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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 Gliclizide 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 that the prepared product matches with that of the innovator product in all aspects in all the parameter.

KEY WORDS

Gliclizide, Controlled release

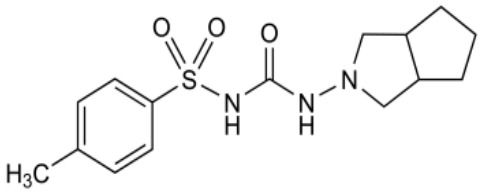
INTRODUCTION

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-(hexahydocyclopenta©pyroll-2(1H)-yl)-3-(p-tolysulfonyl) urea
M.Formula & M.Wt	$C_{15}H_{21}N_3O_3$ & 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.	Gliclazide
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:

- Diamicron 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 sillica**	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 sillica**	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 sillica**	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

- FORMLATION 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**

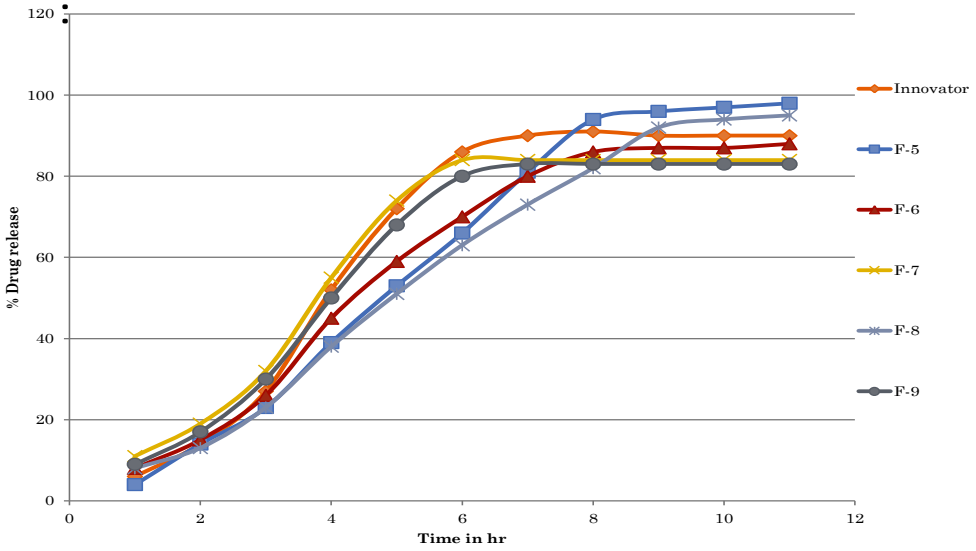
Occupancy in Blender	BD	TD	CI	HR
53.16%	0.560	0.651	14.00	1.163

- **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$ 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**	

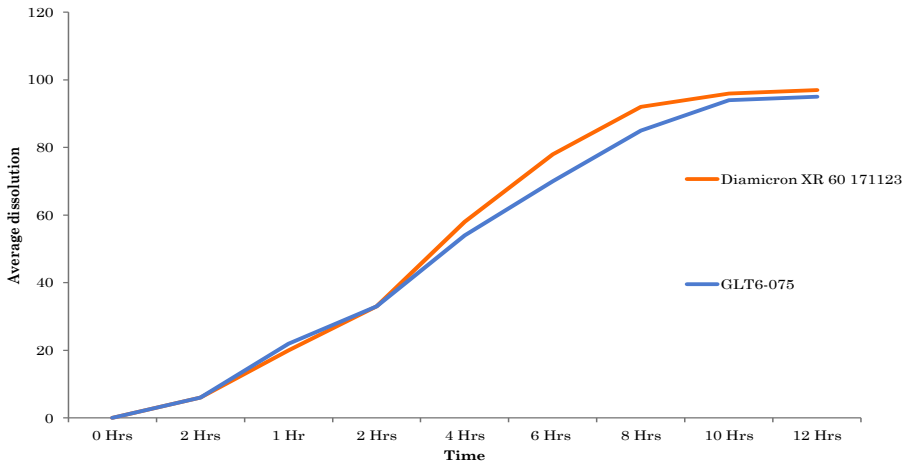
SCIENTIFIC RATIO :

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.D

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



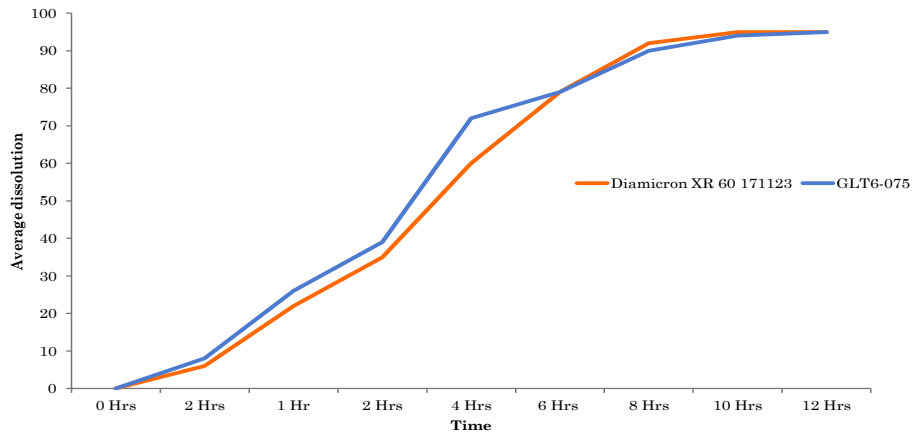
- Dissolution: In 0.01N HCL pH 7.4 Phosphate

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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