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Research Article

FORMULATION AND EVALUATION OF MODIFIED RELEASE TRI-LAYERED TABLET USING A FIXED DOSE COMBINATION OF METFORMIN HCL AND VILDAGLIPTIN

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ABSTRACT

The aim of present investigation is to formulate the tri-layered tablet of an Anti-Hyperglycaemic drug comprising Metformin HCl as sustained release layer and Vildagliptin as an immediate release layer in a fixed dose combination along with a fast dissolving intermediate layer or barrier layer in between the two layers just like a sandwich. Vildagliptin is well-known for its instability in presence of Metformin HCl. Hence, Vildagliptin degrades in formulation of single unit dosage form. The in vitro release layer of Metformin HCl was prepared using combination of sustained release polymer HPMC K100M & HPMC K4M and binder used in formulation is Povidone K90 which was prolonged up to 10 - 12 hours. The In-vitro release of Vildagliptin is rapid from tablet and showed highest drug release of more than 90% in 30 Minutes. Final formulation was tested for accelerated stability study. Intermediate barrier layer was optimised using Lactose Monohydrate and Microcrystalline cellulose as a diluents and Croscarmellose sodium as a disintegrant. The disintegration time of tablet into two halves for final formulation was 51 seconds. Combination of lactose monohydrate and microcrystalline cellulose as well as thickness of the intermediate layer was found important to achieve quick disintegration.

KEYWORDS: Metformin, Vildagliptin, Tri-Layer, Barrier Layer, Incompatibility, FDC, Modified Release

INTRODUCTION

Tablet dosage form is the most conventional dosage form. Multi-layered tablet is the novel technology for the development of controlled release formulation. Today, the use of multi-layered tablets has been increased as it provides various key advantages and overcoming problems associated with conventional dosage form. Multi-layered tablet is more suitable for gradual release of two active ingredients in combination. Multi-layered tablet technology helps in separating the two incompatible substances using a separating layer or an inert layer between layers of two different drugs[1]. Metformin Hydrochloride is a Biguanide anti-hyperglycaemic agent used in the treatment of non-insulin dependent diabetes mellitus (NIDDM). Metformin is the only anti-diabetic drug that has been conclusively shown to prevent the cardiovascular complications of diabetes. Metformin has been used in humans for nearly fifty years[2]. It is indicated for type 2 diabetes mellitus. Type 2 diabetes mellitus used to be known as 'non-insulin-dependent diabetes mellitus (NIDDM)' or 'maturity onset diabetes'. In spite of its favourable clinical response and lack of significant draw backs, chronic therapy with Metformin hydrochloride is associated with certain problems. The marketed immediate release products need to be administered 2-3 times daily. The current metformin therapy is associated with high incident of GI side effects seen in about 30% of patients[3]. Moreover inherent compressibility, very high solubility (i.e. >300 mg/ml at 25° C), initial burst effect of drug from immediate release tablets and less bioavailability (60%) due to saturable absorption process can lead to difficulty in providing an optimum therapeutic effect from a single formulation[4]. Vildagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor class of drugs[5]. It inhibits the inactivation of GLP-1 (Glucagon-like peptide-1) by DPP-4 (Dipeptidyl peptidase-4), allowing GLP-1 to potentiate the secretion of insulin in the beta cells[6]. Vildagliptin makes pancreas to produce insulin which helps to improve the glycaemic control in body and Metformin makes a better use of insulin in body. Both drugs do not alter pharmacokinetics of one another. A broad and complementary spectrum of anti-diabetic actions is available when using the fixed dose combination of a Vildagliptin (DPP-4 Inhibitor) with Metformin[7]. Such fixed dose combination does not increase the risk of hypoglycaemia, does not promote weight gain, and does not cause adverse effects caused by various other oral anti-diabetic combinations[8]. Both the drugs have a complimentary and possibly synergistic effect on glycaemic control and reduced glycosylated haemoglobin and hence an attempt was made to formulate multilayer tablet of these two drugs to improve patient compliance, bioavailability, reduce dosing frequency and reduce GI (Gastrointestinal) side effect of Metformin. But, the challenge is to formulate Vildagliptin in a single dosage form. Vildagliptin is very well-known for its instability as it is sensitive and degrades in presence of Metformin Hydrochloride shows degradation upon stability study on accelerated condition[9]. For such combination therapy with chemical incompatibility, multi-layered dosage form is advantageous in preparing a stable formulation and extend the product shelf life. The current research is an attempt to design sustained release layer of Metformin and an immediate release layer of Vildagliptin in a single tablet formulation. Bilayer tablets have only one inter phase between two drug layers so incompatibility between two drugs may occur at this point. A feasibility trail of Bilayered tablet has been prepared and stability study has been evaluated. Trilayer tablets can solve this kind of interphase incompatibility problem between two drugs[10]. Introduction of an intermediate or immediate release layer between drug layers will result into no direct contact of the drugs and will help us to achieve a stable formulation. Moreover,

Metformin Hydrochloride and Vildagliptin is orally administered separately, two times a day. Patient compliance is more problematic with a regimen that requires administration of two separate dosage form[11]. A need of once a day formulation is required to meet patient compliance. Hence, the sustained release formulation is required for combination therapy of Metformin Hydrochloride and Vildagliptin. A multi-layered tablet dosage form using various grades of hydrophilic and lipophilic polymers can be used to prepare a sustained release dosage form. In current research work, Metformin Hydrochloride part was optimized using different hydrophilic polymer whereas Vildagliptin part was optimized and stabilize in accelerated condition and then both the parts were combine with an intermediate layer. Intermediate layer was acted as a barrier layer which has prevented direct contact between two drugs and hence overcome the chemical incompatibility. Such formulation can offer longer transit time in the stomach and can act as an in vivo reservoir that releases drug at controlled rate continuously over a prolonged time for absorption in the stomach and the intestine[12].

MATERIALS AND METHOD

Metformin HCl was received as a gift sample from Granules India Ltd., India. Vildagliptin was received as a gift sample from Lee Pharma Ltd., India. Microcrystalline Cellulose (Avicel PH 102), FMC Biopolymer, India. Lactose Monohydrate (Pharmatose 200M), DFE Pharma, India. Hypromellose K4M (Methocel K4M), Hypromellose K15M (Methocel K15M) and Hypromellose K100M (Methocel K100M), Dow Polymer, India. Povidone (Plasdone K-30& Plasdone K-90), Ashland Inc, India, Croscarmellose Sodium (Ac-Di-Sol), FMC Biopolymer, India, Colloidal Silicon Dioxide (Aerosil 200), Evonik, India. Magnesium Stearate (Ligamed MF-2-V), Peter Greven, India. FD&C Blue #1/Brilliant Blue FCF Aluminum Lake, Roha, India. All other excipients and chemicals used were of pharmaceuticals grade and analytical grade respectively.

Preformulation study of Drugs

Preformulation studies were carried out to investigate physicochemical properties of drug substance alone and in combination with other drug as well as excipients. Following studies were performed to characterize drugs and their interaction with and excipients.

Identification of drugs by Melting Point

Melting point was determined by taking small amount of pure drug in a different capillary tube closed at one end. The capillary tube was placed in an electrically operated digital melting point apparatus and the temperature at which the drug melts was recorded.

Identification of Drugs and Compatibility Study by HPLC method

Identification of pure drugs, their mixture with excipients as well as mixture of both drugs was taken and spectrum was recorded. The retention time of the principal peak obtained in sample solution be concordant with that of the standard solution, as obtained in the assay. Samples were prepared by mixing individual drugs, both drugs together and drugs along with excipients uniformly. Scanned graph of pure drug was compared with standard range.

Quantification of Drugs and Compatibility Study by Assay Method

Assay of pure drugs, their mixture with excipients as well as mixture of both drugs was taken and wavelength was recorded. Samples were prepared by mixing individual drugs, both drugs together and drugs along with excipients uniformly. Samples were scanned in the range of 200 to 400 nm for the determination of wavelength having maximum absorbance using a UV-visible Spectrophotometer (Shimadzu). Scanned curve of pure drug was compared with standard range.

PREPARATION OF TRI-LAYER TABLETS

Preparation of Sustain release Metformin HCl Layer

Different batches of Sustain release layer of Metformin HCl (Trial No.1 to 22) were prepared by wet granulation technique using Povidone K90 as a binder as per the composition given in Table 1, Table 2 & Table 3. Metformin HCl was milled through 0.5mm Multi-mill screen. Milled Metformin Hydrochloride, Microcrystalline cellulose (Avicel PH 101) and Methocel K100M was co-sifted using 24# sieve. Sifted materials were loaded in the Fluid Bed Processor (FBP) GPCG 1.1. Granulation is performed using PovidoneK30 solution as a binder. Granules were dried in Fluid Bed Dried and LOD was kept NMT 2.5%. Dried granules were shifted from 20# sieve and loaded in double cone blender. Magnesium stearate sifted through 60# was added in above blender & lubricated for 5 Minutes.

Preparation of immediate release Vildagliptin Layer

Different batches of immediate release layer of Vildagliptin (Formulation No. 23 to 33) were prepared by wet granulation technique using Hydroxy Propyl Cellulose as a binder and Sodium Starch Glycolate as a Disintegrant as per the composition given in the Table 4, Table 5 & Table 6. Vildagliptin, Microcrystalline cellulose (Avicel PH 101) and Lactose Anhydrous was co-sifted using 24# sieve. Sifted material was loaded in the Rapid Mixer Granulator (RMG) and dry mixing was performed for 10 Minutes at Impeller – Fast and Chopper – Off. Granulation is performed using Hydroxy Propyl Cellulose solution. Granules were dried in Fluid Bed Dried and LOD was kept NMT 2.5%. Dried granules were shifted from 20# sieve. Extra granular Sodium Starch Glycolate and Aerosil 200 were sifted through 20# and blended with dried granules for 10 Minutes. Magnesium stearate was added in above step and lubricated for 5 Minutes.

Preparation of Immediate release Intermediate layer / Barrier Layer

Different batches of immediate release intermediate layer (Formulation No.34 to 36) were prepared by direct compression technique as per the composition given in the Table 7.

Microcrystalline cellulose, Lactose Monohydrate, Povidone K30 and Croscarmellose Sodium were co-sifted using 40# sieve. Co-sifted material of above step is geometrically mixed with Brilliant blue FCF aluminium lake (E133) manually and sifted through 40# and loaded in above blender and blending was performed for 15 Minutes at 10 rpm. Sift Magnesium Stearate through 60# and add to above step. Blending was performed for 5 Minutes at 10 rpm. Lubricated blend of Metformin HCl Part, Intermediate layer and Vildagliptin part were filled in the die cavity and compressed into Tablet using Karnavati 18 station Compression machine using 22.5 X 10.4 mm, Oblong, Standard Concave, Plain punches.

Evaluation of the Powder Blend and Tablet

Before compression the lubricated blends were evaluated for different parameters like bulk density, tapped density, Carr's index and Hausner's ratio to determine the flow behaviour. Prepared tablets of both layers were evaluated for physical parameters like, hardness, thickness, weight variation and friability. For hardness testing, Electrolab hardness tester and for friability, Roche friabilator, Electrolab, were used. Weight variation was performed as per the official method. Digital Vernier calliper was used to measure thickness and Electrolab disintegration test apparatus was used to determine disintegration time for Metformin HCl layer.

Drug Content Estimation

Ten tablets were selected randomly; average weight was calculated and finely powdered. Accurately weighed amount was taken from the crushed blend equal to tablet weight. The drug content was estimated after suitable dilution at λmax 210 nm of Vildagliptin and at λmax 218 nm of Metformin HCl.

Determination of Drug Release Kinetics

To understand the rate and mechanism of drug release from the prepared formulation of Metformin Sustained Release Layer, the dissolution data was fitted to Zero order, First order, Higuchi, Hixon-Crowell and Krosmeyer Peppas equations. Regression coefficient values were calculated and used to find the fitness of the data.

Stability Study

Short term stability study was carried out for optimized trilayer tablets of batch No. 36. The study was carried out according to ICH guidelines by storing the samples at 40°C ±2°C and 75% ± 5% RH for 3 month. The tablets were evaluated for hardness, drug content, and dissolution study and compared with tablets which were evaluated immediately after manufacturing.

RESULTS AND DISCUSSION

Identification of Drugs by Melting Point

Melting point of Metformin HCl and Vildagliptin was found to be 223°C – 226°C and 148°C - 150°C respectively. Both values were same as reported in literature.

Identification of Drugs and Compatibility Study by HPLC Method

The HPLC chromatogram of both drugs showed peaks corresponding with standard solution as shown in Figure 1, Figure 2, Figure 3 and Figure 4. The compatibility study data of the powdered drugs and their mixture with excipients showed no interaction between drugs-excipients as well as mixture of both drugs showed clear interaction between both drugs as shown in Table 8 and Table 9. Hence, it was concluded that, the studied excipients and drugs were compatible whereas drugs combination is not compatible.

Evaluation of Powder Blends

Powder and flow characteristics of the blend can affect the formulation of tablets. The results shown in Table 10 and Table 11 indicated that, the all blends possessed good flow properties.

Evaluation of Tablets

The prepared tablets were characterized for different parameters such as hardness, friability, thickness, diameter, weight variation and drug content, which are summarized in Table 12. For all formulations hardness, thickness and average weight of tablets were found within proper range as mentioned in table. Friability was found to be less than 1.0%. The percentage drug content of the prepared tablets was in the range of 98% to 100%. The percentage drug content of the tablets containing Vildagliptin layer was in the range of 97% to 100%. Intermediate layer plays an important role into disintegration of the two layers. Tablet disintegrates into two halves. Each halves then acts as an individual tablets or units. Vildagliptin layer disintegrate and get absorbed in the stomach immediately while Metformin layer release drugs for 12 hrs. The thickness of the inert intermediate layer and combination of two diluents i.e. microcrystalline cellulose and lactose monohydrate and different concentration of disintegrant has a significant impact on the disintegration time into two halves as showed in Table 13. The disintegration time into two halves reduced to 51 seconds of optimized formulation. All the trails were evaluated in trilayer formulation keeping other two compositions constant.

In vitro Drug Release Study

In vitro drug release studies were carried out as mentioned in methodology for all formulations. In vitro drug release profiles for Metformin HCl and Vildagliptin tablets are showed in Table 14 & Table 15 respectively & Figure 5 and Figure 6 respectively. Dissolution of Formulation No. 3 & 11 containing Metformin HCl has 52% & 46% respectively at 4 hrs. Rest all formulation showed out of the range of 45% - 65%. Both these trails have HPMC as a sustained release polymer. Hence, HPMC is selected as a sustained release polymer. Dissolution of Formulation No. 24 has highest F2 value of 86 but fails to get good flow properties. Hence, in order to improve the flow, we have increased the binder concentration which will give good granules: fines ratio. Increasing Binder concentration (Trail No. 30) from 1.6%w/w to 3.0%w/w decreased F2 value from 86 to 56. To further improve the drug release we have optimized the disintegrant concentration and found drug release with F2 value of 89. Disintegrant concentration of 5.5%w/w (Formulation No. 32) is sufficient to get required drug release with highest F2 values. Trilayer tablet formulation prepared using optimized layer of Metformin HCl and Vildagliptin, formulation no. 36 also showed identical release profile to that of individual layers and drug release was achieved for prolonged period of time.

Drug Release Kinetics

To determine the release model, which best describes the pattern of drug release, in vitro drug release data of Metformin sustained release layer from trilayer tablet was fitted to zero order, first order, Hixon-Crowell, Krosmeyer Peppas and Higuchi models. Regression coefficient values were found to be 0.9821, 0.812, 0.9504, 0.8716 and 0.9437 respectively as shown in Figure 7, Figure 8, Figure 9, Figure 10 and Figure 11. The Highest regression coefficient R2 value was obtained for Zero order model and was found to be 0.9821. Hence, Fickian diffusion was considered as predominant release mechanism for tablet. Zero-order release kinetics systems are when the drug dissolution is constant over a period of time.

Design of Experiments

This method is used to explain the effect of one factor on the other factor. It is use to explain whether this effect is significant or not,

if significant how it influence the response. In this present work the effect of one factor on other two factors is explained for Metformin layer and Vildagliptin Layer. ANOVA for Response surface Model and Lack of fit test were evaluated. The response surface for Metformin and Vildagliptin dissolution are shown in Figure 12, Figure 13, Figure 14, Figure 15, Figure 16, Figure 17 and Figure 18.
The final equation of dissolution in terms of coded factors and actual factors are shown in

Final Equation of dissolution in Terms of Coded Factors for Metformin dissolution:
Dissolution at 4 Hrs = + 51.50 - 6.51 * A - 9.13* B - 3.41 * C
Dissolution at 8 Hrs = +87.63 - 3.43 * A - 13.37 * B - 1.89 * C - 2.37 * A * B - 0.87 * A * C
- 1.37 * B* C - 1.41 * A^2 - 3.53 * B^2 - 1.59 * C^2
Dissolution at 12 Hrs = + 99.23 - 1.44* A - 6.98 * B - 0.86 * C - 2.25 * A * B - 1.50 * A
* C - 1.25 * B * C - 1.00 * A^2 - 4.54 * B^2 - 1.00 * C^2
Where, A = Methocel K4M,
B = Methocel K100M, C = Povidone K90

Final Equation of dissolution in Terms of Actual Factors for Metformin dissolution:
Dissolution at 4Hrs = + 91.87008 - 0.13027 * Methocel K4M - 0.18266 * Methocel K100M
- 0.34148 * Povidone K90
Dissolution at 8Hrs = + 76.74052 + 0.18801 * Methocel K4M + 0.18943 * Methocel
K100M + 0.98137 * Povidone K90 - 9.50000E - 004 * Methocel
K4M * Methocel K100M - 1.75000E - 003 * Methocel K4M *

Povidone K90 - 2.75000E - 003 * Methocel K100M* Povidone K90
- 5.63756E - 004 * Methocel $K4M^2$ - 1.41228E - 003 * Methocel
$K100M^2$ - 0.015862 * Povidone $K90^2$

Dissolution at 12Hrs = + 66.85639 + 0.21602 * Methocel K4M + 0.39124 * Methocel
K100M + 0.93375 * Povidone K90 - 9.00000E - 004 * Methocel
K4M * Methocel K100M -3.00000E - 003 * Methocel K4M *

Povidone K90 - 2.50000E - 003 * Methocel K100M * Povidone K90
- 4.01624E - 004 * Methocel $K4M^2$ - 1.81584E - 003 * Methocel
$K100M^2$ - 0.010041 * Povidone $K90^2$

Final Equation of Flow properties (Carr's Index) for Metformin in Terms of Coded Factors:
Flow properties (Carr's Index) = + 9.72 + 0.097 * A- 0.27 * B- 6.95 * C + 0.38 * A * B+
0.13* A * C+ 1.63 * B * C + 0.21 * A^2+ 0.39 * B^2+ 3.04 * C^2

Final Equation of dissolution in Terms of Actual Factors for Metformin:
Flow properties (Carr's Index) = + 52.46473 - 0.036948 * Methocel K4M - 0.12519*
Methocel K100M - 2.39963 * Povidone K90 + 1.50000E -
004 * Methocel K4M * Methocel K100M + 2.50000E - 004

* Methocel K4M * Povidone K90 + 3.25000E - 003 *

Methocel K100M * Povidone K90 + 8.39466E - 005 *

Methocel $K4M^2$+ 1.54657E - 004* Methocel $K100M^2$ +

0.030383 * Povidone $K90^2$

Stability Study

Trilayer tablet was placed in the modified stability chamber for accelerated stability study at 40°C ± 2°C and 75± 5 % RH for 3 months. After a period of one month, the samples were observed for any change in physical appearance. Tablets were analysed for percentage drug content and in vitro drug release studies. It was observed that surface was devoid of any change in colour or appearance of any kind of odour in it. Results also revealed that, there were no significant changes in percentage drug content or In vitro drug release.

CONCLUSION

Drug-excipients compatibility study of Vildagliptin was performed and it was observed that there was no interaction between the drug and the excipients except with Metformin HCl and Povidone K90. All other excipients are found compatible with the drug. Bilayer tablet on stability study fails in 2 Month at 40°C/75%RH, hence there was a need of intermediate or barrier layer. Trilayer tablets with intermediate Layer / Barrier layer was formulated and optimised in current research. Optimised formulation was placed for accelerated stability study at 40°C ± 2°C and 75± 5 % RH for 3 months. Stability study results were found optimum and formulation was stable up to 3months. Another aspect of Tri-layer tablet is to get dual release profile so as to reduce dosing frequency and thereby increasing patient compliance. Dissolution for Metformin with HPMC as an extended-release polymer showed F2 value greater than 50. F2 values in ratio of HPMC K100M and HPMC K4M (of 1:0.75) is 83. Dissolution of Vildagliptin immediate release layer with ratio 1:0.5 of Microcrystalline cellulose to Lactose monohydrate has highest F2 value of 89. Disintegration time of intermediate or barrier layer also play an important role in drug dissolution. Disintegration of the tablet into two halves was found 51 seconds for the optimized tri-layered tablet. Drug dissolution of Tri-layer tablet with final formulation of Metformin and Vildagliptin found satisfactory. Trilayer tablet of Metformin HCl sustain release layer and Vildagliptin immediate release layer is useful to improve patient compliance towards the effective management of type 2 diabetes mellitus ('non-insulin-dependent diabetes mellitus (NIDDM)' or 'maturity onset diabetes') with improved dosing frequency, dual release profile and bioavailability.

Table 1 Formulation Details with different extended release Polymer

Ingredients	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Metformin Layer											
Metformin Hydrochloride	850	850	850	850	850	850	850	850	850	850	850
Avicel PH 101	12	12	12	12	12	12	12	12	12	12	12
Methocel K4M	210	---	---	---	---	---	---	---	---	---	---
Methocel K15M	---	210	---	---	---	---	---	---	---	---	---
Methocel K100M	---	---	210	---	---	---	---	---	---	---	---
Sodium Alginate	---	---	---	210	---	---	---	---	---	---	---
Ethyl Cellulose (Ethocel 45)	---	---	---	---	210	---	---	---	---	---	---
Xanthan Gum	---	---	---	---	---	210	---	---	---	---	---
Carbopol 71G	---	---	---	---	---	---	210	---	---	---	---
Carbopol 940	---	---	---	---	---	---	---	210	---	---	---
Carbopol 980	---	---	---	---	---	---	---	---	210	---	---
Polyox WSR 303	---	---	---	---	---	---	---	---	---	210	---
Povidone K90	22	22	22	22	22	22	22	22	22	22	22
Purified Water	q.s										
Methocel K100M	---	---	---	---	---	---	---	---	---	---	210
Magnesium Stearate	11	11	11	11	11	11	11	11	11	11	11
Total weight (mg)	**1105**	**1105**	**1105**	**1105**	**1105**	**1105**	**1105**	**1105**	**1105**	**1105**	**1105**
Avicel PH 102	55	55	55	55	55	55	55	55	55	55	55
Pharmatose 200M	28.3	28.3	28.3	28.3	28.3	28.3	28.3	28.3	28.3	28.3	28.3
Povidone K30	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Croscarmellose Sodium	7.50	7.50	7.50	7.50	7.50	7.50	7.50	7.50	7.50	7.50	7.50
Magnesium Stearate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Blue Color*	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20
Total weight (mg)	**95**	**95**	**95**	**95**	**95**	**95**	**95**	**95**	**95**	**95**	**95**
Vildagliptin	50	50	50	50	50	50	50	50	50	50	50
Avicel PH 101	45.5	45.5	45.5	45.5	45.5	45.5	45.5	45.5	45.5	45.5	45.5
Lactose Anhy. Supertab 21AN	44	44	44	44	44	44	44	44	44	44	44
Hydroxy Propyl Cellulose	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50
Isopropyl Alcohol	q.s										
Sodium Starch Glycolate	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Aerosil 200	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
Magnesium Stearate	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
Total weight (mg)	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**

* Brilliant blue FCF aluminum lake (E133)

Table 2 Formulation Trials with combination of rate controlling polymers

Ingredients	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Metformin HCl	850.00	850.00	850.00	850.00	850.00	850.00	850.00
Avicel PH 101	12.00	12.00	12.00	12.00	12.00	12.00	12.00
Methocel K15M	---	---	---	105.00	---	105.00	---
Methocel K100M	110.00	110.00	110.00	105.00	---	---	105.00
Cetostearyl Alcohol	100.00	---	---	---	---	---	---
Compritol 888	---	100.00	---	---	---	---	---
Stearic Acid	---	---	100.00	---	---	---	---
Povidone K90	22.00	22.00	22.00	22.00	22.00	22.00	22.00
Purified Water	q.s						
Methocel K15M	---	---	---	---	105.00	---	105.00
Methocel K100M	---	---	---	---	105.00	105.00	---
Magnesium Stearate	11.00	11.00	11.00	11.00	11.00	11.00	11.00
Total weight (mg)	**1105.0**	**1105.0**	**1105.0**	**1105.0**	**1105.0**	**1105.0**	**1105.0**
Intermediate Layer / Barrier Layer / Inactive Layer							
Avicel PH 102	55.00	55.00	55.00	55.00	55.00	55.00	55.00
Pharmatose 200M	28.30	28.30	28.30	28.30	28.30	28.30	28.30
Povidone K30	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Croscarmellose Sodium	7.50	7.50	7.50	7.50	7.50	7.50	7.50
Magnesium Stearate	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Brilliant blue FCF aluminum lake (E133)	0.20	0.20	0.20	0.20	0.20	0.20	0.20
Total weight (mg)	**95.00**	**95.00**	**95.00**	**95.00**	**95.00**	**95.00**	**95.00**
Vildagliptin Layer							
Vildagliptin	50.00	50.00	50.00	50.00	50.00	50.00	50.00
Avicel PH 101	45.50	45.50	45.50	45.50	45.50	45.50	45.50

Lactose Anhydrous (Supertab 21AN)	44.00	44.00	44.00	44.00	44.00	44.00	44.00
Hydroxy Propyl Cellulose	2.50	2.50	2.50	2.50	2.50	2.50	2.50
Isopropyl Alcohol	q.s						
Sodium Starch Glycolate	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Aerosil 200	1.50	1.50	1.50	1.50	1.50	1.50	1.50
Magnesium Stearate	1.50	1.50	1.50	1.50	1.50	1.50	1.50
Total weight (mg)	**150.00**	**150.00**	**150.00**	**150.00**	**150.00**	**150.00**	**150.00**

Table 3 Formulation Trials with different ratio of HPMC K100M and HPMC K15M

Ingredients	**19**	**20**	**21**	**22**
(HPMC K100M : K15M)	**1:1**	**1:0.75**	**1:0.50**	**1:0.25**
Metformin Hydrochloride	850.00	850.00	850.00	850.00
Avicel PH 101	12.00	12.00	12.00	12.00
Methocel K15M	105.00	120.00	140.00	168.00
Methocel K100M	105.00	90.00	70.00	42.00
Povidone K90	22.00	22.00	22.00	22.00
Purified Water	q.s			
Magnesium Stearate	11.00	11.00	11.00	11.00
Total weight (mg)	**1105.0**	**1105.0**	**1105.0**	**1105.0**
Intermediate Layer / Barrier Layer / Inactive Layer				
Avicel PH 102	55.00	55.00	55.00	55.00
Pharmatose 200M	28.30	28.30	28.30	28.30
Povidone K30	3.00	3.00	3.00	3.00
Croscarmellose Sodium	7.50	7.50	7.50	7.50
Magnesium Stearate	1.00	1.00	1.00	1.00
Brilliant blue FCF aluminum lake (E133)	0.20	0.20	0.20	0.20
Total weight (mg)	**95.00**	**95.00**	**95.00**	**95.00**
Vildagliptin Layer				
Vildagliptin	50.00	50.00	50.00	50.00
Avicel PH 101	45.50	45.50	45.50	45.50
Lactose Anhydrous (Supertab 21AN)	44.00	44.00	44.00	44.00
Hydroxy Propyl Cellulose	2.50	2.50	2.50	2.50
Isopropyl Alcohol	q.s			
Sodium Starch Glycolate	5.00	5.00	5.00	5.00
Aerosil 200	1.50	1.50	1.50	1.50
Magnesium Stearate	1.50	1.50	1.50	1.50
Total weight (mg)	**150.00**	**150.00**	**150.00**	**150.00**

Table 4 Formulation Details with different ratio of diluents

Ingredients	**23**	**24**	**25**	**26**	**27**	**28**	**29**
Vildagliptin Layer							
Vildagliptin	50.00	50.00	50.00	50.00	50.00	50.00	50.00
Avicel PH 101	44.75	59.67	29.83	51.14	38.36	71.60	17.90
Lactose Anhydrous (Supertab 21AN)	44.75	29.83	59.67	38.36	51.14	17.90	71.60
Hydroxy Propyl Cellulose	2.50	2.50	2.50	2.50	2.50	2.50	2.50
Isopropyl Alcohol	q.s						
Sodium Starch Glycolate	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Aerosil 200	1.50	1.50	1.50	1.50	1.50	1.50	1.50
Magnesium Stearate	1.50	1.50	1.50	1.50	1.50	1.50	1.50
Total weight (mg)	**150.00**	**150.00**	**150.00**	**150.00**	**150.00**	**150.00**	**150.00**
Intermediate Layer / Barrier Layer / Inactive Layer							
Avicel PH 102	55.00	55.00	55.00	55.00	55.00	55.00	55.00
Pharmatose 200M	28.30	28.30	28.30	28.30	28.30	28.30	28.30
Povidone K30	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Croscarmellose Sodium	7.50	7.50	7.50	7.50	7.50	7.50	7.50
Magnesium Stearate	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Brilliant blue FCF aluminum lake (E133)	0.20	0.20	0.20	0.20	0.20	0.20	0.20
Total weight (mg)	**95.00**	**95.00**	**95.00**	**95.00**	**95.00**	**95.00**	**95.00**
Metformin Layer							
Metformin HCl	850.00	850.00	850.00	850.00	850.00	850.00	850.00
Avicel PH 101	12.00	12.00	12.00	12.00	12.00	12.00	12.00
Methocel K15M	120.00	120.00	120.00	120.00	120.00	120.00	120.00
Methocel K100M	90.00	90.00	90.00	90.00	90.00	90.00	90.00
Povidone K90	22.00	22.00	22.00	22.00	22.00	22.00	22.00
Purified Water	q.s						

Magnesium Stearate	11.00	11.00	11.00	11.00	11.00	11.00	11.00
Total weight (mg)	**1105.0**	**1105.0**	**1105.0**	**1105.0**	**1105.0**	**1105.0**	**1105.0**

Table 5 Formulation trails with different concentration of binder in Vildagliptin layer

Ingredients	**24**	**30**	**31**
Vildagliptin Layer			
Vildagliptin	50.00	50.00	50.00
Avicel PH 101	59.67	58.33	56.33
Lactose Anhydrous (Supertab 21AN)	29.83	29.17	28.17
Hydroxy Propyl Cellulose	2.50	4.50	7.50
Isopropyl Alcohol	q.s		
Sodium Starch Glycolate	5.00	5.00	5.00
Aerosil 200	1.50	1.50	1.50
Magnesium Stearate	1.50	1.50	1.50
Total weight (mg)	**150.00**	**150.00**	**150.00**
Intermediate Layer / Barrier Layer / Inactive Layer			
Avicel PH 102	55.00	55.00	55.00
Pharmatose 200M	28.30	28.30	28.30
Povidone K30	3.00	3.00	3.00
Croscarmellose Sodium	7.50	7.50	7.50
Magnesium Stearate	1.00	1.00	1.00
Brilliant blue FCF aluminum lake (E133)	0.20	0.20	0.20
Total weight (mg)	**95.00**	**95.00**	**95.00**
Metformin Layer			
Metformin Hydrochloride	850.00	850.00	850.00
Avicel PH 101	12.00	12.00	12.00
Methocel K15M	120.00	120.00	120.00
Methocel K100M	90.00	90.00	90.00
Povidone K90	22.00	22.00	22.00
Purified Water			
Magnesium Stearate	11.00	11.00	11.00
Total weight (mg)	**1105.0**	**1105.0**	**1105.0**

Table 6 Formulation Trials with different concentration of disintegrant in Vildagliptin layer

Ingredients	**30**	**32**	**33**
Vildagliptin Layer			
Vildagliptin	50.00	50.00	50.00
Avicel PH 101	59.67	56.17	51.67
Lactose Anhydrous (Supertab 21AN)	29.83	28.08	25.83
Hydroxy Propyl Cellulose	2.50	4.50	7.50
Isopropyl Alcohol	q.s		
Sodium Starch Glycolate	5.00	8.25	12.00
Aerosil 200	1.50	1.50	1.50
Magnesium Stearate	1.50	1.50	1.50
Total weight (mg)	**150.00**	**150.00**	**150.00**
Intermediate Layer / Barrier Layer / Inactive Layer			
Avicel PH 102	55.00	55.00	55.00
Pharmatose 200M	28.30	28.30	28.30
Povidone K30	3.00	3.00	3.00
Croscarmellose Sodium	7.50	7.50	7.50
Magnesium Stearate	1.00	1.00	1.00
Brilliant blue FCF aluminum lake (E133)	0.20	0.20	0.20
Total weight (mg)	**95.00**	**95.00**	**95.00**
Metformin Layer			
Metformin Hydrochloride	850.00	850.00	850.00
Avicel PH 101	12.00	12.00	12.00
Methocel K15M	120.00	120.00	120.00
Methocel K100M	90.00	90.00	90.00
Povidone K90	22.00	22.00	22.00
Purified Water			
Magnesium Stearate	11.00	11.00	11.00
Total weight (mg)	**1105.0**	**1105.0**	**1105.0**

Table 7 Formulation Trials with intermediate layer or separating layer

Ingredients	34	35	36
Metformin Layer			
Metformin Hydrochloride	850.00	850.00	850.00
Avicel PH 101	12.00	12.00	12.00
Methocel K15M	120.00	120.00	120.00
Methocel K100M	90.00	90.00	90.00
Povidone K90	22.00	22.00	22.00
Purified Water	q.s	q.s	q.s
Magnesium Stearate	11.00	11.00	11.00
Total weight (mg)	**1105.0**	**1105.0**	**1105.0**
Intermediate Layer / Barrier Layer / Inactive Layer			
Avicel PH 102	58.30	56.65	55.00
Pharmatose 200M	30.00	29.15	28.30
Povidone K30	3.00	3.00	3.00
Croscarmellose Sodium	2.50	5.00	7.50
Magnesium Stearate	1.00	1.00	1.00
Brilliant blue FCF aluminum lake (E133)	0.20	0.20	0.20
Total weight (mg)	**95.00**	**95.00**	**95.00**
Vildagliptin Layer			
Vildagliptin	50.00	50.00	50.00
Avicel PH 101	56.17	56.17	56.17
Lactose Anhydrous(Supertab 21AN)	28.08	28.08	28.08
Hydroxy Propyl Cellulose	4.50	4.50	4.50
Isopropyl Alcohol	q.s	q.s	q.s
Sodium Starch Glycolate	8.25	8.25	8.25
Aerosil 200	1.50	1.50	1.50
Magnesium Stearate	1.50	1.50	1.50
Total weight (mg)	**150.00**	**150.00**	**150.00**

Table 8 Initial Results of Drug-Excipients Compatibility Studies

Material	Ratio	Initial							
		Description	RRT-0.60	Amide (RRT-0.85)	Acid (RRT-0.91)	RRT-0.94	RRT-1.54	Single max	Total impurity
API [Vildagliptin]	-	White powder	ND	0.00	0.00	ND	0.01	ND	0.01
API + Metformin HCl	1:5		ND	0.00	0.07	ND	0.02	0.01	0.11
API + Cellulose Microcrystalline	1:2		0.03	0.01	0.00	ND	0.01	0.03	0.05
API + Lactose Anhydrous	1:2		ND	0.01	0.01	ND	0.02	ND	0.04
API + Hydroxy Propyl Cellulose	1:0.2		ND	0.02	0.00	ND	0.00	ND	0.02
API + Povidone K90	1:0.2		ND	0.02	0.05	ND	0.01	0.01	0.09
API + HPMC K100 Premium	1:0.5		ND	0.01	0.01	ND	0.00	0.01	0.04
API + Sodium Starch Glycolate	1:0.2		ND	0.01	0.01	0.01	0.01	0.00	0.01
API + Aerosil 200	1:0.2		ND	0.02	0.01	ND	0.00	ND	0.05
API + Magnesium Stearate	1:0.2		ND	0.02	0.02	ND	0.00	ND	0.04

ND- Not detected

Table 9 Results of Drug-Excipients Compatibility Studies after 1 Month

Material	Ratio	1M – 40°C/75%RH							
		Description	RRT-0.60	Amide (RRT-0.85)	Acid (RRT-0.91)	RRT-0.94	RRT-1.54	Single max	Total impurity
API [Vildagliptin]	-	No change	ND	0.00	0.00	ND	0.01	ND	0.02
API + Metformin HCl	1:5		ND	0.05	**0.89**	ND	0.05	0.03	**1.12**
API + Cellulose Microcrystalline	1:2		0.00	0.03	0.01	ND	0.01	ND	0.05

API + Lactose Anhydrous	1:2		ND	0.02	0.01	ND	0.01	ND	0.04
API + Hydroxy Propyl Cellulose	1:0.2		ND	0.03	0.01	ND	0.01	0.01	0.05
API + Povidone K90	1:0.2		ND	0.05	**0.51**	ND	0.04	0.04	**0.77**
API + HPMC K100 Premium	1:0.5		ND	0.02	0.02	ND	0.01	0.01	0.09
API + Sodium Starch Glycolate	1:0.2		ND	0.01	0.01	ND	0.01	ND	0.03
API + Aerosil 200	1:0.2		ND	0.02	0.01	ND	0.00	ND	0.05
API + Magnesium Stearate	1:0.2		ND	0.09	0.02	ND	0.01	ND	0.12

ND- Not detected

Table 10 Blend properties of Metformin HCl layer and Vildagliptin Layer

Formulation (Trial No.)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's Ratio
Blend Properties of Metformin HCl IR Layer				
1	0.59	0.68	13.24	1.15
2	0.63	67.00	5.97	1.06
3	0.61	0.69	11.59	1.13
4	0.57	0.67	14.93	1.18
5	0.64	0.74	13.51	1.16
6	0.60	0.68	11.76	1.13
7	0.61	0.67	8.96	1.10
8	0.59	0.64	7.81	1.08
9	0.63	0.69	8.70	1.10
10	0.58	0.67	13.43	1.16
11	0.58	0.71	18.31	1.22
12	0.61	0.68	10.29	1.11
13	0.63	0.67	5.97	1.06
14	0.59	0.69	14.49	1.17
15	0.61	0.67	8.96	1.10
16	0.64	0.71	9.86	1.11
17	0.60	0.68	11.76	1.13
18	0.61	0.72	15.28	1.18
19	0.61	0.72	15.28	1.18
20	0.63	0.71	11.27	1.13
21	0.59	0.73	19.18	1.24
22	0.64	0.75	14.67	1.17
Blend Properties of Vildagliptin SR Layer				
23	0.51	0.62	22.73	1.29
24	0.55	0.68	19.12	1.24
25	0.50	0.63	20.63	1.26
26	0.57	0.69	17.39	1.21
27	0.54	0.66	18.18	1.22
28	0.53	0.68	22.06	1.28
29	0.51	0.62	17.74	1.22
30	0.58	0.67	13.43	1.16
31	0.60	0.69	13.04	1.15
32	0.55	0.64	14.06	1.16
33	0.61	0.72	15.28	1.18

Table 11 Blend properties of Metformin HCl layer and Vildagliptin Layer

Formulation (Trial No.)	% Cumulative Retention on			
	30#	40#	60#	Pan
Blend Properties of Metformin HCl Layer				
1	15	39	66	100
2	24	45	75	100
3	28	49	79	100
4	19	41	71	100
5	32	51	82	100
6	24	41	69	100
7	20	45	71	100
8	25	50	73	100
9	27	54	76	100
10	22	49	73	100
11	18	41	69	100
12	22	43	76	100
13	26	48	71	100

14	20	44	74	100
15	21	48	78	100
16	29	53	82	100
17	19	40	74	100
18	22	45	78	100
19	24	41	70	100
20	21	47	64	100
21	27	51	77	100
22	19	46	71	100
Blend Properties of Vildagliptin Layer				
23	8	24	36	100
24	3	22	37	100
25	9	23	32	100
26	6	21	34	100
27	8	23	32	100
28	4	21	38	100
29	7	30	41	100
30	12	35	54	100
31	19	45	68	100
32	14	33	51	100
33	15	31	52	100

Table 12 Post-compression parameters of Metformin HCl and Vildagliptin Tri-layer Tablet

Trail No.	Weight Variation (mg)	Hardness (N)	Thickness (mm)	Friability (%)	Drug Content (%)	
					Metformin	Vildagliptin
1	1350 ± 15	270 – 350	7.80 – 8.10	0.24	98.5	99.5
2	1350 ± 15	270 – 350	7.80 – 8.10	0.44	99.4	97.9
3	1350 ± 15	270 – 350	7.80 – 8.10	0.31	98.7	98.6
4	1350 ± 15	270 – 350	7.80 – 8.10	0.22	99.1	99.2
5	1350 ± 15	270 – 350	7.80 – 8.10	0.41	99.1	99.1
6	1350 ± 15	270 – 350	7.80 – 8.10	0.39	99.8	99.9
7	1350 ± 15	270 – 350	7.80 – 8.10	0.35	101.1	100.8
8	1350 ± 15	270 – 350	7.80 – 8.10	0.31	100.4	101.4
9	1350 ± 15	270 – 350	7.80 – 8.10	0.27	100.7	99.8
10	1350 ± 15	270 – 350	7.80 – 8.10	0.44	99.8	102.1
11	1350 ± 15	270 – 350	7.80 – 8.10	0.41	98.7	98.7
12	1350 ± 15	270 – 350	7.80 – 8.10	0.55	99.6	99.4
13	1350 ± 15	270 – 350	7.80 – 8.10	0.61	99.1	99.7
14	1350 ± 15	270 – 350	7.80 – 8.10	0.49	99.9	98.6
15	1350 ± 15	270 – 350	7.80 – 8.10	0.54	98.6	99.1
16	1350 ± 15	270 – 350	7.80 – 8.10	0.45	98.1	99.8
17	1350 ± 15	270 – 350	7.80 – 8.10	0.51	97.9	97.5
18	1350 ± 15	270 – 350	7.80 – 8.10	0.55	99.6	98.3
19	1350 ± 15	270 – 350	7.80 – 8.10	0.42	99.1	99.9
20	1350 ± 15	270 – 350	7.80 – 8.10	0.38	99.8	100.7
21	1350 ± 15	270 – 350	7.80 – 8.10	0.47	99.2	99.3
22	1350 ± 15	270 – 350	7.80 – 8.10	0.51	99.7	100.0
23	1350 ± 15	270 – 350	7.80 – 8.10	0.28	99.3	100.7
24	1350 ± 15	270 – 350	7.80 – 8.10	0.45	98.8	99.9
25	1350 ± 15	270 – 350	7.80 – 8.10	0.19	98.9	98.4
26	1350 ± 15	270 – 350	7.80 – 8.10	0.34	99.1	99.1
27	1350 ± 15	270 – 350	7.80 – 8.10	0.51	99.5	97.6
28	1350 ± 15	270 – 350	7.80 – 8.10	0.29	100.3	99.4
29	1350 ± 15	270 – 350	7.80 – 8.10	0.37	100.1	100.2
30	1350 ± 15	270 – 350	7.80 – 8.10	0.31	99.8	97.1
31	1350 ± 15	270 – 350	7.80 – 8.10	0.28	99.1	98.6
32	1350 ± 15	270 – 350	7.80 – 8.10	0.37	98.9	99.1
33	1350 ± 15	270 – 350	7.80 – 8.10	0.21	98.5	100.2

Table 13 Post-compression parameters of Tri-layer Tablet with different concentration of disintegrant in Intermediate Layer / Barrier Layer

Trail No.	Weight Variation (mg)	Hardness (N)	Thickness (mm)	Friability (%)	Drug Content (%)		DT* (Secs)
					Met	Vilda	
34	1350 ± 15	270 – 350	7.80 – 8.10	0.31	98.5	99.5	190
35	1350 ± 15	270 – 350	7.80 – 8.10	0.41	99.4	97.9	110
36	1350 ± 15	270 – 350	7.80 – 8.10	0.28	98.7	98.6	51

*Disintegration Time (DT)

Table 14 Dissolution profile of Metformin HCl SR layer

Time (Hrs.)	Glumetza	1	2	3	4	5	6	7	8	9	10
2	30	49	43	35	48	49	47	55	48	47	49
4	55	75	70	52	71	70	68	78	72	68	75
6	72	92	85	62	85	84	84	92	85	79	92
8	82	98	94	71	98	91	94	99	92	89	96
10	90	99	98	81	99	95	99	98	97	95	98
12	96	99	98	90	98	99	101	99	99	99	98
F_2	---	**40**	**47**	**54**	**42**	**44**	**45**	**36**	**44**	**47**	**40**

Time (Hrs.)	11	12	13	14	15	16	17	18	19	20	21	22
2	28	41	45	50	36	35	43	38	34	28	22	18
4	46	64	68	70	61	59	64	61	60	54	45	40
6	64	79	83	84	79	75	79	79	77	71	65	72
8	76	89	92	94	91	89	88	90	88	83	88	91
10	89	94	98	98	96	96	96	97	94	92	96	98
12	98	98	99	98	98	99	99	99	98	99	98	98
F_2	**62**	**55**	**47**	**43**	**60**	**65**	**53**	**59**	**67**	**83**	**57**	**49**

Table 15 Dissolution profile of Vildagliptin layer

Time (Mins.)	Galvus	23	24	25	26	27	28	29	30	31	32	33
5	35	25	36	19	27	21	44	16	29	26	36	42
10	62	48	64	40	51	44	74	37	58	54	64	73
15	85	66	84	59	75	62	94	55	77	71	84	89
20	96	83	94	75	89	80	99	72	86	82	95	98
30	99	95	99	90	95	94	99	95	95	93	99	99
45	101	100	100	99	99	99	99	101	99	99	99	99
F_2	---	**42**	**86**	**33**	**52**	**37**	**52**	**30**	**56**	**47**	**89**	**58**

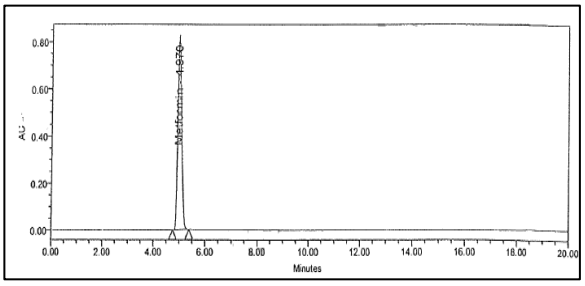

Figure 1 Standard Solution for Metformin (at 218 nm)

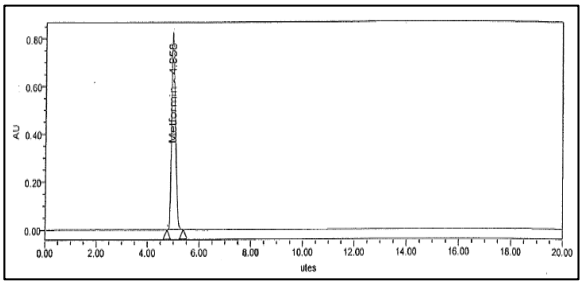

Figure 2 Sample Solution for Metformin (at 218 nm)

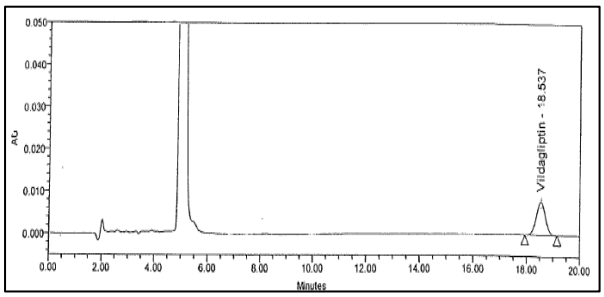

Figure 3 Standard Solution for Vildagliptin (at 210 nm)

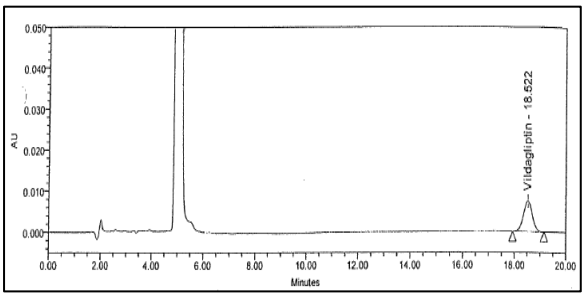

Figure 4 Sample Solution for Vildagliptin (at 210 nm)

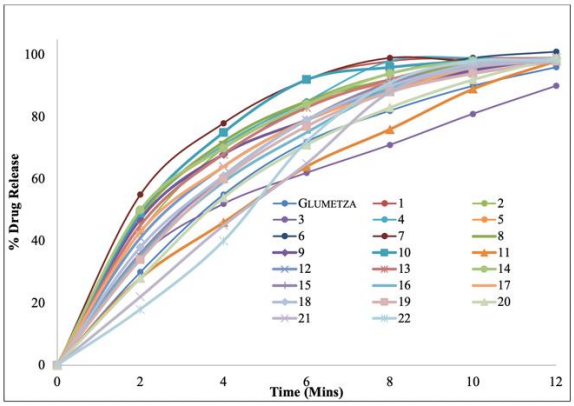

Figure 5 Dissolution profile of Metformin HCl SR Tablets

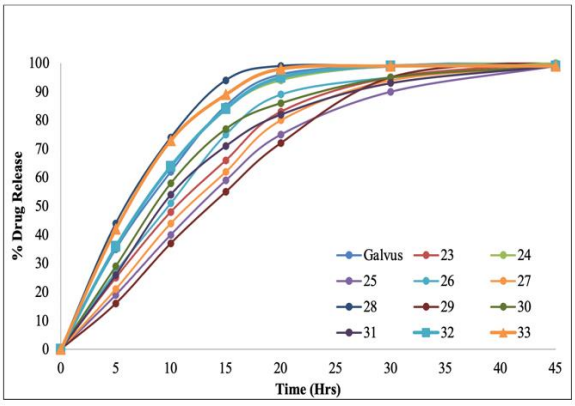

Figure 6 Dissolution profile of Vildagliptin IR layer Tablet

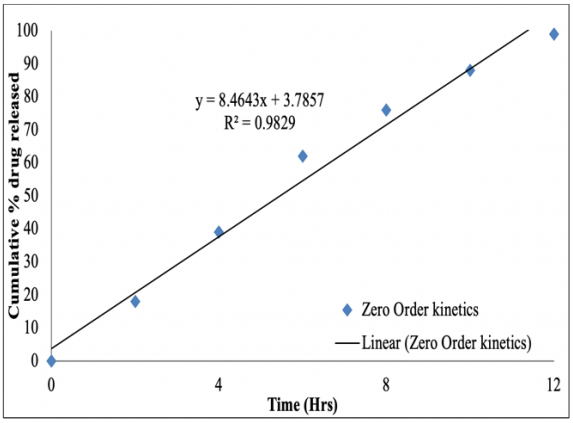

Figure 7 Graphical presentation of Zero Order Kinetic Model of Metformin HCl SR Tablet

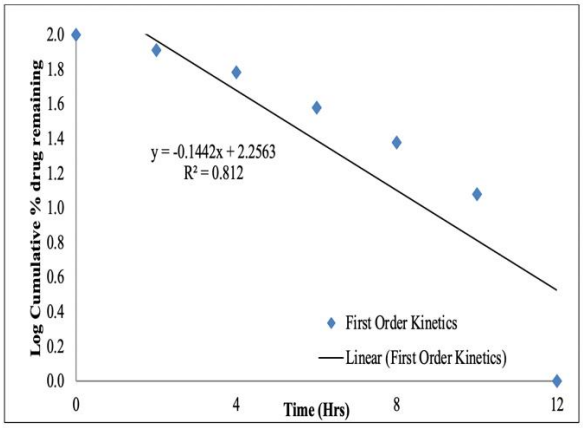

Figure 8 Graphical presentation of First Order Kinetic Model of Metformin HCl SR Tablet

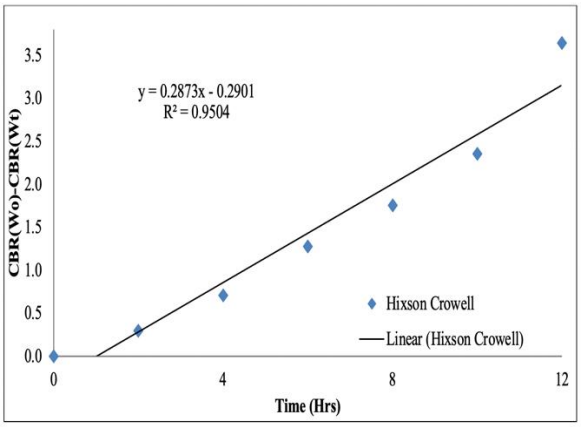

Figure 9 Graphical presentation of Hixson Crowell Model of Metformin HCl SR Tablet

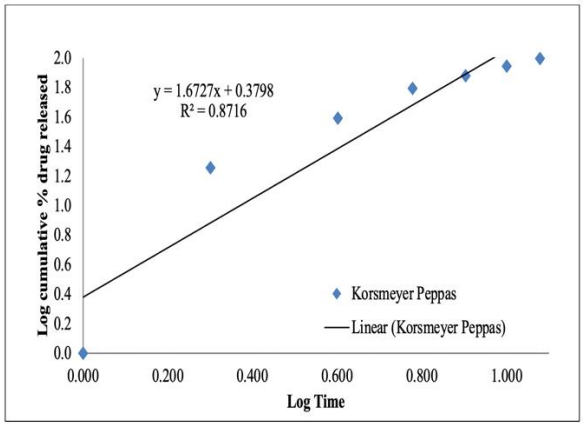

Figure 10 Graphical presentation of Korsmeyer Peppas Model of Metformin HCl SR Tablet

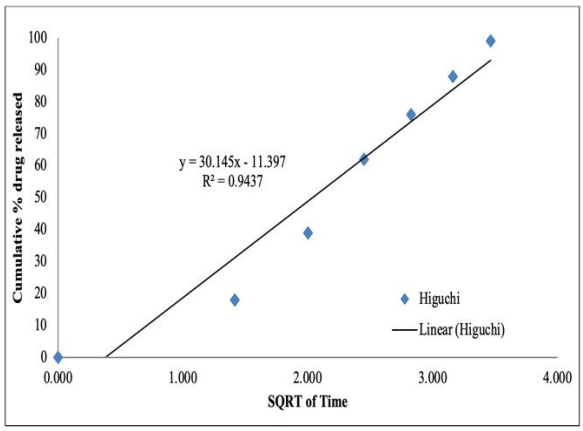

Figure 11 Graphical presentation of Higuchi Model of Metformin HCl SR Tablet

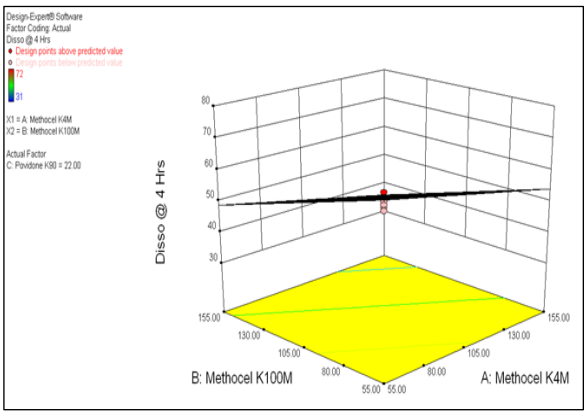

Figure 12 Response surface plot showing the influence of polymer on the release profile of Metformin HCl for cumulative %Drug Release at 4 Hrs.

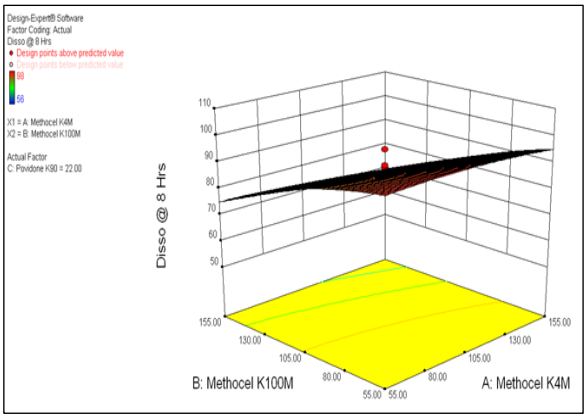

Figure 13 Response surface plot showing the influence of amount of polymer on the release profile of Metformin HCl for cumulative %Drug Release at 8 Hrs.

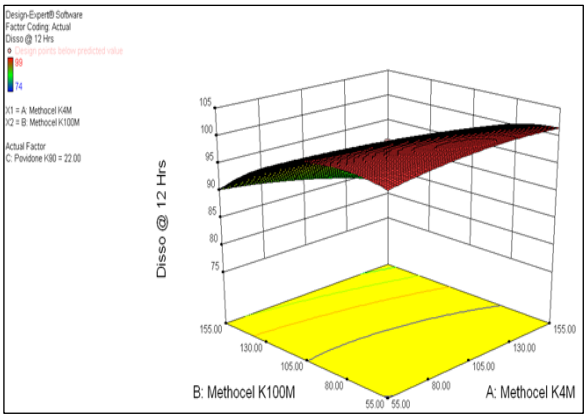

Figure 14 Response surface plot showing the influence of polymer on the release profile of Metformin HCl for cumulative %Drug Release at 12 Hrs.

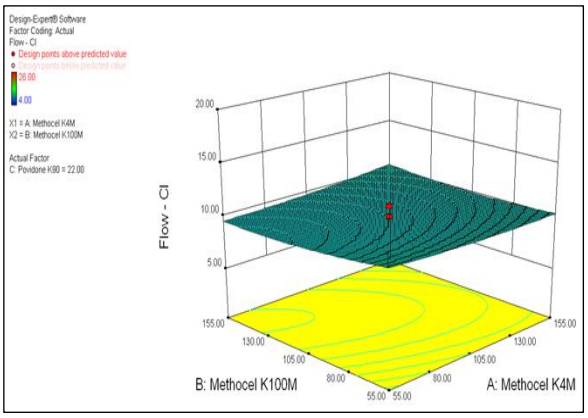

Figure 15 Response surface plot showing the influence of polymer on flow properties (Carr's Index) – Metformin Layer

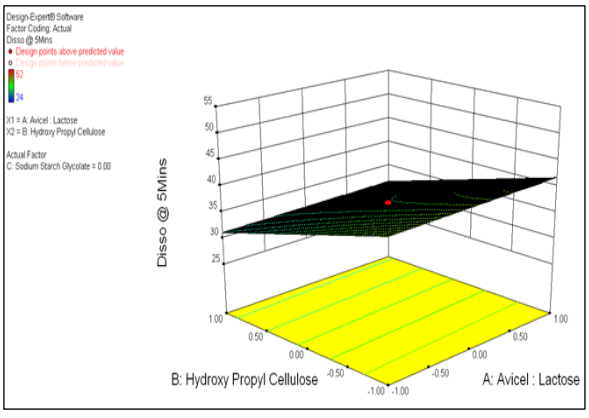

Figure 16 Response surface plot showing the influence on the release profile of Vildagliptin for cumulative %Drug Release at 5 Mins.

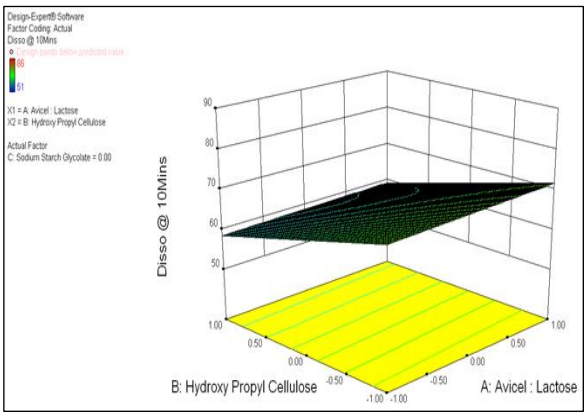

Figure 17 Response surface plot showing the influence on the release profile of Vildagliptin for cumulative %Drug Release at 10 Mins.

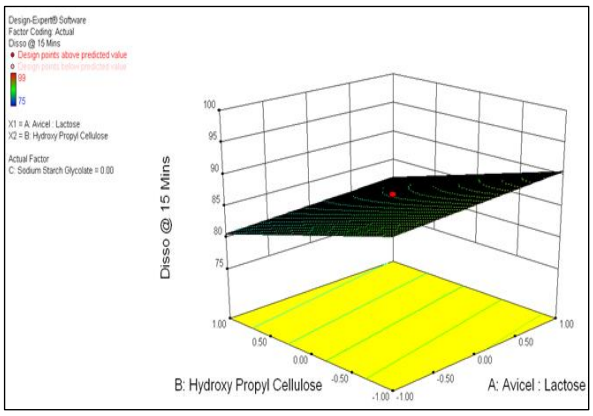

Figure 18 Response surface plot showing the influence on the release profile of Vildagliptin for cumulative %Drug Release at 15 Mins.

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