. All the tablets passed weight variation test as the % weight

variation was within the USP Pharmacopoeia's limits of ±5% of the weight. The % drug content of all the formulated tablets were found within the limit. % drug content value of vildagliptin was within 98.85±0.45% to 99.78±0.32%.The results within the range indicate uniform of mixing. The Table no 5.13 shows the % drug content in each formulation. The disintegration time of instant layer of vildagliptin IF1, IF2, IF3, IF4, IF5, IF6, IF6, IF7, IF8 and IF9 was found to be 120 ± 5, 110 ± 4, 98 ± 3, 125 ± 4, 115 ± 4, 99 ± 5, 110 ± 6, 83 ± 4 and 98 ± 6 respectively. The minimum disintegration time was found in formulation IF7 (83 ± 4), select as optimized formulation. Direct compression was followed to manufacture the floating tablets of metformin. Eight different formulations (F1, F2, F3, F4, F5, F6, F7, & F8) were prepared by direct compression. The control layer also evaluated for pre-compression and post- compression properties. In Vitro dissolution study was performed for optimization of control layer of metformin. Formulation F7 showed release from formulation 33.21, 40.23, 60.32, 71.12, 78.89, 82.23, 89.98, 95.59 and 99.12% after 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0 and 12 Hrs. Optimized formulation IF-7 of Instant release layer and optimized formulation of F-7 for control release used for formulation of Bi-layer tablet. Further bilayer tablets were evaluated for general appearance, thickness and diameter, hardness, friability, uniformity of weight, drug content and dissolution rate studies. A dissolution study shows the release of Vildagliptin and Metformin. The Instant layer of vildagliptin release approx 98.85 percent drug within 1.5 Hrs. and control layer metformin shows release up to 12 Hours Approx 99.85 percent of drug release in 12 hours. A study involving preparation and evaluation of instant layer of vildagliptin, matrix layer of metformin as well as bilayer tablets of both the drug were made. Physicochemical parameters of instant layer, matrix layer and bilayer tablets were performed.

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