



FORMULATION DEVELOPMENT SCALE UP AND OPTIMIZATION OF CONTROLLED RELEASE HYDROPHILIC MATRIX ORAL DOSAGE FORM OF GLICLAZIDE

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ABSTRACT

The main aim of the experiment is to prepare matrix tablets of Gliclazide and compare them with that of the marketed release formulations and to report the results. Different formulations of tablets were prepared by wet granulation followed by direct compression method and subjected to different evaluation parameters along with comparing with marketed formulations and from the results concluded that the prepared product matches with that of the innovator product in all aspects in all the parameter.

KEY WORDS

Gliclazide, Controlled release

INTRODUCTION

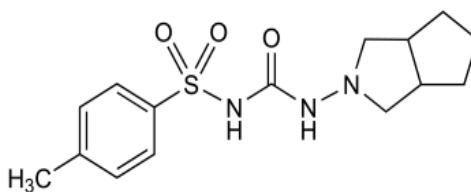
The main aim of this study is Formulate & Optimization of controlled release hydrophilic matrix oral dosage form of Gliclazide by Wet granulation method.

DRUG PROFILE

Gliclazide is an oral antihyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). It belongs to the sulfonylurea class of insulin secretagogues, which act by stimulating β cells of the pancreas to release insulin. Sulfonylureas increase both basal insulin secretion and meal-stimulated insulin release. Medications in this class differ in their dose, rate of absorption, duration of action, route of elimination and binding site on their

target pancreatic β cell receptor. Sulfonylureas also increase peripheral glucose utilization, decrease hepatic gluconeogenesis and may increase the number and sensitivity of insulin receptors. Sulfonylureas are associated with weight gain, though less so than insulin. Due to their mechanism of action, sulfonylureas may cause hypoglycemia and require consistent food intake to decrease this risk. The risk of hypoglycemia is increased in elderly, debilitated and malnourished individuals. Gliclazide has been shown to decrease fasting plasma glucose, postprandial blood glucose and glycosolated haemoglobin (HbA1c) levels (reflective of the last 8-10 weeks of glucose control). Gliclazide is extensively metabolized by the liver; its metabolites are excreted in both urine (60-70%) and feces (10-20%).

GLICLAZIDE :



Chemical class	Sulfonylureas derivative
Chemical name	1-(hexahydrocyclopenta[b]pyrrol-2(1H)-yl)-3-(p-tolylsulfonyl) urea
M.Formula & M.Wt	C ₁₅ H ₂₁ N ₃ O ₃ & 323.4
Melting point	181°C
Solubility	Practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone, slightly soluble in ethanol.
UV absorption	235 nm
Therapeutic category	Hypoglycemic agent

type two diabetes.

• EXCIPIENT PROFILE:

1.	Glimepiride
2.	Lactose monohydrate
3	Hypromellose 100 cps
4	Maltodextrin/Povidone/pregelatinized starch/HPMC low viscosity/ xylitol
5	Colloidal anhydrous silica
6	Magnesium stearate

• INNOVATOR DETAILS:

- Diamicon XR 60 Mg
- Indication: TYPE II diabetes mellitus

SNO		INGREDIENTS	AMOUNT
	Internal Phase:		
1		Gliclazide	60mg
2		Lactose	71.36
3		HPMC 100 cp	64.00
4		Maltodextrin	22.00
5		Anhydrous colloidal silica	4.4
	External Phase:		
6		Hpmc 100cp	96.00 mg
7		Magnesium stearate	1.6 mg
8		Anhydrous colloidal silica	0.64
		Total weight	320.00

FORMULATION 1:

OBJECTIVE: Formulation of controlled release tablets was found by using formula

SNO	EXCIPIENTS	FORMULATION 1
1	Intragranular	With 18% FU, 3 min KT
2	Gliclazide	300
3	HPMC 100CP	350
4	Lactose Monohydrate	456.8
5	Anhydrous colloidal silica	22
6	Maltodextrin	110
Total		1239
7	P.Water	223
8	Extragranular	
9	HPMC 100 CP	350
10	Anhydrous colloidal silica	3.2
11	Magnesium Stearate	8
	Total weight of tablet	1600

- **Formulation 2:**

- **Objective:** To take a trial similar to F-1 except for maltodextrin to be replaced with povidone k30

SNO	EXCIPIENTS	FORMULATION 2
1	Intragranular	With 14% FU, 2min KT
2	Gliclazide	300
3	HPMC 100CP	350
4	Lactose Monohydrate	456.8
5	Anhydrous colloidal silica	22
6	Povidone K30	110
Total		1239
7	P. Water	173
8	Extragranular	
9	HPMC 100 CP	350
10	Anhydrous colloidal silica	3.2
11	Magnesium Stearate	8
	Total weight of tablet	1600

- **Formulation 3:**

- **Objective:** To take a trial similar to f-1 except for maltodextrin to be replaced with pregelatinised starch.

SNO	EXCIPIENTS	FORMULATION 3
1	Intragranular	With 22% FU, 4 min KT
2	Gliclazide	300
3	HPMC 100CP	350
4	Lactose Monohydrate	456.8
5	Anhydrous colloidal silica	22
6	Pre gelatinised starch	110
Total		1239
7	P. Water	273
8	Extragranular	
9	HPMC 100 CP	350
10	Anhydrous colloidal silica	3.2
11	Magnesium Stearate	8
	Total weight of tablet	1600

• Dissolution Media: pH 7.5 Phosphate buffer

TIME	FORMULATION 3	
	Avg dissolution	%RSD
1	10	7.4
2	22	6.6
4	44	5.5
6	64	4.2
8	80	4.2
10	92	3.8
12	99	2.5
16	101	2.1

• RESULT & CONCLUSION:

- The dissolution profile is comparatively slower than innovator dissolution profile.
- Therefore to pocessed with povidone batchby forming light granules.

• FORMULATION 4 :

- **Objective :** To take a trial similar to F-2 by preaparing light granules by reducing water quantity from 250g to 200g.

Gliclazide	60mg
HPMC K100LVCR	70mg
Lactose monohydrate	91.36mg
aerosil 200	4.4mg
Povidone K30	22mg
P. water	200g
HPMC K100LVCR	70mg
aerosil 200	0.64mg
magnesium stearate	1.6mg
Total	320mg
Fluid uptake%	15%
Binder addition time	90 sec
Kneading time	5 min

Occupancy in Blender	BD	TD	CI	HR
60.3%	0.51	0.675	24.528	1.325

SCIENTIFIC RATIONAL:

- In trial GLT-003 (with povidone) the release of the tablet is slower compared to innovator therefore to match the dissolution profile by making lighter granules.

• Dissolution in 0.01N HCL followed by ph 6.8 Phosphate

	2hr 0.01N HCL	6.8 PB	6.8 PB	6.8 PB	6.8 PB	6.8 PB	6.8 PB	6.8 PB	6.8 PB	6.8 PB	6.8 PB
TIME	2hr	1hr	2hr	4hr	6hr	8hr	10hr	12hr	16hr	20hr	24hr
	4	13	22	38	50	62	74	84	87	88	89

• FORMULATION 5:

- Objective:** To take a trial similar to F-4 except by increasing the aerosol in intragranular part (from 4.4 mg/tab to 6.0/tab) by preparing light granules by reducing water quantity from 250 to 200g.

Gliclazide	60mg
HPMC K100LVCR	70mg
Lactose monohydrate	91.36mg
aerosil 200	4.4mg
Povidone K30	22mg
P. water	200g
HPMC K100LVCR	70mg
aerosil 200	6.0mg
magnesium stearate	1.6mg
Total	320mg
Fluid uptake%	12%
Binder addition time	90 sec
Kneading time	12 min

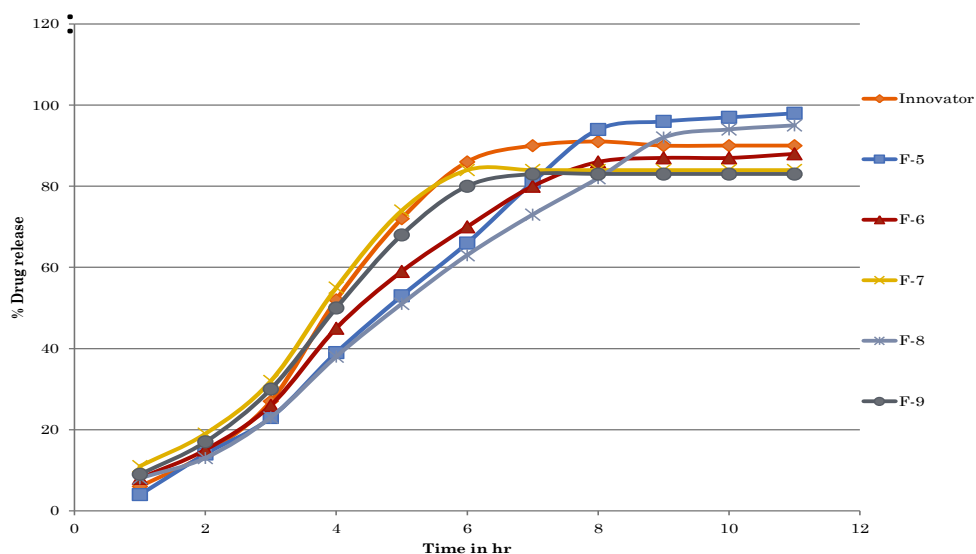
Occupancy in Blender	BD	TD	CI	HR
53.16%	0.560	0.651	14.00	1.163

- SCIENTIFIC RATIONAL:**
- In trial GLT-003(with povidone) release of the tablet is slower compared to innovator therefore to match the Dissolution profile by making lighter granules.

Dissolution in 0.01N HCl followed by pH 6.8 Phosphate buffer (TYPE I,100 rpm)

	2hr 0.01N HCL	6.8 PB	6.8 PB	6.8 PB	6.8 PB	6.8 PB	6.8 PB	6.8 PB	6.8 PB	6.8 PB	6.8 PB
TIME	2hr	1hr	2hr	4hr	6hr	8hr	10hr	12hr	16hr	20hr	24hr
	4	14	23	39	53	66	81	94	87	96	97

- Dissolution graph of different formulation**



• Dissolution Media: pH 7.5 Phosphate buffer

TIME	FORMULATION 5	
	Avg dissolution	%RSD
1	10	8.9
2	21	10.0
4	41	7.7
6	59	6.5
8	76	6.0
10	89	5.2
12	98	3.2
16	101	0.8

RESULT & CONCLUSION: The dissolution profile has slightly increased. To perform a trial batch to see the impact of povidone on dissolution.

- **Formulation 6:**
- **Confirmatory Batch for Gliclazide Extended Release tablets 60mg: Objective**
:Based on the in process and finished product analytical data confirmatory batch was planned to scale up manufacturing process of Gliclazide extended release tablets 60mg

S. No.	Ingredients	mg / tablet	(Confirmatory batch) Kg
1	Gliclazide * IP	60.00	24.00
2	Hypromellose (Methocel K100LVCR) USP	70.00	28.000
3	Lactose monohydrate (Impalpable)** NF	91.36	36.544
4	Colloidal Silicon Dioxide NF	4.40	1.760
5	Povidone (Plasdone K29/32) IP	22.00	8.80
6	Purified water ^s IP	qs	11.892
7	Hypromellose (Methocel K100LVCR) USP	70.00	28.000
8	Colloidal Silicon Dioxide NF	0.64	0.256
9	Magnesium stearate IP	1.60	0.64
Total weight		320.00	

SCIENTIFIC RATIO :

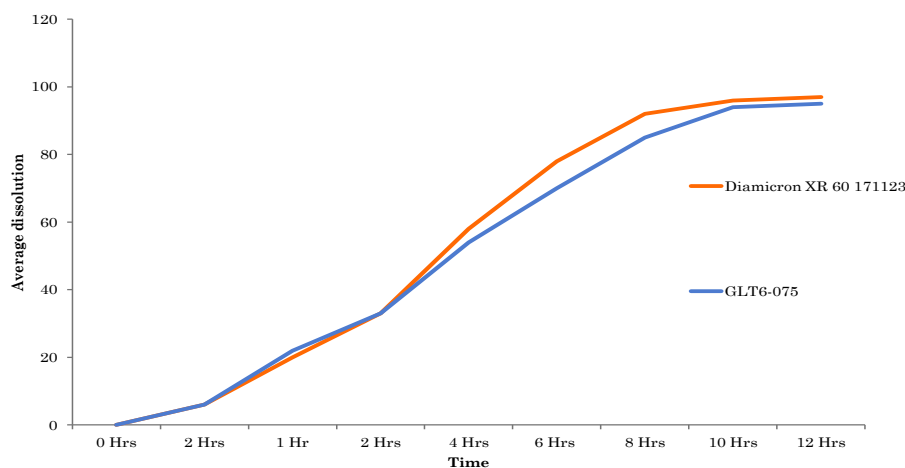
The release of Gliclazide MR 60 MG tablets is slower by 8% in 6 th hour in pH 6.9 phosphate buffer, therefore the conc. of anhydrous colloidal silica in increased from 4.4 mg/tab to 5.0 mg/tab as it acts as hydrophylising

agent.

Media	Time	F 6	% RSD
0.01 N HCl	2 Hrs	6	63.7
pH 6.8	1 Hr	22	8.7
	2 Hrs	33	5.5
	4 Hrs	54	4.2
	6 Hrs	70	3.2
	8 Hrs	85	3.5
	10 Hrs	94	6.3
	12 Hrs	95	7.8

Dissolution in 0.01N HCl followed by pH 6.8 Phosphate buffer, USP Type I, 900mL, 100rpm

Dissolution in 0.01N HCl followed by pH 6.8 Phosphate buffer



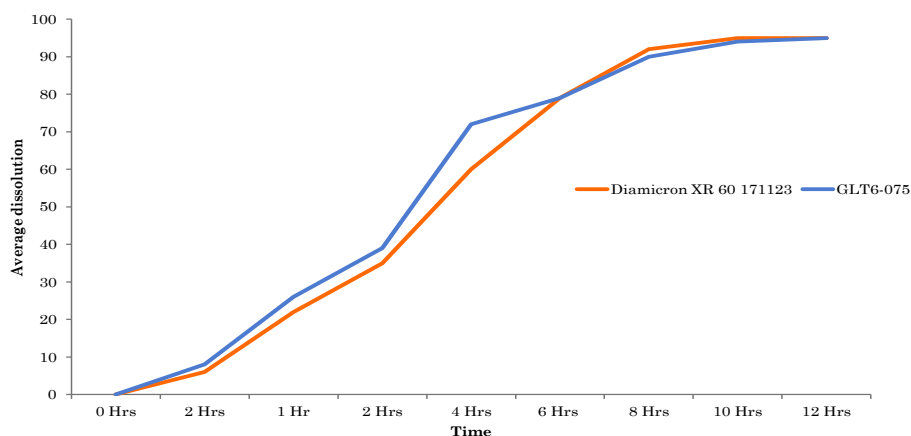
• Dissolution: In 0.01N HCL pH 7.4 Phosphate

TIME		FORMULATION 5	
		Avg dissolution	%RSD
Media	Time(hr)		
0.01 N HCl	2 Hrs	8	69.8
pH 7.4	1 Hr	26	7.9
	2 Hrs	39	5.4
	4 Hrs	72	6.7
	6 Hrs	79	8.1
	8 Hrs	90	9.9
	10 Hrs	94	12.2
	12 Hrs	95	12.5

RESULT & CONCLUSION:

The dissolution profile is similar to innovator weight to check feasibility and cost effectiveness

Dissolution in 0.01N HCl followed by pH 7.4 Phosphate buffer



CONCLUSION

- The results of the tablets were matching with the innovator in release media pH 7.5 phosphate buffer.
- The results of the tablets were matching with the Innovator in 0.01N HCl followed by pH 6.8 phosphate buffer.
- The results of the tablets were matching with the Innovator in 0.01N HCl followed by pH 7.4 phosphate buffer.
- The results of the tablets were matching with the Innovator in pH 5.8 FeSSIF.
- The results of the half tablet were matching with the Innovator in pH 7.5 phosphate buffer.

- The results of the half tablet were matching with the Innovator in 0.01N HCl followed by pH 6.8 phosphate buffer.
- The results of the half tablet were matching with the Innovator in 0.01N HCl followed by pH 7.4 phosphate buffer

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