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FORMULATION AND EVALUATION OF BILAYERED TABLETS OF HP-β- CYCLODEXTRIN COMPLEXED GLIMEPIRIDE WITH METFORMIN HYDROCHLORIDE FOR IMMEDIATE AND SUSTAIN RELEASE

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ABSTRACT

The aim of present study is to formulate and evaluate the bilayered tablets containing immediate release layer of HP-β-Cycloextrin inclusion complexed Glimepiride to produce immediate therapeutic effect and sustained release layer containing Metformin Hcl by using HPMC as release retardant. Glimepiride act by stimulating the release of insulin from functioning pancreatic beta cells. Metformin hydrochloride helps to suppress appetite and diminishes hepatic glucose excretion, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. It doesn't stimulate insulin release and the combination of these two drugs is more effective than single drug therapy to treat NIDDM (Non insulin dependent Diabetes mellitus). The reason for Bi-layer tablet formulation is to separate physically or chemically incompatible ingredients and to produce repeat action or prolonged action tablet. Total seven trial batches have been manufactured to optimize and develop a robust and stable formulation, both wet & dry granulation processes were used for formulation. The compressed tablets were evaluated for physico-chemical properties. The stability studies of the products also comply with ICH guidelines. FTIR studies clearly indicate that there is no drug polymer interaction. This formulation also exhibited the best fitted formulation into zero order kinetics and non-Fickian transport of the drug from the tablets was confirmed. The present study concluded that bilayer tablets of Glimepiride & Metformin Hcl shall be a good method to improve bioavailability of drugs.

KEYWORDS; Bilayered tablets, Glimepiride, Metformin Hcl, HP-β-CD inclusion Complex, HPMC, Sustained release.

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INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of the drug to the proper site in the body to achieve promptly and maintain the desired drug concentration. [1]
Combination therapy has various advantages over mono-therapy such as problem of dose-dependent side effects is minimized. A low-dose combination of two different drugs reduces the dose related risk using low dosage of two different agents minimize the clinical and metabolic effects that occur with maximal dose of individual component of the combined tablet. Combination therapy of biguanides along with sulfonylureas is important for the adequate control of blood glucose level. [2]
Bi-layer tablets are novel drug delivery systems where combination of two or more drugs in a single unit having different release profiles which improves patient compliance, prolongs the drug action. This study shows how to formulate the Bi-layered tablets of HP-β-Cycloextrin inclusion complexed Glimepiride as immediate release component and Metformin Hydrochloride by using HPMC as sustained release component. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances. Bi-layer tablets are preferred when the release profiles of the drugs are different from one another. Bi-layer compression is becoming more prevalent across the pharmaceutical industry. [3]
Glimepiride, 1-(p-(2-(3-ethyle-4-methyl-2-oxo-3-pyrroline -1-carboxamido) ethyl) phenyl) sulfonyl)-3-(trans-4-methylcyclohexyl) urea is a third-generation sulfonylurea used for oral treatment of type 2 diabetes [4, 5]. It causes an intensification of insulin secretion by the β-cells of the pancreas by closing the potassium channels and depolarizing the cell membrane which leads to the initiation of metabolic processes which result in a release of insulin [6]. Glimepiride is a white or off white crystalline powder, relatively insoluble in water, but the predicated water solubility is (1.6 µg/ml)(pKa=6.2).Which causes large variations in its bioavailability [7]. Also, during storage, the excipients may interact with the drug and affect its dissolution characteristics. There are several reports showing marked changes due to aging which adversely affect dissolution and, hence, the bioavailability of oral sulphonylurea drugs [8, 9]. To overcome these difficulties, several approaches have been used, namely, the formation of a complex between Glimepiride and β-CD, Hydroxylpropyl- β-CD or sulfobutylether-β-CD in presence and absence of different water soluble polymers [7, 10, 11].
Metformin is an orally administered biguanide, which is widely used in the management of type 2 diabetes.(Stith et al., 1996). It is a hydrophilic drug and is slowly and incompletely absorbed from GI Tract and the absolute bioavailability of a single 500 mg dose is reported to be 50-60% [12]. It has relatively short plasma elimination half-life of 1.5 – 4.5 hours (Defang et al., 2005; Scheen et al., 1996).hence Metformin Hcl has to be administered two or three times per day. A sustained release (SR) formulation that would maintain plasma levels of the drug for 10-16 hours might be sufficient for once daily dosing of Metformin (Montvale, 1999; [12]).
Cyclodextrins are cyclic oligosaccharides, containing six, seven or eight glucopyranose units (α, β or γ respectively) obtained by the enzymatic degradation of starch [13]. These are torus shaped molecules with a hydrophilic outer surface and lipophilic central cavity, which can accommodate a variety of lipophilic drugs. Cyclodextrins are able to form inclusion complexes with poorly water-soluble drugs and have been shown to improve pharmaceutical properties like solubility, dissolution rate, bioavailability, stability and even palatability without affecting their intrinsic lipophilicity or pharmacological properties. Out of the three parent cyclodextrins, β-cyclodextrin (β-CD) appears most useful as a pharmaceutical complexing agent because of its complexing ability, low cost and other properties [13, 14]. Natural cyclodextrins have limited water

solubility. However, a significant increase in water solubility has been obtained by alkylation of the free hydroxyl groups of the cyclodextrins resulting in hydroxyalkyl, methyl and sulfobutyl derivatives. The ability of cyclodextrins to form inclusion complexes may also be enhanced by substitution on the hydroxyl group.

The objective of present study is to prepare inclusion complexes of Glimepiride with HP-Beta-cyclodextrins in 1:1 molar ratio by kneading method the inclusion complexes and to develop and study release characteristics of a bilayer tablet containing immediate release layer of HP-β-Cycloextrin inclusion complexed Glimepiride and sustained release layer of Metformin Hcl which is used as an anti-hyperglycemic agent which improves glucose tolerance in a patients with type 2 diabetes by lowering both basal and post- prandial plasma glucose by inhibiting the α-glucosidase inhibitor.

MATERIALS AND METHODS

Materials

Glimepiride was a gift sample obtained from M/s. Amsal Chem Pvt. Ltd., Mumbai, India. Metformin Hcl was a gift sample obtained from M/s. Medley Pharmaceuticals Ltd., Daman and all other excipients such as Tabettose 80, Lake Brillient Blue,Avicel pH-101, HPMC, Sodium CMC, PVPK30, Aerosil, Hyroxypropyl-β-Cyclodextrin, Crospovidone, Talc, Microcrystalline cellulose (Avicel pH-102), and Magnesium Stearatewere procured from M/s. Yarrow Chem Products., Mumbai, India. All other chemicals/reagents used were of analytical grade.

Potency Calculation of Active Pharmaceutical Ingredients:

Actual quantity of Active drug required per tablet

$$\text{Potency} = \frac{\text{label claim}}{\text{Effective assay}} \times 100 \times \frac{100}{100 - \text{water content}}$$

Calculation of Theoretical Release Profile of the Metformin from Bilayered Tablets:

The total dose of Metformin for a once daily SR Tablets shall be calculated by the following equation using available pharmacokinetic data (Rawlins, 1997; [15]).

$$Dt = \text{Dose}\left\{1 + 0.693 \times t / t1/2\right\}$$

Where,

Dt = Total dose of the drug

Dose = Dose of the Immediate release part

t = time (hrs) during which the Sustained release is desired (8 hrs)

t1/2 = Half life of the drug (3 hrs)

Methods

Phase Solubility Studies

Phase solubility studies were carried out according to the method reported by Higuchi and Connors [16]. An excess of Glimepiride (200 mg) was added to 15 ml portions of distilled water, each containing variable amount of β -CD or HP- β -CD such as 0, 1, 3, 6, 9, 12, and 15 x 10-3 moles/liter. All the above solutions with variable amount of HP- β -CD were shaken for 72 hours. After shaking, the solutions were filtered and their absorbance was noted at 228 nm [17]. The solubility of the Glimepiride in every HP- β -CD solution was calculated and phase solubility diagram was drawn between the solubility of Glimepiride and different concentrations of HP- β –CD as shown in Figure 1.

Preparation of HP- β -Cyclodextrin – Glimepiride Inclusion Complexes by Kneading Method [18]

Glimepiride with HP- β -CD in ratio of 1:1M was taken. First cyclodextrin is added to the mortar, small quantity of 50% ethanol is added while triturating to get slurry like consistency. Then slowly drug is incorporated into the slurry and trituration is further continued for one hour. Slurry is then air dried at 25C for 24 hours, pulverized and passed through sieve No. 80

and stored in desiccators over fused calcium chloride.

IR Spectroscopy

The IR spectra of Glimepiride and their complexes were obtained by KBr pellet method by JASCO FT/IR-5300 spectrometer.

Differential Scanning Calorimetry (DSC)

The samples were analyzed by DSC using a Mettler Toledo SR System. The samples were placed into pierced aluminum container.

Drug Content Estimation in HP- β - Cyclodextrin –Glimepiride Inclusion Complexes [19]

50 mg of complex was accurately weighed and transferred to 50 ml volumetric flask and volume was made up to the mark with methanol. From this 1ml was taken in 10 ml volumetric flask and the volume is adjusted up to the mark with same solvent. The absorbance of the solution was measured at 228 nm using appropriate blank. The drug content of GMP was calculated using calibration curve.

Preparation of Glimepiride Blend by Dry granulation Method:

1. Weighed all the ingredients as per the quantities defined in Table No.1
2. Passed all the ingredients through appropriate sieves such as #22, #40, # 60 & #80 mesh and collected the individual materials in separate poly bags.
3. Mixed measured quantity of Glimepiride inclusion complex and Tablettose 80 geometrically then added MCC and Crospovidone to it and blend for 10 min.
4. Mixed Aerosil and Talc in a ploy bag and added this mixture to the above step (3) and blended for 20 min.
5. Mixed Magensiun stearate and Brilliant Blue in a poly bag and added to the above step (4) and blended for 5 min.
6. Compressed final blend by using double rotary, D- tooling, bilayer compression machine using 20X9 mm Caplet shaped punches and corresponding dies.
7. Formulation code for the final blend is marked as FG-I and for bilayer Tablets as TF1, TF2, TF3, TF4, TF5, TF6 and TF7.

Table No. 1
Composition of Granules for Glimepiride Immediate Release Layer

Sr. No.	Ingredients	Quantity Per 10 Tablets (in mg)
	Formulation Code : FG-I	
1	GMP : HP-β-CD (1:1)	41.60
2	Crospovidone	100.00
3	MCC (Avicel pH-102)	900.00
4	Tablettose 80	808.40
5	Talc Purified	20.00
6	Magnesium Stearate	20.00
7	Lake Brillient Blue	10.00
	Total	1900.00

Preparation of Metformin Hcl Blend by Wet Granulation Method:

1. Weighed all the ingredients as per the quantities defined in Table No.2
2. Passed all the ingredients through appropriate sieves such as #40, # 60 & #80 mesh and collected the individual materials in separate poly bags.

3. Prepared binder solution by dissolving PVPK30 in purified water.
4. Mixed all the materials except lubricants for 25 min.
5. Added binder solution to the above step (4) and mixed until uniform dough mass granules are formed.
6. Dried the granules in FBD at 50-55°C temperature till LOD of the granules reaches to 1.5 – 2%.
7. Passed the dried granules through #16 mesh.
8. Transferred all the sifted granules to the blender and lubricants were added except Mg.stearate and blended for 5 min.
9. Added magnesium stearate to the above step (8) and mixed for 2 min.
10. Compressed final blend using Double rotary, D-tooling, bilayer compression machine using 20X9 mm Caplet shaped punches and corresponding dies.
11. Formulation code for the different batches is marked as FM-I, FM-II, FM-III. FM-IV, FM-V, FM-VI and FM-VII and for bilayer Tablets as TF1, TF2, TF3, TF4, TF5, TF6 and TF7

Table No. 2
Composition of Granules for Metformin Hcl Sustained Release Layer

Sr. No.	Ingredients	Formulation Code						
		FM-I	FM-II	FM-III	FM-IV	FM-V	FM-VI	FM-VII
		Quantity per 10 Tablets (in mg)						
1	Metformin Hcl	5000	5000	5000	5000	5000	5000	5000
2	MCC (Avicel pH-101)	2560	2210	1860	1510	1210	860	810
3	HPMC K-100M	150	250	350	450	500	500	500
4	HPMC 15cps	-	-	-	-	-	100	150
5	Sodium CMC	1000	1250	1500	1750	2000	2250	2250
6	PVP K-30	100	100	100	100	100	100	100
7	Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
8	Aerosil	50	50	50	50	50	50	50
9	Purified Talc	70	70	70	70	70	70	70
10	Mg.Stearate	70	70	70	70	70	70	70
	Total	9000	9000	9000	9000	9000	9000	9000

Evaluation of Granules:

To assess physicochemical properties and release characteristics of the granular blend, all formulations are subjected to pre-formulation studies like bulk density, tapped density, Angle of repose, compressibility index, Hausner's ratio and particle size distribution as shown in Table. No. 3 and 4. (1987;Akihiko I *et al*., 1996; Reddy KR *et al*., 2003) ;**[20]**

Table No. 3
Evaluation of Granules of Metformin Sustained Release Layer

Formulation Code	Parameters				
	Angle of repose (θ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner's Ratio
MF-I	29.71	0.43	0.53	23.25	1.23
MF-II	26.42	0.47	0.56	19.19	1.19
MF-III	28.54	0.47	0.58	23.40	1.23

MF-IV	27.11	0.50	0.57	14.00	1.14
MF-V	25.65	0.46	0.54	17.39	1.17
MF-VI	26.72	0.45	0.56	24.44	1.24
MF-VI	27.72	0.47	0.56	19.14	1.19
MF-VII	27.74	0.56	0.64	14.28	1.14

Table No. 4

Evaluation of Granules of Glimepiride Immediate Release Layer

Formulation Code	Parameters				
	Angle of repose (θ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner's Ratio
GF-I	25.24	0.50	0.57	14.00	1.14

Angle of Repose

This is the maximum angle possible between the surface of a pile of granules and the horizontal plane.

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

Where, θ = angle of repose

h = height of the heap

r = radius of the heap

Particle Size Distribution of Granules

The particle size distribution was measured using sieve analysis method.

Bulk Density (BD) & Tapped Density (TD) of Granules

The bulk density and tapped bulk density were determined and calculated by the following formulas.

BD = weight of the powder / initial volume

TD = weight of the powder / final volume

Compressibility of Granules

The compressibility index was determined by Carr's compressibility index and Hausner's ratio..

Carr's index = TD – BD X 100 / BD

Hausner's ratio: Hausner's ratio = TD / BD

Evaluation of Compressed Tablets: [21]

The prepared tablets were evaluated for weight variation, disintegration test, dissolution test, thickness, hardness uniformity of dosage units and friability.

The Weight Variation

test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average.

The Hardness

of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm2. The hardness of 6 tablets was determined using the Monsanto hardness tester.

The Friability

was determined by first weighing 10 tablets after dusting and placing them in a friability tester (Roche friabilator), which was rotated for 4 min at 25 rpm. After dusting, the total remaining mass of tablet was recorded and the percent friability was calculated.

The Thickness

of the each 10 tablets was measured with a Varnier Caliper.

The Uniformity of Dosage Units

is assessed according to the USP requirements for content uniformity. The batch meets the USP requirements if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 85% to115% of the label claim and the RSD is less than or equal to 6%. According to the USP criteria, if one of these conditions is not met, an additional 20 tablets need to be tested. Not

more that 1 unit of the 30 tested should be outside the range of 85% and 115% of the label claim and no unit outside the range of 75% to 125% of label claim. For all RSD should not exceed 7.8%.

The Disintegration Test

for immediate release layer is determined using the disintegration test apparatus. One tablet was placed in each of six tubes placed in

a beaker containing 1000 ml of purified water maintained at 37 ±2°C and the apparatus was operated. The time taken for the tablets to disintegrate and pass through the mesh was noted.

***In- vitro D*rug Release [22]**

In vitro drug release was performed according to the USP dissolution apparatus II at 50 rpm and 37±0.5ºC temperature over a 24 hrs period for Metformin HCl SR and 1 hr for Glimepiride IR , using an automated paddle dissolution system. A minimum of 6 tablets per batch were tested.

The media used was 0.1N HCl at a pH 2.0 and a volume of 750 ml for the first 2 hours after which 250 ml of 0.2 M sodium phosphate, tribasic, was added to give a final pH of 6.8 and maintained at 37+ 0.5◦C. Test sample (5ml) was withdrawn at particular time interval and replaced with fresh dissolution media maintained at the same temperature and the concentration of dissolved drug was determined using UV (ultraviolet) spectrophotometer at λmax 232 nm for Metformin and 228 nm for Glimepiride (Akihiko I *et al*., 1996; Reddy KR *et al*., 2003; Rahman Z *et al*., 2006).

The evaluation results of the different tablet formulations are shown in Table No.5, 6 and 7.

Table No. 5

Evaluation of Parameters of Bilayer Tablets of Glimepiride IR and Metformin Hcl SR

Formulation Code	Hardness (kg/cm^2)	Friability (% w/w)	Weight Variation (mg)	Thickness (mm)
TF_1	8.5	0.27	1061 ±0.07	6.51
TF_2	8.0	0.31	1109 ± 0.01	6.11
TF_3	8.0	0.16	1099 ± 0.04	6.25
TF_4	8.5	0.19	1115± 0.03	6.43
TF_5	9.0	0.23	1075± 0.02	6.32
TF_6	8.5	0.15	1097 ± 0.05	6.19
TF_7	9.0	0.11	1119 ± 0.07	6.27

Table 6

Evaluation of In- vitro Drug Dissolution Profile of different bilayer formulation

Sr. No.	Test	Speciifcation	PERCENT DRUG RELEASE							
			Innovator product	TF 1	TF2	TF3	TF4	TF5	TF6	TF7
	Glimepiride		Average							
1	0 min	NLT 85% of the labeled amount dissolved in 45 min	0	0	0	0	0	0	0	0
	10 min		90	90	89	91	90	89	90	90
	15 min		94	92	91	93	92	91	92	92
	30 min		97	95	94	95	94	95	95	95
	45 min		97	99	99	98	99	98	99	99
2	**Metformin Hcl**		Average							

	0 Hr	0 %	0	0	0	0	0	0	0	0
	1st Hr	25-40%	32	65	59	51	42	29	31	32
	4th Hr	60-80 %	65	84	81	75	72	59	65	69
	8th Hr	NLT 85%	84	93	93	81	87	83	92	96
	12th hr	NLT 85%	101	105	102	101	102	104	103	103

Table 7
Evaluation of Assay profile of different bilayer formulations

Sr.No.	Test	Speciifcation	PERCENT DRUG RELEASE							
			Innovator product	TF1	TF2	TF3	TF4	TF5	TF6	TF7
1	Glimepiride	95 - 110% of the labeled amount	97	99.1	99.0	99.5	100.2	99.99	102	101.5
2	Metformin Hcl		99	99.5	99.1	99.4	99.7	99.3	99.9	99.7

Stability Studies [23]

The optimized formulation was subjected for two month stability study according to ICH guidelines**.** The selected formulations were packed in aluminium foils, which were in wide mouth bottles closed tightly. They were then stored at Room Temperature 40ºC / 75% RH for 2 months and evaluated for their permeation study.

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RESULTS AND DISCUSSION

Phase Solubility Studies

The complexation of GMP with HP- β -CD was investigated by Phase Solubility Studies. The phase solubility diagram for complex formation is shown in Fig.1.The aqueous solubility of GMP was increased linearly as a function of concentration of CD. The phase solubility diagram can be classified as type AL according to Higuchi and Connors. It is assumed that the increase in solubility observed was due to the formation of a 1:1 M inclusion complex. The solubility constant (Kc) was calculated from the slope of the linear plot of the phase solubility diagram according to equation

$$K_{a:b} = \frac{\text{slope}}{S_0\,(1\text{-slope})}$$

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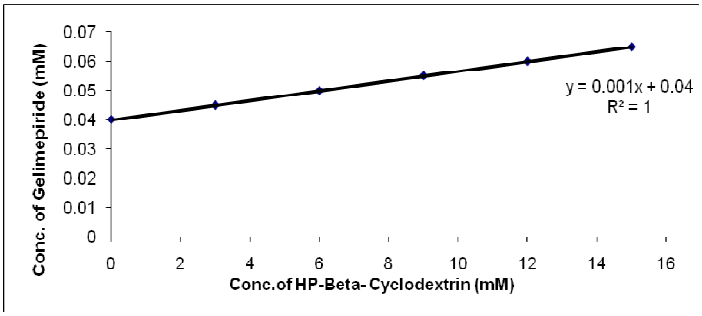

Figure. 1
Plot of Phase Solubility Diagram of Glimepiride with HP-β-CD

Where **So** is the solubility of the drug in absence of CD. The calculated Kc value was 42.57 M^{-1} with HP- β -CD.(Table No.8)

Table 8
Phase Solubility Studies of Glimepiride: HP-β-Cyclodextrin Complexes

Concentration of HP-β-CD (mM)	Concentration of GMP (mM)
0	0.04
3	0.045
6	0.05
9	0.055
12	0.06
15	0.065

B

***Drug Content Estimation in Glimepiride-Inclusion Complex*:**

The inclusion complexes prepared by kneading method showed nearly 100 % drug content.

IR Spectroscopy

IR Spectra of pure drug and inclusion complexes tablets of Glimepiride with HP- β -CD prepared by kneading method as shown in Fig. 2. As clearly seen from the spectra, the characteristic peaks of Glimepride at 709, 1082, 1444, 1674, 1705, 2360 and 3369 were modified significantly as a result of complex formation with HP-Beta-Cyclodextrin

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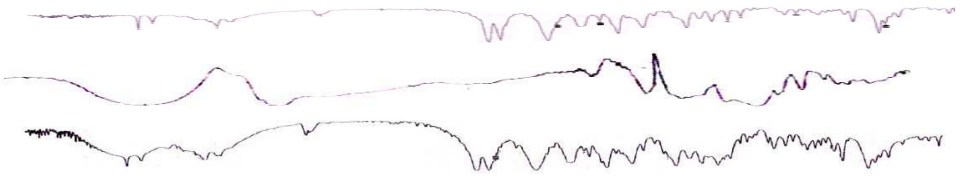
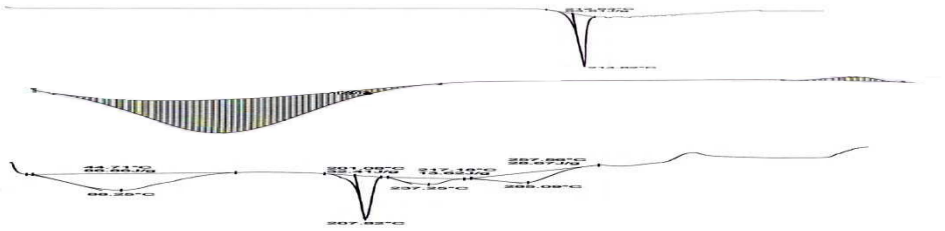


Figure. 2
F.T.I.R. Spectra of (A) Pure Glimepiride, (B)HP-β-CD and (C) Prepared Formulation - FG-I

Differential Scanning Calorimetry (DSC)

The thermal behavior Glimepiride -HP-β-CD complex was studied using DSC in order to confirm the formation of complex. DSC thermogram of Glimepiride, HP-β-CD and FG-I formulation are shown in Fig. 3. The DSC thermogram of Glimepiride showed an endothermic peak at 214°C corresponding to its melting point. The thermogram of FG-I formulation showed endothermic peak at 237°C which is different from the pure drug, which gives clear evidence that there is formation of the complex.



(A)

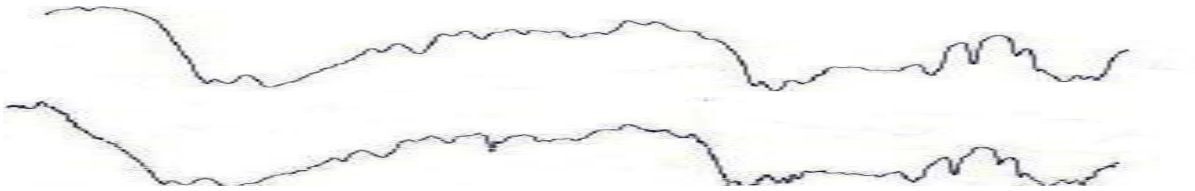
(B)

(C)

Figure. 3
DSC Thermograms of (A) Pure Glomepiride, (B) HP-β-CD and (C) Prepared Formulation - FG-I

Evaluation of Blend

The micromeritic properties such as of bulk density, tapped density, Angle of repose, compressibility index, Hausner's ratio and particle size distribution of Cyclodextrin inclusion complexed Glimepiride immediate release layer blend and Metformin Hcl sustained release layer were studied. The overall results were shown in Table No. 3 and 4.The value of bulk density indicates good packing characteristics. The compressibility index of the formulation found to be below 15 indicating excellent flow properties of granules which were further confirmed by determining the angle of repose, it is in the range of 25° to 27° which indicates good flow properties.



(A)

(B)

Figure. 4
F.T.I.R. Spectra of (A) Pure Metformin Hcl, (B) Prepared Formulation - FM-VII

Evaluation of Tablets

The compressed Tablets were evaluated for weight variation, thickness, hardness uniformity of dosage units and friability. The results of all the 7 formulations (TF1 to TF7) are shown in Table No.5

The drug content of the tablets was assayed by HPLC. The assay results of all the 7 formulations (TF1 to TF7) are shown in Table No. 7

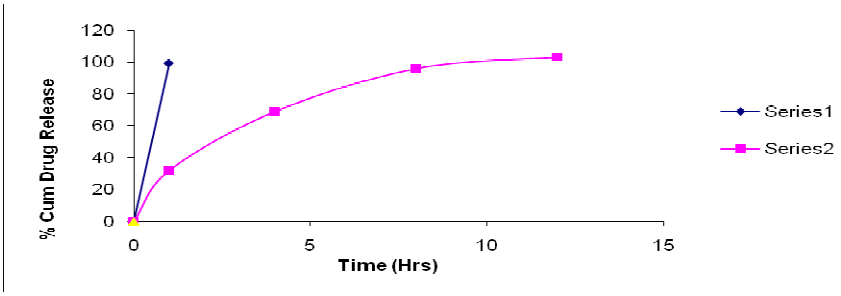


Figure. 5
Plot of Glimepiride IR Layer and Metformin SR Layer for bilater Tablet of best formulation TF7

In vitro Dissolution Study

The *in-vitro* dissolution characteristics of inclusion complexed Glimepiride and Metformin Hcl bilayer tablets are shown Table No.6.Based on the *in-vitro* release profile of drug formulations of TF1 to TF7, the formulation TF7 shown better drug release which was achieved by increasing the polymer concentration ratio of HPMC K-100M and by adding HPMC 15cps which release the drug in a controlled rate at regular time intervals in appropriate concentrations as per the limits. Hence formulation TF7 was selected for further stability studies.

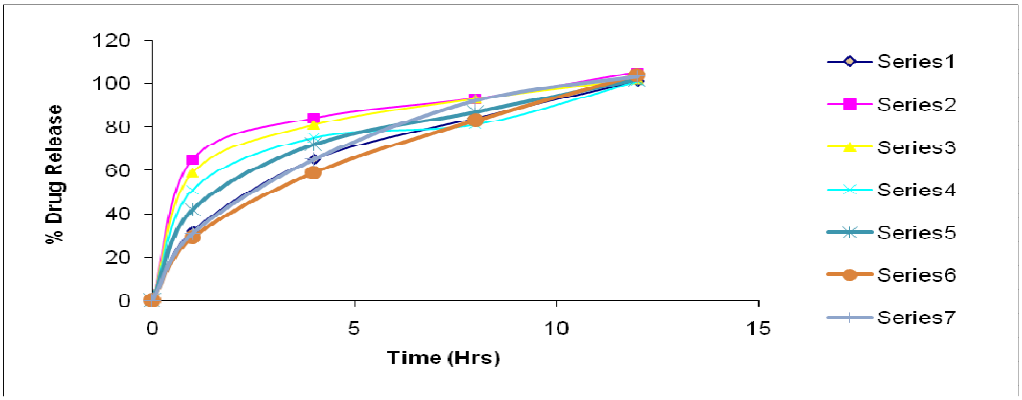


Figure. 6
Plot of Different formulations of Metformin Hcl SR Layer (MF-I to MF-VII)

Stability Studies

The selected formulation TF7 was subjected to accelerated stability studies for 60 days at Room Temperature 40^0C / 75% RH, *in vitro* permeation study was performed on every week and showed negligible change in permeation profile. The formulation subjected for stability studies was found to have no change in the physical appearance and drug content as shown in Table No.9

Table 9
Evaluation of In- vitro Drug Dissolution and Assay Profile of bilayer Tablets of Stability Batch (TF7)

Sr.No.	Test	Speciifcation	CUMULATIVE PERCENT DRUG RELEASE		
			Initial Results	1st Month Results	2nd Month Results
		Glimepiride			
1		NLT 85% of the labeled amount dissolved in 45 min	99.3	99.5	99.2
		Metformin Hcl			
2	1st Hr	25-40%	31	27	29
	4th Hr	60-80 %	69	71	69
	8th Hr	NLT 85%	89	91	90
	12th hr	NLT 85%	101	103	99
		ASSAY			

1	**Glimepiride**	95 - 110% of the labeled amount	100.5	100.1	100.3
2	**Metformin Hcl**		99.7	99.5	99.4

CONCLUSION

The present study was carried out to prove that HP- β –Cylodextrin can be used to used to prepare inclusion complex of Glimepiride with improved solubility of the drug and to develop a bilyaer tablet of inclusion complexed Glimepiride as IR layer and Metformin Hcl as SR layer. HPMC-K-100M, Sodium CMC & HPMC 15cps are used for sustaining the layer of Metformin Hcl. The system provides zero order and near zero order release. This concept also explains the applications of IR/SR from single dosage form.

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