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Formulation Development and Validation of Metformin hydrochloride and Gliclazide sustained release bilayer tablet.

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ABSTRACT

The aim of this study was to Design and Process Validate Bi-layer Tablet of Metformin Hydrochloride (MTH) and Gliclazide (GZ) effective for the treatment of Non-Insulin Dependent Diabetes Mellitus (NIDDM). For formulation of bi-layer tablet, initially both layer optimized individually. MTH and Gliclazide were formulated as sustained release layers (L1 and L2) by using various Hydrophilic polymers such as Methocel CR, HPMC K100, HPMC 15Cps and Methocel K100 LV. The effect of concentration of hydrophilic matrix (Methocel CR, HPMC 15Cps), binder (Polyvinyl Pyrollidone [PVP K90/PVP K30] on MTH and GZ drug release rate from matrix system was studied. The dissolution study of sustained release layer showed that an increasing amount of Methocel CR and HPMC or PVP K30/90 results in reduced drug release. Optimized batch of both drug formulations were used for formulation of bi-layer tablet. The rational for formulation of bi-layer tablet of these two drugs in combination was from class second generation sulphonylureas and biguanides was suitable for the treatment of NIDDM. Bi-layer tablet was suitable for preventing direct contact of these two drugs and maximize the efficacy of combination of two drugs for treatment of NIDDM.

Keywords: Metformin Hydrochloride, Gliclazide, Bi-layer Tablet, Methocel CR, PVPK30/90.

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INTRODUCTION

Formulation Development and Process Validation of Metformin Hydrochloride and Gliclazide sustained release bilayer tablet. Bilayer Tablets are mainly suitable for administration of fixed dose combination (FDC's) of different active pharmaceutical ingredients (API).Bilayer tablets aim to separate incompatible API from each other, to control release of API from one layer by utilizing fictional property of other layers along with property of maintaining chemical and microbial stability over all oral dosage form.

The Objective of this project is to formulate an effective and acceptable sustained release Anti-diabetic solid dosage from; tablets the intention is to develop a cost effective generic product using Excipients similar to the reference product and other well established Excipients so as to match the in-vitro dissolution profile of reference product and thus to develop stable generic product which is bioequivalent to the innovator product.

The present study focuses on to development of polytherapy for the treatment of NIDDM. Though there are numerous drugs for treating type II diabetes, sulphonylureas and biguanides are used commonly by a wide section of patients. Gliclazide is a second generation of sulphonyl urea; Whereas Metformin Hydrochloride belongs to biguanide group. Hence the combination of Gliclazide/Metformin Hydrochloride would help in treatment of NIDDM and probably prevention of its associated macromolecular and micro vascular complications.[4-6]

MATERIALS AND METHOD

All the Material and Facility's were provided by S.P Pharmaceuticals (Jalgaon, India), Drugs and Excipients was provided as gift sample, Solvents and reagents used in this study were of analytical grade or HPLC grade and used as provided.

Equipment

Analytical Balance, Vibratory Sifter, Rapid Mixer Granulator, Paste Preparation Kettle, Tray Dryer, 27 Station Double Rotary Compression Machine, I.R. Moisture Balance, HPLC, Hardness Tester, Vernier Caliper, Dissolution Test Apparatus.

Granule preparation of Sustained release layer of Metformin Hydrochloride:

The dose of Metformin Hydrochloride for Sustained release was fixed as 500 mg. Metformin Hydrochloride sustained release granules were prepared by Wet granulation method employing various excipients as mentioned in the Table 1. Weighed quantity of Metformin Hydrochloride, Microcrystalline cellulose pH 101, Methocel CR and Hydroxy propyl methyl cellulose K15Cps were sifted through #40 mesh and mixed for 30 mins in rapid mixer granulator. The binding

solution containing PVP K-90 in water was added slowly to the above ingredients and mixed at slow speed and an additional chopper time during addition of slurry for 30 sec and after addition on slurry 5 min and mixed well till granules are obtained (25 min) in RMG. The wet granules were loaded in tray drier and dried till the moisture content of granules was between 2 to 3%. The dried granules were sifted through #20 mesh. Weighed amount of Magnesium Stearate, Aerosil and purified talc were sifted through #30 mesh and loaded to the planetary mixer along with dried granules and mixed well for 3 min at slow speed for lubrication of granules.

Granule preparation of sustained release layer of Gliclazide:

Gliclazide sustained release granules were prepared by employing various excipients as mentioned in the Table 2. Weighed quantity of Gliclazide, Microcrystalline cellulose pH 102 (Diluent), HPMC 15 Cps and Sodium Starch Glycolate were sifted through #30 mesh sieve and Dry mixed for 30 mins in Rapid Mixer Granulater. The binding solution containing PVP K-30 in IPA was added slowly to the above ingredients and mixed at slow speed and an additional chopper time during addition of slurry for 30 sec and after addition on slurry 5 min and mixed well till granules are obtained (20 min). The wet granules were loaded in tray drier and dried till the moisture content of granules are between 2 to 3%. The dried granules were sifted through #20 mesh. Weighed amount of Magnesium Stearate and purified talc were sifted through #30 mesh and loaded to the planetary mixer along with dried granules and mixed well for 3 mins at slow speed for lubrication of granules.

Table 1: Composition of Sustained Release Layer of Metformin Hydrochloride:

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Dry Mixing/mg									
Metformin HCL	500	500	500	500	500	500	500	500	500
Methocel CR	100	110	120	140	120	130	140	140	140
HPMC 15 Cps	40	30	20						
MCC	24	24				24	24	24	24
Dicalcium Phosphate			24						
Lactose				24					
Starch					24				
Lubrication/mg									
Mag. Starate	12	12	12	12	12	12	12	12	12
Aerosil	8	8	8	8	8	8	8	8	8
Talc	10	10	10	10	10	10	10	10	10
Binding/mg									
PVP K 90	56	56	56	56	76	66	56	56	56
PEG	2	2	2	2	2	2	2	2	2
Total Weight/Tab	**752**	**752**	**752**	**752**	**752**	**752**	**752**	**752**	**752**

Table 2: Composition of Sustained Release Layer of Gliclazide

Contents	F1	F2	F3	F4	F5	F6	F7	F8	F9
Dry Mixing/mg									
Gliclazide	60	60	60	60	60	60	60	60	60
HPMC K 100	20	13							
HPMC 15 Cps	7	5	8	8	20	20	20	20	20
Methocel K100 LV			30	20					
MCC	65	70	60	70	70	60	60	60	60
Dicalcium Phosphate	12	16			7	10	10	10	10
Sodium Starch Glycolate			6	6					
Colloidal Anhydrous Silica					8	8	8	8	8
Sodium Lauryl Sulphate						7	7	7	7
Lubrication/mg									
Mag. Starate	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4
Binding/mg									
PVP K 30	8	8	8	8	7	7	7	7	7
Yellow Iron Oxide	1	1	1	1	1	1	1	1	1
Total Weight/Tab	**181**	**181**	**181**	**181**	**181**	**181**	**181**	**181**	**181**

Compression method:

Final bilayer tablets were compressed as one layer only for Metformin HCl(pre-compression stage) and second layer for Gliclazide using 19.50×9.00mm Elongated shape punches with one side break line in rotary tablet compression machine. The tablet was compressed as bilayer tablets using both Metformin HCl and Gliclazide granules. In this Metformin HCl granules was introduced first into the die cavity and pre compression was made so the layer was uniformly distributed after that Glimepiride granules were added and final compression was carried out.[4,5]

PROCESS VALIDATION:

The purpose is to provide documentary evidence that the manufacturing process of Metformin Hydrochloride + Gliclazide SR Bilayer Tablet (500/60), Meets the predefined specification and quality attributes**.** Concurrent Process Validation was carried out by monitoring the critical parameters of the process while taking three production batches, sampling and testing at different Process Steps to provide the efficacy of the Process.[1-3] Process Validation was performed on three consecutive batches F7, F8 and F9.

Tablet 3: Process Validation - Batch No and Batch Size

Batch No.	Batch Size
F7	5000
F8	5000
F9	5000

Preventive maintenance had been satisfactorily established. The status of the equipment's / instruments used during whole validation activity were reported to be qualified and calibrated satisfactorily and The results for review of raw material used in validation i.e. Active ingredients and raw materials used for the product formulation were found to be approved and procured from qualified vendor only.

Sampling:

Table 4: Sampling Plan, Testing Plan and Acceptance Criteria for different stages during Process Validation of bilayer tablet Manufacturing

Sampling plan		**Testing plan**		**Acceptance criteria**
Stage /Sampling point	**Sampling Quantity**	**No. of Samples**	**Test Parameters**	
Dry Mixing (Top, middle, Bottom) at 10, 20, 30 min.	1 gm each	03	- % Assay of API	±10 % Assay of API
Drying (Top, middle, Bottom) at 10,20,30 min.	2 gm each	03	- Loss of drying	2 – 4 %
Lubricated Granules Collect samples from Top, Middle, Bottom at 10,20,30 minute	3 gm each	10 min=1No 20 min =1No 30 min= 1No Total Samples =3No	- % Assay of API - Loss on drying	±10 % Assay of API 2 – 4 %
Compression	20 Tablet each	1.Starting Time 2.Middle Time 3.End Time Total Samples =3No	- Weight Variation -Diameter -Thickness - Hardness	±5 % of Average weight 18.5 ± 2 mm 6.5 – 7 mm 9 – 10 Kg/Cm^2
Complete Analysis of Batch	Random sampling, 2 strip collect 10 x10 tablet	01	Test parameter as per the specification	Test parameter as per the specification

Evaluation Tests for Bilayer Tablets Of Metformin Hcl and Gliclazide:

All the formulations were evaluated for Weigh variation test, Hardness, Thickness, Width, Length, Drug content, Disintegration etc.

Average Weight:

Weigh 20 tablets randomly from the analytical sample and record the weight & and out the average.

Uniformity of Weight:

Select 20 tablets randomly from the analytical sample and weigh. Note down the individual weight of 20 tablets and out the deviation. Tablets should not deviate by more than ± 5.0 % of the average weight.

Thickness:

Take 5 tablets selected randomly & check the thickness of each tablet with Vernier Caliper.

Length:

Take 5 tablets selected randomly & check the length of each tablet with Vernier Caliper.

Width:

Take 5 tablets selected randomly & check the width of each tablet with Vernier Caliper.

Hardness:

Take 5 tablets selected randomly & check the hardness of each tablet in kg/cm2 with calibrated hardness tester.

Loss on drying:

Take 500 gm of sample powder. Place into the sample pan Dry the sample for at 60-65 °C for 30 minutes. Loss Weight is displayed in IR moisture balance, calculate % loss on drying Loss on drying (% w/w) = Loss in wt. (g) X 100/Wt. of sample (g)

Estimation of Drug Content:

Tablet 5: HPLC details for Assay Procedure

Column	A stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5µm) (C18)
Column Temp	Ambient
Flow rate	1.0 ml per min.
Inject volume	20 µl
Run time	10 Minutes
Wave length	228 nm

Mobile phase Preparation:

A mixture of 550 volume of mixed buffer solution prepared by dissolving 1.6253 gm of

potassium dihydrogen orthophosphate and 0.2996 gm of dipottasium hydrogen orthophosphate in 490 ml Distilled water, 450 volumes of Acetonitrile, adjust the PH 3 using orthophosphoric acid. Finally filter through the filter paper of 0.45 µm.

Standard Preparation:

Dissolve together accurately weighed both 250 mg of Metformin Hydrochloride WS and 30 mg Gliclazide WS in a volumetric flask containing 100 ml Mobile phase, to obtain a solution having a known concentration of about 2.5 mg per ml of Metformin Hydrochloride and 0.3 mg per ml of Gliclazide, sonicate till the solution gets clear, filter it through membrane filter of pore size 0.45 µm.

Sample Preparation:

Weight and powder 20 Tablets accurately weigh quantity of powder containing 250 mg of Metformin hydrochloride and 30 mg of Gliclazide in 100 ml Mobile phase, sonicate to obtain a solution having a known concentration of about 2.5 mg per ml and 0.3 mg per ml respectively and filter it through membrane filter of pore size 0.45 µm

Procedure:

Separately inject equal volumes (about 20 µl) of the Standard preparation and the test preparation, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity in mg of Metformin Hydrochloride and Gliclazide in Tablet.

$$\text{Assay} = \frac{\text{Sample Area}}{\text{STD Area}} \times \frac{\text{Wt. of WS in mg}}{\text{Dilution in ml}} \times \frac{\text{Dilution in ml}}{\text{Wt. of sample in mg}} \times \frac{\text{Potency}}{\text{Label claim}} \times \text{Average wt. of tab}$$

Gliclazide and Metformin HCl Sustained Release Tablet Dissolution:

Tablet 6: Parameters for Dissolution Procedure

Dissolution medium -1	0.1 N HCl
Dissolution medium -2	Phosphate buffer pH=7.4
Volume	900 ml
RPM	50
Apparatus	USP 2 (paddle)
Temperature	37^{o} C
Dissolution Time	Dissolution Medium 1 For 1 Hr& 2 hr Dissolution Medium 2 For remaining Hours.

Mobile phase Preparation:

A mixture of 550 volume of mixed buffer solution prepared by dissolving 1.6253 gm of potassium dihydrogen orthophosphate and 0.2996 gm of dipottasium hydrogen orthophosphate

in 550 ml Distilled water, 450 volumes of Acetonitrile, adjust the PH to 6.85 using orthophosphoric acid. Finally filter through the filter paper of 0.45 µm.

STD Preparation:

Weight accurately 60 mg of Gliclazide WS and 500 mg Metformin HCl WS in the 25 ml Methanol, Sonicate for 15 min and make up to 900 ml using dissolution medium 2 (Phosphate buffer pH=7.4) then withdrawn 5 ml of this sample and make up to 10 ml using dissolution medium 2. Inject Replicate the five standards through 0.45 µm size membrane filter.

Sample Preparation:

Weigh and add each tablet separately in each bowl. Withdrawn 5 ml sample from each bowl at definite interval of time.

System Suitability:

Inject the reference solution.

1. The test is not valid unless The tailing factor for each peak is not more than 2.0 and
2. The relative standard deviation for replicate injections is not more than 2.0 percent.

Procedure:

Withdraw 5 ml of sample from each bowl after each hour, Dilute it up to 10 ml using dissolution medium Filter it through the 0.45 µm size membrane filter, inject each sample separately for each bowl and Calculate the of Metformin HCl And Gliclazide by following Formula.

$$\% \text{ Dissolved} = \frac{\text{Sample Area}}{\text{Standard Area}} \times \frac{\text{STD Weight}}{\text{Dilution in ml}} \times \frac{\text{Dilution in ml}}{\text{Individual Tab Weight}} \times \frac{\text{Potency}}{\text{Label claim}} \times 100$$

FTIR Spectra

IR spectra of bulk drugs were taken using FTIR Spectrophotometer (FTIR Bruker Alpha, Software - Opus). FTIR spectrum of drug was taken by using KBr pellet method. Pellets of drug and KBr (1:100) were prepared using hydraulic press.

RESULTS AND DISCUSSION

All the results of various stages were shown as following.

PRE-COMPRESSION STUDY OF POWDER:

Metformin Hydrochloride:

Table 7: Pre-Compression Data of Metformin Hydrochloride Granules

Formulation Code	Angle of Repose	Bulk Density gm/ml	Tapped density (gm/ml)	Carr's Index	Hauser's ratio	LOD (%)
F1	32.82	0.480	0.568	15.49	1.18	2.456
F2	33.41	0.378	0.438	13.69	1.15	3.445
F3	34.55	0.469	0.520	9.80	1.10	3.697
F4	31.21	0.403	0.454	9.44	1.12	2.574
F5	33.69	0.417	0.472	11.6	1.13	3.786
F6	32.82	0.431	0.490	12.04	1.13	3.843
F7	33.69	0.409	0.463	11.6	1.13	3.454
F8	32.58	0.391	0.446	12.33	1.14	2.698
F9	31.46	0.424	0.481	11.85	1.13	3.552

Gliclazide:

Table 8: Pre-Compression Data of Gliclazide Granules

Formulation Code	Angle of Repose	Bulk Density	Tapped density(gm/ml)	Carr's Index	Hauser's ratio	LOD (%)
F1	28.61	0.27	0.31	14.81	1.15	3.436
F2	29.98	0.27	0.29	6.80	1.07	2.289
F3	29.05	0.27	0.30	10.00	1.11	3.337
F4	32.00	0.28	0.31	9.67	1.10	3.596
F5	29.98	0.27	0.29	6.89	1.07	3.648
F6	30.96	0.27	0.29	6.80	1.07	2.878
F7	29.05	0.26	0.28	7.14	1.08	3.384
F8	28.22	0.26	0.30	12.20	1.06	3.688
F9	32.12	0.28	0.29	6.72	1.12	2.486

POST-COMPRESSION STUDY:

Table 9: Post-Compression Data of Bilayer Tablet of MTH and GZ

Formulation Code	Hardness (Kg/cm^2)	Thickness (mm)	Weight Variation(mg)	Friability (%)	Drug Release	
					Layer 1	Layer 2
F1	9-10	6.72	101.0	0.79	114.21	53.67
F2	9-10	6.76	101.4	0.82	86.92	57.29
F3	9-10	6.96	99.2	0.84	97.08	60.47
F4	9-10	6.99	100.8	0.89	97.75	90.18
F5	9-10	6.92	99.9	0.76	96.84	91.06
F6	9-10	6.86	100.2	0.78	100.33	99.12
F7	9-10	6.74	100.1	0.79	98.57	99.40
F8	9-10	6.96	100.2	0.82	99.26	101.09
F9	9-10	6.72	100.4	0.77	98.12	99.91

Drug Release Profile for batches F1 to F9: (For 12 hr)

Table 10: Dissolution Data for Formulation Batches of Metformin Hydrochloride (F1 – F9)

Formula/Time In Hours	F1	F2	F3	F4	F5	F6	F7	F8	F9
1 Hr	37.47	23.94	26.91	21.72	16.23	20.17	17.98	25.45	21.70
2 Hr	53.29	33.46	37.01	29.29	26.31	23.99	23.44	29.75	29.94
3 Hr	71.31	51.07	55.92	43.63	40.86	38.01	37.80	45.49	46.28
4 Hr	83.53	57.70	66.06	56.41	53.90	47.38	48.05	58.14	58.71
5 Hr	95.25	66.66	75.97	68.38	63.20	56.81	55.86	69.84	64.11
6 Hr	104.17	72.21	84.20	77.07	69.57	67.81	66.72	79.33	74.68
7 Hr	109.07	76.78	89.59	84.78	76.44	73.55	77.07	86.32	78.12
8 Hr	113.79	80.96	92.72	91.14	84.67	80.42	83.50	91.39	83.97
9 Hr	113.81	82.62	93.18	92.58	87.42	85.05	86.07	93.22	88.20
10 Hr	114.16	84.28	94.29	96.94	92.86	89.93	93.97	95.95	90.70
11 Hr	114.19	85.78	96.03	97.44	95.98	95.28	96.12	97.09	94.29
12 Hr	114.21	86.92	97.08	97.75	96.84	100.33	98.51	99.26	98.12

Table 11: Dissolution Data for Formulation Batches of Gliclazide (F1 - F9)

Formula/Time In Hours	F1	F2	F3	F4	F5	F6	F7	F8	F9
1 Hr	5.11	12.27	2.82	2.99	2.88	3.45	2.52	3.89	3.81
2 Hr	5.52	12.80	5.87	5.90	5.98	6.29	5.82	6.53	6.45
3 Hr	13.20	27.14	18.19	21.16	18.68	17.25	21.83	23.99	25.45
4 Hr	16.77	31.01	25.61	33.65	29.47	28.77	35.75	38.25	37.76
5 Hr	23.64	34.02	33.30	45.09	39.51	40.10	47.91	51.85	52.91
6 Hr	34.01	36.66	39.41	54.18	51.86	52.61	56.24	62.57	62.25
7 Hr	36.22	41.52	44.60	66.03	67.72	65.42	66.22	69.27	74.25
8 Hr	43.13	46.12	49.62	69.13	75.83	73.78	78.55	76.49	79.34
9 Hr	44.30	48.06	51.60	77.27	82.87	83.46	83.66	84.71	85.59
10 Hr	45.54	52.16	55.04	85.25	88.04	87.11	88.79	90.69	93.52
11 Hr	51.58	55.39	57.26	87.80	89.68	91.25	96.18	97.47	97.12
12 Hr	53.67	57.29	60.47	90.18	91.06	99.12	99.40	101.09	99.91

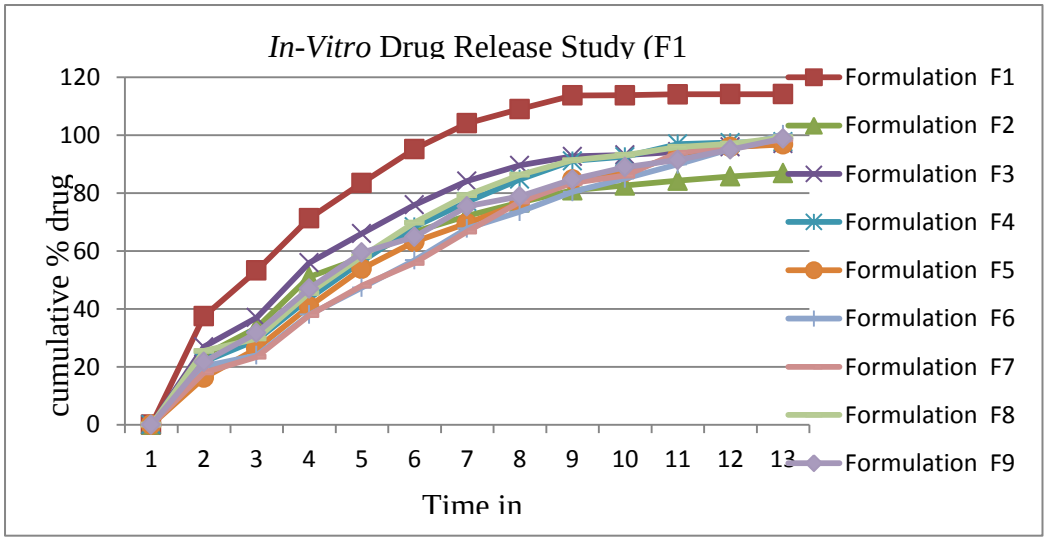

Figure 1: Dissolution Data of Metformin Hydrochloride Sustained Release Layer (F1- F9)

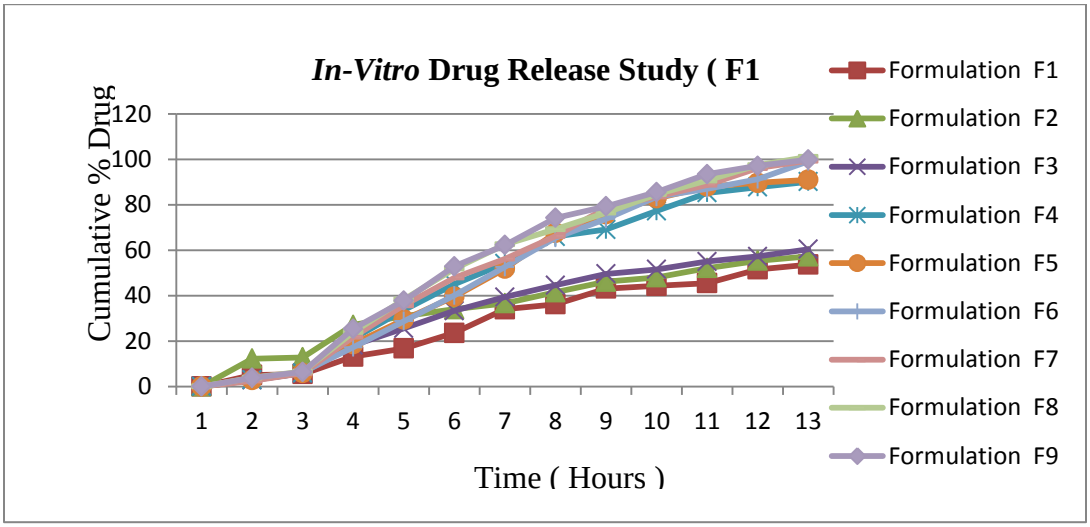

Figure 2: Dissolution test of Gliclazide Sustained Release Layer (F1- F9)

Drug Release Kinetic Study:

Metformin Hydrochloride:

Table 12: Drug Release Kinetic Study Data for MTH and GZ

Formulation	Zero order	First order	Higuchi Equation	Korsmeyer-Peppas equation		Hixon Crowell
	(R^2)	(R^2)	(R^2)	(n)	(R^2)	(R^2)
Metformin Hydrochloride F6	0.9898	0.9772	0.9705	0.4831	0.9093	0.9918
Gliclazide F6	0.9841	0.9424	0.9364	0.4831	0.8502	0.9716

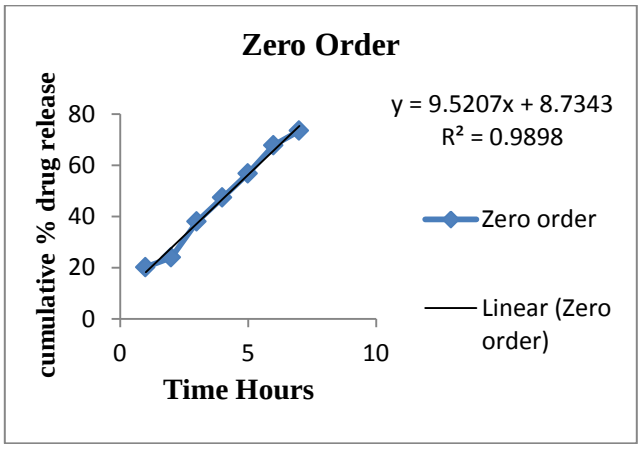

Figure 3: Zero Order Drug Release Kinetic Data for MTH

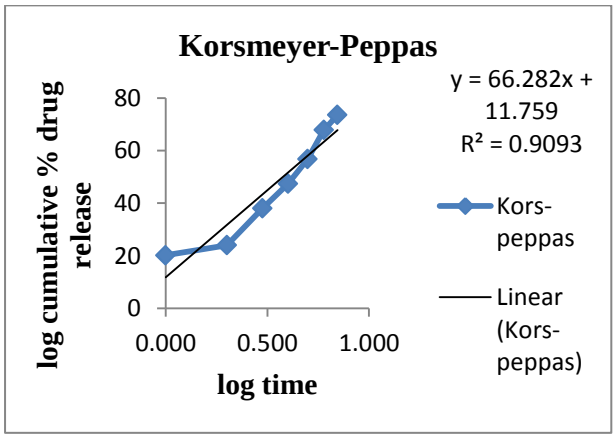

Figure 6: KorsmeyerPeppas Drug Release Kinetic data for MTH

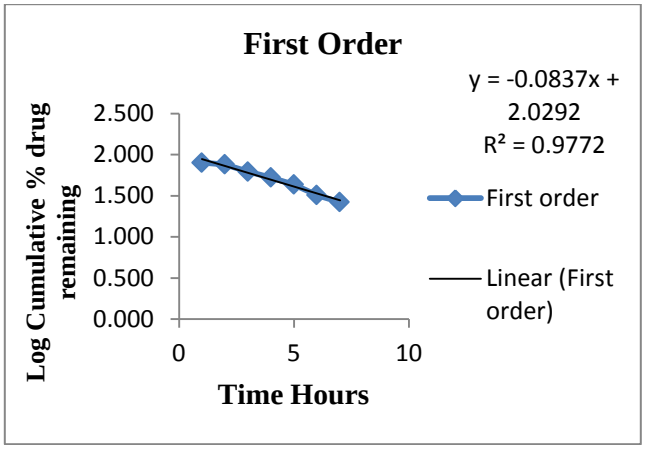

Figure 4: First Order Drug Release Kinetic Data for MTH

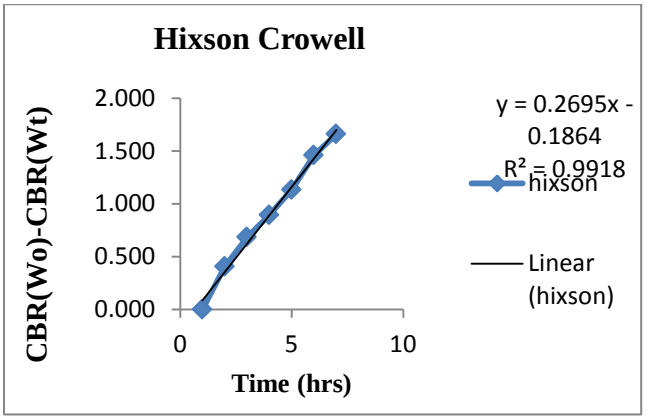

Figure 7: Hixson Crowell Drug Release Kinetic Data for MTH

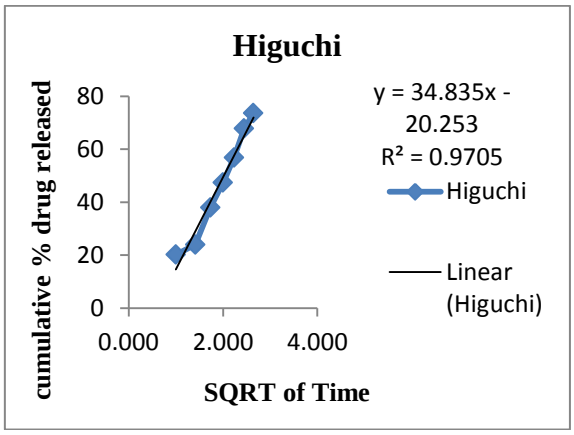

Figure 5: Higuchi Drug Release Kinetic Data for MTH

Gliclazide:

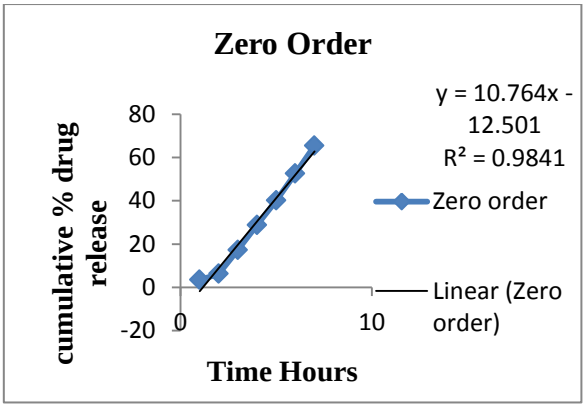

Figure 8: Zero Order Drug Release Kinetic Data for GZ

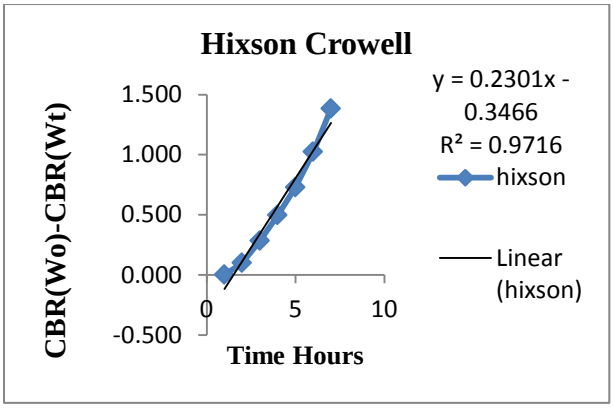

Figure 11: Hixson Crowell Drug Release Kinetic Data for GZ

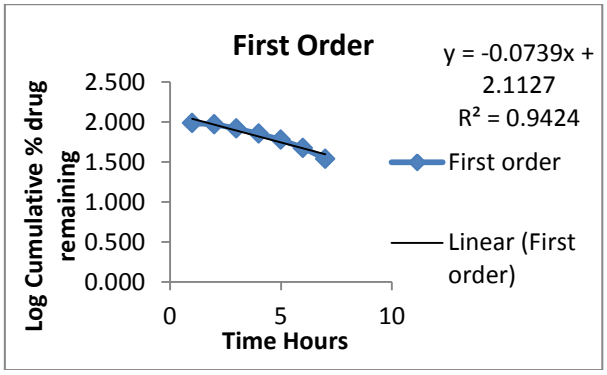

Figure 9: First Order Drug Release Kinetic Data for GZ

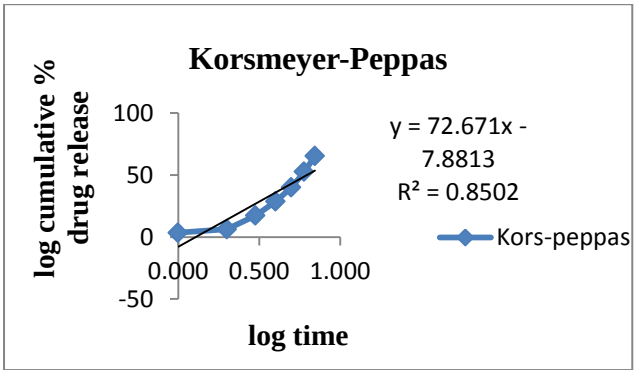

Figure 12: Korsmeyer-Peppas Drug Release Kinetic Data for GZ

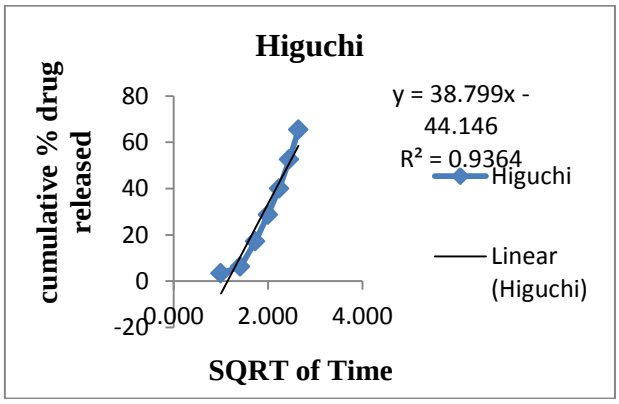

Figure 10: Higuchi Drug Release Kinetic Data for GZ

Corresponding plots for *In-vitro* Dissolution Test of Bi-layer Tablet: (F6)

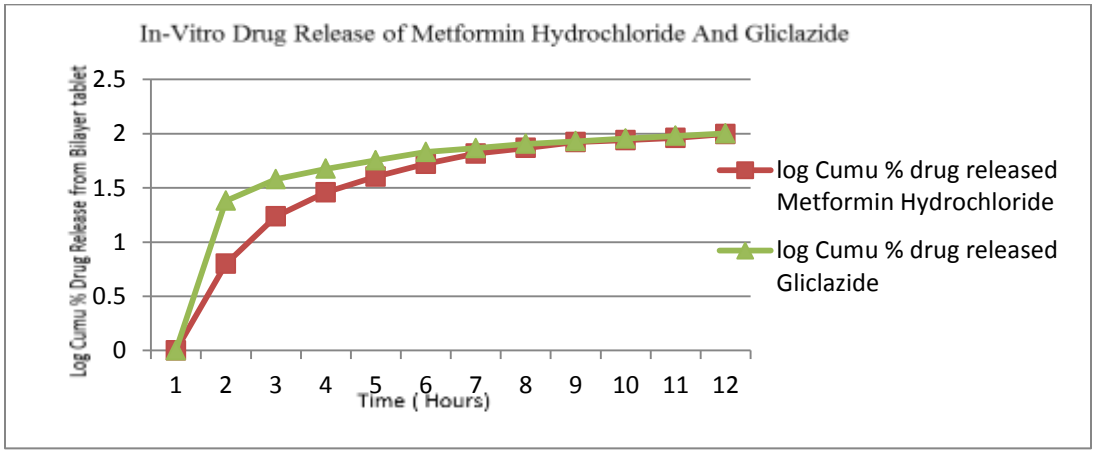

Figure 13: In-Vitro Drug Release of MTH and GZ from Optimized Batch (F6)

From dissolution studies its was interpreted that F6 batch results were most appropriate and meeting the drug release pattern similar to as that of the standard marketed product and In order to establish the mechanism of drug release and swelling kinetics, the experimental data were fitted to zero-order, first order, Higuchi and Korsmeyer–Peppas models. The coefficients of regression were in a range between 0.9898–0.9841 (Zero order), 0.9772–0.9424 (First order), 0.9705–0.9364 (Higuchi), 0.9093–0.8502 (Peppas) and 0.9918–0.9716 (Hixon Crowell). Based

on correlation coefficients (R2), the best fit model were determined for formulation F6which followed Zero Order Kinetic model.

Stability Study of Bi-Layer Tablet:

Table 13: Post compression parameters of bi-layer tablet after stability study

Time (Month)	Weight Variation (mg)	Thickness (mm)	Hardness (Kg/cm2)	Friability (%)	Drug Content Uniformity (%)
0	99.2(1.68)	6.96 (0.4)	9-10 (0.5)	0.82	(M) 101.2 ± 0.8 (G) 102.7 ± 0.5
1	100.8(1.2)	6.99 (0.4)	9-10 (0.2)	0.79	(M) 100.1 ±0.6 (G) 101.8 ± 0.4
2	99.9 (1.21)	6.92 (0.5)	9-10 (0.3)	0.84	(M) 99.2 ± 0.5 (G) 100.8 ± 0.3
3	100.2(1.0)	6.86 (0.5)	9-10 (0.4)	0.82	(M) 99.0 ± 0.4 (G) 100.5 ± 0.4

The formulated bi-layer tablet was subjected to stability studies for three months at 40 ± 10C and 75% RH. The effects of temperature and humidity on the physical and chemical characteristics of the bi-layer tablets were evaluated for 3 month to assess the stability of the prepared formulation. Friability was found to be increased a little more at 40 ± 10C and 75% RH. No significant change was observed in drug content. Bi-layer tablet remained stable after three months stability study.

Drug-Excipient Interaction Study:

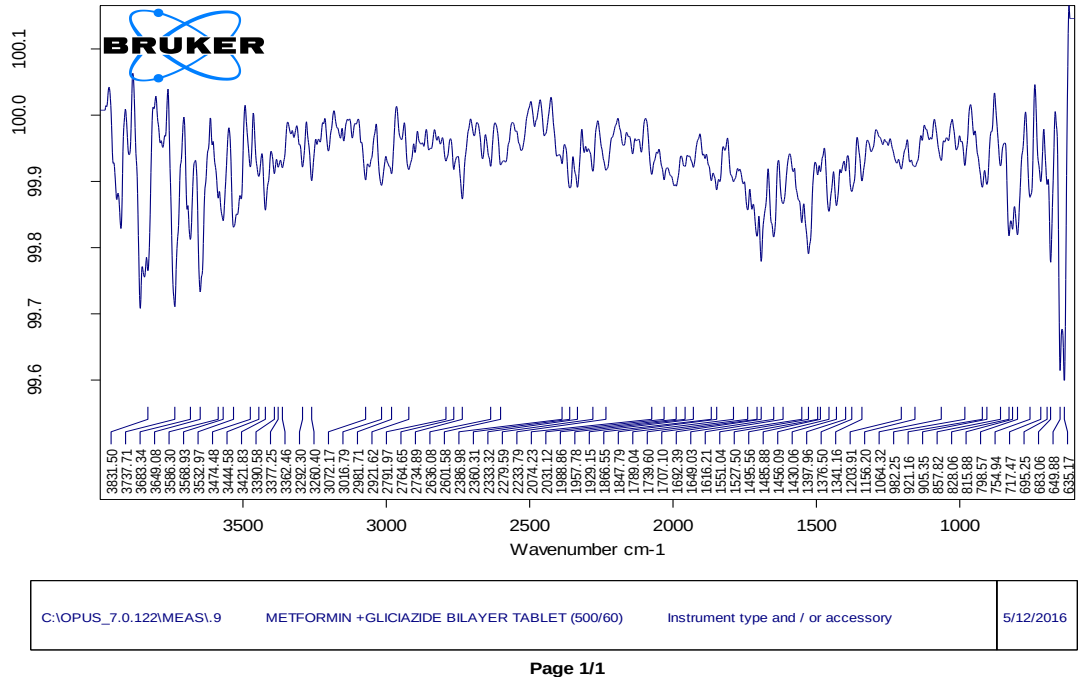

Figure 14: FTIR spectra of Metformin Hydrochloride + Gliclazide (500/60)

Physical Mixture

Table 14: Drug-Drug and Drug-Excipient Interaction study

Sr. no	Metformin Hydrochloride	Gliclazide	Physical Mixture	
			Metformin Hydrochloride	Gliclazide
1	3372	3564	3377	3564
2	3300	3648	3292	3648
3	3176	1706	2816	1693
4	2816	1693	1475	1354
5	1475	1354	1170	1165
6	1170	1165	1061	663
7	1061	663	976	2816
8	1033	2816	736	
9	976			
10	736			

From the above figures it was concluded that vibrational band assignment of Metformin Hydrochloride and Gliclazide and physical mixture of both drugs showed no change or shifting of peak for either of the drugs. From the above results it was concluded that Metformin Hydrochloride had no interaction, when in prolonged contact with Gliclazide.

PROCESS VALIDATION:

Process Validation was performed on three consecutive batches F7, F8 and F9.

REVIEW OF EQUIPMENTS AND UTILITY QUALIFICATIONS:

Table 15: Equipment's/Instruments used during validation of Bilayer Tablet

Processing Stage	Processing Equipment's	Qualification Status	Calibration Status
Weight Verification	Weighing balance	Satisfactory	Ok
Shifting	Mechanical sifter#40 sieve	Satisfactory	Ok
Granulation	RMG	Satisfactory	Ok
Lubrication	RMG	Satisfactory	Ok
Metal Detection	Metal Detector	Satisfactory	Ok
Compression	Tablet Press De-Duster	Satisfactory	Ok

Table 16: Calibration verification of instruments used for in-process testing

Processing Stage	Processing Equipment's	Qualification Status	Calibration Status
Weight Verification	Weighing Balance	Satisfactory	Ok
Length and Diameter	Vernier Caliper	Satisfactory	Ok
Disintegration Time	Disintegration Apparatus	Satisfactory	Ok
Loss on Drying	Halogen Moisture Balance	Satisfactory	Ok

RESULTS FOR VALIDATION ACTIVITY:

After reviewing pre-validation checks, the process validation activity was planned for three consecutive batches named Batch F7, Batch F8 and Batch F9 from dispensing to Compression.

The results for process validation activity are given below

Table 17: Data of Milling and Sifting Process for Metformin Hydrochloride

Sr.	Batch No.		Batch 1	Batch 2	Batch 3
1	Temperature (20°C to 25°C)		22.8°C	22.8°C	22.8°C
2	Relative Humidity		52.3 %	53.3 %	53.3 %
3	Name of Equipment		Mechanical	Mechanical	Mechanical
4	Sieve used		# 40	# 40	# 40
5	Name of Equipment		Co-mill	Co-mill	Co-mill
6	Screen used		1.0 mm	1.0 mm	1.0 mm
7	Sieve and Screen Integrity	Before Use	Intact	Intact	Intact
		After Use	Intact	Intact	Intact

Table 18: Data of Milling and Sifting Process for Gliclazide

Sr.	Batch No.		Batch 1	Batch 2	Batch 3
1	Temperature (20°C to 25°C)		24.5°C	24.5°C	24.5°C
2	Relative Humidity		53.3 %	54.5 %	54.4 %
3	Name of Equipment		Mechanical	Mechanical	Mechanical
4	Sieve used		# 40	# 40	# 40
5	Name of Equipment		Co-mill	Co-mill	Co-mill
6	Screen used		1.0 mm	1.0 mm	1.0 mm
7	Sieve and Screen Integrity	Before Use	Intact	Intact	Intact
		After Use	Intact	Intact	Intact

Observed data indicated that all sieves used for Milling and sifting process found intact before and after Milling and sifting of each and every material of all three batches. Approved raw materials were milled and sifted through the sieve and integrity of sieves/screen measured after completion of the milling and sifting process. Following results were obtained during sieve analysis.

Table 19: Data of Blend Uniformity after Dry Mixing

Sample	Metformin HCl Assay (%)		
Location	Batch A	Batch B	Batch C
Top-1	101.56	100.49	100.74
Mid-1	100.56	100.48	101.26
Bot-1	100.61	101.32	100.71
Mean	100.91	100.76	100.90
SD	0.5594	0.5360	0.5528
Sample	Gliclazide Assay (%)		
Location	Batch A	Batch B	Batch C
Top-1	100.23	101.34	100.34
Mid-1	101.68	100.42	101.58
Bot-1	100.55	100.37	100.32
Mean	100.82	100.71	100.74
SD	0.5594	0.5360	0.5528

SD: Standard Deviation

The mixing of actives and diluents for all the three batches were performed utilizing High Shear Mixer Granulator. The samples were collected from top, middle and bottom of mixer. The results of mixing uniformity were found within the control range.

Table 20: Data of Loss on Drying after Drying

Sample		**Metformin HCl - LOD (%)**	
Location	Batch A	Batch B	Batch C
Top-1	2.254	3.482	3.323
Mid-1	3.332	3.676	3.882
Bot-1	3.567	3.899	3.941
Mean	3.154	3.685	3.712
Sample		Gliclazide - LOD (%)	
Location	Batch A	Batch B	Batch C
Top-1	3.536	3.383	3.496
Mid-1	3.332	3.429	3.588
Bot-1	3.867	3.753	3.812
Mean	3.578	3.521	3.632

Table 21: Data after Lubrication stage

Parameter	Batch F7		Batch F8		Batch F9	
	MET	**GZ**	**MET**	**GZ**	**MET**	**GZ**
Bulk density	0.44	0.28	0.47	0.32	0.39	0.29
Angle of Repose	32.52	32.00	33.42	29.26	31.44	28.22
LOD	2.867	2.632	3.226	3.879	3.347	3.453
% Assay of API	100.42	100.67	100.61	100.53	100.88	100.65
Sieve Analysis	% retained on 20#: 0.0%	% retained on 20#: 0.0%	% retained on 20#:0.0%	% retained on 20#:0.0%	% retained on 20#: 0.0%	% retained on 20#: 0.0%
	% retained on 30#: 0.0%	% retained on 30#: 0.0%	% retained on 30#: 0.0%	% retained on 30#:0.0%	% retained on 30#: 0.0%	% retained on 30#: 0.0%
	% retained on 40 #: 0.0%	% retained on 40 #: 0.0%	% retained on 40 #: 0.0%	% retained on 40#:0.0%	% retained on 40 #: 0.0%	% retained on 40 #: 0.0%
	Passed through 40#:100%	Passed through 40#:100%	Passed through 40#:100%	Passed through40#:100%	Passed through 40#:100%	Passed through 40#:100%

The mixing of dry mixture with binding paste was performed using High Shear Mixer granulator. The control variables like quantity of addition of water, mixing pattern, Temp of the binding paste, binding time were in accordance with the set target.

Table 22: Parameters to be checked during Granulation in RMG

Parameters	Limit	Batch F7		Batch F8		Batch F9	
		MET	GZ	MET	GZ	MET	GZ
Temperature of Binding paste or solution added	55 °C – 60 °C	57	59	55	56	57	55
Quantity of Extra water added		-	-	-	-	-	-

The drying of wet granules was carried out in Tray Dryer. The control variables like inlet temperature, outlet temperature, drying temperature and drying time were in accordance with the acceptance criteria. The samples for analysis were collected from top, middle and bottom of Tray Dryer. The results of loss on drying after drying stage were recorded and were within the range. Lubrication was carried out in Rapid Mixer Granulator. The Final blending process parameters like temperature, relative humidity and blender rpm, direction of mixing, material loading and mixing pattern, were in compliance with the protocol specifications. The samples collected at this stage were analyzed for the blend uniformity analysis and particle size distribution.

Table 23: Data of Pre-compression of Metformin Hydrochloride Layer

Sr. No	Parameters	Limits	Batch F7		Batch F8		Batch F9	
1	Appearance of tablets	Elongated Shape with one side Break Line, Uncoated	Complies		Complies		Complies	
2	Uniformity of Weight	±5 % of Average Weight	Complies		Complies		Complies	
3	Average Weight of Tablets	933 mg ±5 % w/w	937.6	934.3	935.4	936.3	938.4	937.2

Table 24: Data of Pre-compression of Gliclazide Layer

Sr. No	Parameters	Limits	Batch F7		Batch F8		Batch F9	
1	Appearance of tablets	Elongated Shape, Yellow Iron Oxide colour	Complies		Complies		Complies	
2	Uniformity of Weight	±5 % of Average Weight	Complies		Complies		Complies	
3	Average Weight of Tablets	933 mg ±5 % w/w	938.3	935.6	934.4	937.3	932.4	938.5

LHS : Left Hand Side

RHS : Right Hand Side

Pre-compression for all three batches of Metformin HCl was performed using 27 station double rotary compression machines. The samples were collected from LHS and RHS and analysed for physical parameters. The results were found complying with the protocol specifications.

Table 25: Data for Process Validation Parameters of Bilayer Tablet Formulation

Steps	**Parameters**		**B. No. F7**		**B. No. F8**		**B. No. F9**	
			M	**G**	**M**	**G**	**M**	**G**
Appearance	Elongated Shape, One Side Break Line Yellow Iron Oxide colour		Complies	Complies	Complies	Complies	Complies	Complies
Uniformity of Weight	±5 % of Average Weight		Complies	Complies	Complies	Complies	Complies	Complies
Dry Mixing	% Assay		100.91	100.82	100.76	100.71	100.90	100.74
Drying	Loss on drying		4.446	3.534	3.549	4.552	3.522	3.899
	% Assay of API		100.42	100.67	100.61	100.53	100.88	100.65
Lubricated Granules	Loss on drying		2.867	2.632	3.226	3.879	3.347	3.453
	Angle of Repose		32.52	32.00	33.42	29.26	31.44	28.22
Compression	Weight Variation		100.2(1.0)		100.1(1.3)		100.2(1.2)	
	Diameter		18.22 (0.2)		18.36(0.2)		18.24(0.4)	
	Thickness		6.86 (0.2)		6.74 (0.5)		6.96 (0.3)	
	Hardness		9-10 (0.4)		9-10 (0.2)		9-10 (0.5)	
	Friability		0.82		0.79		0.84	
	Assay		**(M)** 100.1 **(G)** 100.8		**(M)** 99.7 **(G)** 100.5		**(M)** 99.8 **(G)** 100.7	
	Dissolution							
	2 Hr	20-30% 4 – 8%	23.44	5.82	29.75	6.53	29.94	6.45
	3 Hr	40-50% 20-30%	37.80	21.83	45.49	23.99	46.28	25.45
	12Hr	90-110%	98.51	99.40	99.26	101.09	98.12	99.91
Complete Analysis	As per Finish Product Specification		Complies		Complies		Complies	

CONCLUSION:

Sustained Release tablet was prepared suitably by wet granulation method. Methocel CR and HPMC 15Cps is suitable for Sustained release of drug Metformin Hydrochloride and Gliclazide from the matrix system. Methocel CR and HPMC 15Cps was found best among all polymers due to higher swelling capacity. Process Validation was performed on three consecutive batches F7, F8 and F9 to produce an documented evidence of pre-determined quality of the product. The combination of Metformin Hydrochloride and Gliclazide is suitable for effective treatment of diabetes as the combination consists of both Biguanide and Sulfonylureas one which overcomes the insulin resistance and another to enhance the insulin secretion.

It also concluded through the observations and results that each unit process involved in the manufacturing of Metformin HCl and Gliclazide tablets were efficient enough and capable of producing the desired tablets consistently and uniformly. Dry mixing, wet mixing, drying, lubrication, pre-compression and compression in-process parameters were found acceptable for all the three batches. No parameter was observed deviating outside the range of acceptance criteria.

Concluding this study, in concern with the results of the three batches taken for process validation it was concluded that the manufacturing process for the Metformin HCl and Gliclazide tablets was efficient enough to provide a high degree of assurance that it would produce the tablets consistently and uniformly with acceptable and uniform results.

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