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Research Article

Formulation and evaluation of bilayered tablets of sustained release metformin HCl and gliclazide

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ABSTRACT

The aim of the present work is to formulate and evaluate a bilayered tablet (BT) of Metformin HCl as Sustained release and Gliclazide as Immediate release (IR). The polymer used in sustained release is HMPC K100M and the super disintegrate used in immediate release in proportion of Gum Karaka & Croscarmellose sodium by direct compression method. In this study, a bilayered tablet containing Gliclazide in IRL and Metformin in SRL was made using the wet granulation method, with the goal of making the formulations IRL as small as possible, Will release Gliclazide as soon as possible to combat postprandial hyperglycemic level, followed by steady-state plasma glucose management by Metformin with a long-term release. The hardness of the different formulations ranged from 7.5-8.5 kg/cm. All the formulations exhibited less than1% friability. The drug content analysis of Metformin and Gliclazide in all formulations was found within the IP limits (±5%) which indicate that the drug was uniformly distributed in the tablets. The inviter dissolution study was performed for layer I (Metformin) up to 12 hrs (after every 1hour intervals) and for layer II (Gliclazide) up to 40 min (after every 5 min interval). The bilayered tablet contributing initial loading dose and dissolves rapidly, the remainder of the drug in the extended release was constant rate till the end of the dissolution process. The I.R spectra proved that there was no interaction between the polymer, Excipients and Metformin, Gliclazide.

Keywords: Metformin HCl, gliclazide, Immediate release layer

INTRODUCTION

Diabetes is a disease that occurs when your blood glucose, also called blood sugar, is too high. Blood glucose is your main source of energy and comes from the food you eat. Insulin, a hormone made by the pancreas, helps glucose from food get into your cells to be used for energy. Sometimes your body doesn't make enough—or any—insulin or doesn't use insulin well. Glucose then stays in your blood and doesn't reach your cells.

Over time, having too much glucose in your blood can cause health problems. Although diabetes has no cure, you can take steps to manage your diabetes and stay healthy.

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TYPES OF DIABETES

TYPE 1:

- This type is an autoimmune disease, meaning your body attacks itself. In this case, the insulin-producing cells in your pancreas are destroyed. Up to 10% of people who have diabetes have Type1.
- It's usually diagnosed in children and young adults (but can develop at any age). It was once better known as "juvenile" diabetes. People with Type 1 diabetes need to take insulin every day. This is why it is also called insulin-dependent diabetes.

TYPE 2:

- With this type, your body either doesn't make enough insulin or your body's cells don't respond normally to the insulin. This is the most common type of diabetes. Up to 95% of people with diabetes have Type2.
- It usually occurs in middle-aged and older people. Other common names for Type 2 include adult-onset diabetes and insulin-resistant diabetes. Your parents or grandparents may have called it "having a touch ofsugar.

PREDIABETES

This type is the stage before Type 2 diabetes. Your blood glucose levels are higher than normal but not high enough to be officially diagnosed with Type 2diabetes.

GESTATIONAL DIABETES

This type develops in some women during their pregnancy. Gestational diabetes usually goes away after pregnancy. However, if you have gestational diabetes you're at higher risk of developing Type 2 diabetes later on in life.

CAUSES OF DIABETES

Causes of Type-1 Diabetes: This is an immune system disease. Your body attacks and destroys insulin-producing beta cells in your pancreas. Without insulin to allow glucose to enter your cells, glucose builds up in your bloodstream. Genes may also play a role in some patients. Also, a virus may trigger the immune system attack.

Causes of Type 2 Diabetes and Prediabetes: Your body's cells don't allow insulin to work as it should to let glucose into its cells. Your body's cells have become resistant to insulin. Your pancreas can't keep up and make enough insulin to overcome this resistance. Glucose levels rise in your bloodstream. Diabetes is more common in people who are overweight, obesity, not physically active.

Gestational Diabetes: Hormones produced by the placenta during your pregnancy make your body's cells more resistant to insulin. Your pancreas can't make enough insulin to overcome this resistance. Too much glucose remains in your bloodstream.

SYMPTOMS:

Symptoms of diabetes include:

- Increased thirst
- Weak, tired
- Feeling
- Blurred vision
- Numbness or tingling in the hands or feet
- Slow-healing sores or cuts
- Unplanned weight loss
- Frequent urination
- Dry mouth.
- Frequent unexplained infections.

TREATMENT

MEDICATION FOR TYPE -1DIABETES INSULIN:

Insulin is the most common type of medication used in type 1 diabetes treatment.

SHORT-ACTING INSULIN:

Regular insulin (Hamelin and Novo in N)

IMMEDIATE – ACTING INSULIN:

Insulin ecophene (Hamelin N, Novo in N)

LONG-ACTING INSULINS:

Insulin delude (Teresina) Insulin deemed (Lexemic) Insulin glaring (lentos) Insulin glaring (Toupee)

MEDICATION FOR TYPE -2 DIABETES

Diet and exercise can help some people manage type 2 Diabetes. If lifestyle changes aren't enough to lower your blood sugar, you'll need to take medication

Types of drug	How they work	Example(s)
Alpha-glycosidase inhibitors	Slow your body's breakdown of sugars and starchy foods	Carbone (Precise) and miglitol (Gayest)
Iguanids	Reduce the amount of glucose your liver makes	Metformin (Glucophage)
DPP-4 inhibitors	Improve your blood sugar without making it drop too low	Sitagliptin (Trident), sitagliptin (Anglia), and sitagliptin (Jan via)
Glucagon-like peptides	Change the way your body produces insulin	Dulaglutide (Trulicity), exenatide (Byetta), and liraglutide (Victoza)
Meglitinides	Stimulate your pancreas to release more insulin	Nateglinide (Starlit) and repaginate (Prancing)
SGLT2 inhibitors	Release more glucose into the urine	Canagliflozin (Invokana) and dapagliflozin (Farxiga)
Sulfonylurea's	Stimulate your pancreas to release more insulin	Glyburide (Diabetes, Glynatsis), glipizide (Glucotrol), and glimepiride (Am aryl)
Thiazolidinediones	Help insulin work better	Pioglitazone (Actos) and rosiglitazone (Avanti)

Aim: Formulation and evaluation of Metformin HCL and Gliclazide sustained release bilayered tablets.

Objectives: The main objective of the present investigation is to develop sustained-release (SR) formulation to optimize the postprandial evaluation of glucose level in type 2 diabetic subjects using combination therapy. In the present research work bilayered sustained release formulation of Metformin HCL (MFH) and (GLZ), based on monolithic-matrix technology is to be developed and evaluated

MATERIALS REQUIRED

- Metformin HCL
- Hydroxy propyl methyl cellulose K100M(HPMC)
- Polyvox WSR Coagulant
- Micro crystalline cellulose (MCC)
- Mannitol
- Polyvinyl pyrrolidone (PVP) K 30
- Isopropyl Alcohol (IPA)
- Gliclazide
- Dicalcium Phosphate (DCP)
- HPMC K4M
- HPMC K 15M
- Iron oxide yellow
- Sodium alignate
- Magnesium stearate

CALIBRATION CURVE OF METFORMIN

UV SPECTROPHOTOMETRIC ANALYTICAL METHOD FOR METFORMIN HCL

PRINCIPLE: Metformin HCL is reported to exhibit λ_{max} at 234nm

100 mg of metformin HCL was accurately weighed and dissloved in 100 ml to get a stock solution of 1 mg/ml. Further, an aliquot was pipette out and diluted suitably to get the concentration in the Beer's range. The aliquot was scanned in the wavelength region nm to record the wavelength of maximum absorption (λ_{max})

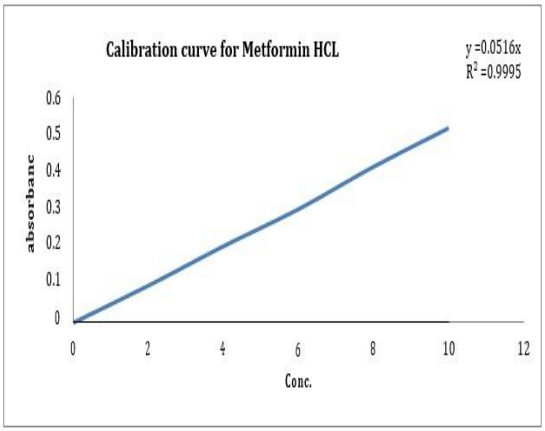
ASSAY OF METFORMIN HCL

Metformin HCL accurately weighed and transferred into 100ml volumetric flask about 10 ml of 0.1N HCL was added, sonicated it for 10 min with occasional shaking, then about 50 ml of diluent was added and sonicated for 10 min with occasional swirling to dissolve and volume was made with diluent. Solution was filtered through 0.**45** µm membrane filter (200 µg/ml of metformin HCL). Percentage purity of metformin HCL was determined.

CALIBRATION CURVE FOR METFORMIN HCL

Preparation of standard stock solution: 100mg of metformin HCL was accurately weighed and transferred into 100 ml volumetric flask. About 100 ml diluent is added, sonicated for 10 min, diluted and mixed (200 µg/ml of metformin HCL). Serial concentration of 0, 2,4,6,8, and 10 µg/ml solutions were prepared and scanned for absorbance and graph is plotted between concentration (µg/ml) and absorbance on x –axis and y-axis respectively.

CONCENTRATION (µg)	ABSORBANCE (234nm)
0	0
2	0.099
4	0.204
6	0.303
8	0.416
10	0.519



CALIBRATION CURVE OF GLICLAZIDE

UV SPECTROPHOTOMETRIC ANALYTICAL METHOD FOR GLICLAZIDE

Principle: Gliclazide is reported to exhibit λ_{max} at 217nm

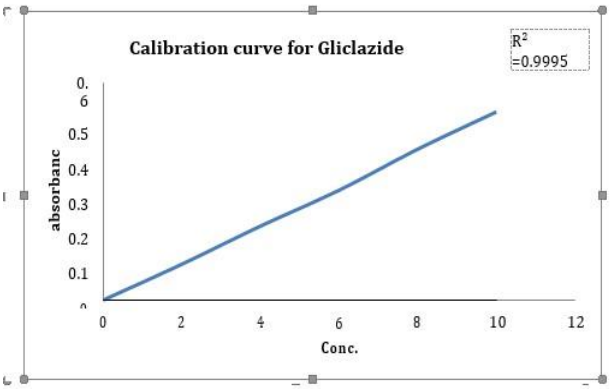
Procedure: **100 mg** of gliclazide was accurately weighed and dissolved in 100 ml to get a stock solution of 1 mg/ml. Further, an aliquot was pipette out and diluted suitably to get the concentration in the Beer's range. The aliquot was scanned in the wavelength region nm to record the wavelength of maximum absorption (λmax).

ASSAY OF GLICLAZIDE: Gliclazide accurately weighed and transferred into 100ml volumetric flask, about 10 ml of 0.1N gliclazide was added, sonicated it for 10 min with occasional shaking, then about 50 ml of diluent was added and sonicated for 10 min with occasional swirling to dissolve and volume was made with diluent. Solution was filtered through 0.45 µm membrane filter (200 µg/ml of gliclazide). Percentage purity of gliclazide was determined.

CALIBRATION CURVE FOR GLICLAZIDE

Preparation of standard stock solution: 100mg of gliclazide was accurately weighed and transferred into 100 ml volumetric flask. About 100 ml diluent is added, sonicated for 10 min, diluted and mixed (200 µg/ml of gliclazide f). Serial concentration gliclazide f 0, 2,4,6,8, and 10 µg/ml solutions were prepared and scanned for absorbance and graph is plotted between concentration (µg/ml) and absorbance on x –axis and y-axis respectively.

CONCENTARION(µg)	ABSORBANCE(217nm)
0	0
2	0.065
4	0.137
6	0.204
8	0.271
10	0.353



METHOD OF PREPARATION:

PREPARATION OF METFORMIN HCL

All the ingredients passed through a 60 mesh sieve a blend of all ingredients was mixed thoroughly in a rapid mixer granulator resulting in a homogenization and granulated manually with a binder solution. It was prepared by dissolving PVP K30 in IPA the wet masses were passed through a 12 mesh sieve. The wet granules produced was initially air –dried for 10 min and finally at 45-50 centigrade in a tray dryer for 2 hr until the LOD

(loss on drying) of granules reached moisture limit between 2-3 %w/w. The dried granules sieved by 16 mesh sieves were lubricated with magnesium stearate and compressed to tablets. Formulations were prepared using polio WSR coagulant as retardant along with other recipients. The ingredients passed through a 60-mesh sieve, mixed thoroughly in a rapid mixer granulator, lubricated and compressed. Before compression, the final blend was evaluated for its flow and compressibility characteristics. All the tablets compressed using cad mach single punch tablet compression machine with 12 mm concave punch were stored in airtight containers for further study.

Composition of Metformin HCL Layer:

Ingredients (mg)	**Formulation**		**code**				
	M1	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**
Metformin hydrochloride	100	100	100	100	100	100	100
HPMC K100M	120	160	200	240	-	-	-
PolyvoxWSR coagulant	-	-	-	-	160	220	210
MCC	140	100	60	20	-	-	-
Mannitol	-	-	-	-	95	35	45
PVP K 30	25	25	25	25	25	25	25
IPA	qs	qs	qs	qs	qs	qs	qs

PREPARATION OF GLICLAZIDE

The granules were prepared by wet granulation method. The ingredients passed through a 60 mesh sieve. A blend of all ingredients except gliding and lubricant mixed thoroughly in a rapid mixture granulator resulting in phase homogenization and granulated manually with blender solution prepared by dissolving PVD K30IPA. The wet masses were passed through a 12 mesh sieve and wet granules produced was initially air-dried for 10 min and finally at 45-50 centigrade in a tray dryer for 2hr until the LOD (loss on drying) of granules reached moisture limit between 2-3 %w/w. The dried granules sieved by a 16 mesh sieve were lubricated with magnesium stearate and compressed to tablets. Before compression, the granules were evaluated for pre-compression parameters.

Ingredients (mg)	**Formulation**		**code**				
	G1	**G2**	**G3**	**G4**	**G5**	**G6**	**G7**
Gliclazide	60	60	60	60	60	60	60
DCP	90	70	50	90	80	70	90
HPMC K4M	20	30	40	-	-	-	-
HPMC K15M	-	-		20	30	40	-
HPMC K100M	-	-	-	-	-	-	20
PVP K30	6	6	6	6	6	6	6
Iron oxide yellow	0.5	0.5	0.5	0.5	0.5	0.5	0.5
SA	20	20	20	20	20	20	20
IPA	as	as	as	Qs	as	as	as
Magnesium stearate	4	4	4	4	4	4	4

PREPARATION OF BILAYER TABLET

300mg of Metformin HCL is punched first, and then introduce 200 mg of Gliclazide into die wall of tablet machine then double punch to form bilayered tablet.

RESULTS AND DISCUSSION

Evaluation

All tablets appeared smooth and oblong. The weight of the Metformin hydrochloride layer was kept constant to 800 mg. All tablet batches qualify the tablet weight variation test and found variation 100±5 % within range; friability below 1%; drug content 90-110% within limit and deviation in thickness found less than 5%. Results of post-compression parameters of Metformin hydrochloride tablets were observed in table 6. The optimized Metformin hydrochloride formulation was further used to prepare bilayered tablets using different Gliclazide formulations. Results of post-compression parameters of bilayered tablets were observed in table 7.

Table 6: Post compression parameters of Metformin hydrochloride formulations M1– M7

Formulation code	Weight variation (mg)	Hardness (Kg/Cm^2)	Thickness (mm)	Friability (%)	Content uniformity % (layer 1)
M1	800±0.19	7.5±0.23	5.1±0.21	0.41±0.002	99.28±0.57
M2	800±0.38	7.8±0.24	5.02±0.15	0.68±0.005	99.57±0.86
M3	800±0.79	8.5±0.23	5.04±0.23	0.53±0.005	99.75±0.36
M4	800±0.74	8.9±0.26	5.08±0.42	0.36±0.008	99.78±0.87
M5	800±0.56	8.3±0.93	5.11±0.33	0.86±0.002	98.68±0.28
M6	800±0.49	8.5±0.27	5.04±0.13	0.72±0.004	99.83±0.39
M7	800±0.68	8.4±0.23	5.03±0.26	0.93±0.007	99.95±0.26

Means, n = 3

Table 7: Post compression parameters of Gliclazide formulation G1-G8

Formulation code	Weight variation	Hardness (mg)(Kg/Cm^2)	Thickness (mm)	Friability (%)	Content uniformity (%) (Layer 2)
G1	200±0.67	7.5±0.23	2.11±0.03	0.54±0.0098	98.5±0.83
G2	200±0.29	6.7±0.28	2.01±0.83	0.67±0.0021	99.4±0.75
G3	200±0.57	7.4±0.83	2.13±0.12	0.49±0.0024	99.3±0.62
G4	200±0.75	8.5±0.26	2.17±0.08	0.81±0.0027	99.7±0.69
G5	200±0.38	8.5±0.73	2.04±0.42	0.32±0.0037	99.5±0.62
G6	200±0.32	8.8±0.27	2.08±0.16	0.65±0.0073	98.6±1.04
G7	200±0.61	8.5±0.74	2.04±0.28	0.87±0.0028	98.6±1.67
G8	200±0.85	8.6±0.51	2.03±0.34	0.62±0.0065	99.7±0.19

COMPRESSION PARAMETERS OF METFORMIN HCL FORMULATION

WEIGHT VARIATION TEST: This is an important in process quality control test checked frequently. Any variation in the weight of tablets leads ton under medication or overdose. This is particularly true when drug are potent. All tablets machines have provision to receive a known quantity of powder.

HARDNESS:

Hardness indicates the ability of the tablet to withstand mechanical shocks while handling. The

hardness of tablet was determined using Monsanto hardness tester, Pfizer tester.

THICKNESS:
Tablet thickness is determined by the diameter of the tablet.
Micrometer and vernier caliper are used for checking tablet thickness. Thickness should be controlled within ±5% variation of standard value

FRIABILITY:
The friability of tablets was determined using ruche friabilator. It is expressed in %.Twenty tablets were weighed and transferred into friabilator. The test is performed to ensure the ability of tablets to withstand the shocks during processing handling transportation and shipment. The friabilator was operated at 25 rpm for 4 min or run up to revolutions. The tablet were weighed again, the % friability is calculated.

CONTENT UNIFORMITY:
Weight of contents of 20 tablets was determined and average weight was calculated. Requirements are met if not more than two of the individual weights deviate from average weight by more than 10% and none deviates by more than 20%.

DISINTEGRATION:
Disintegration is defined as that state in which any residue of tablet, except fragments of insoluble coating, remaining on the screen of the test apparatus consisting of a soft mass having no palpably firm, unmoistened core. Disintegration process involves breaking of tablet into small particles. The quicker the disintegration, the faster could be the action. Disintegration roughly indicates the possible of dissolution of active substances. The disintegration time should be as less as possible unless otherwise specifies as in case of special type-controlled release products.

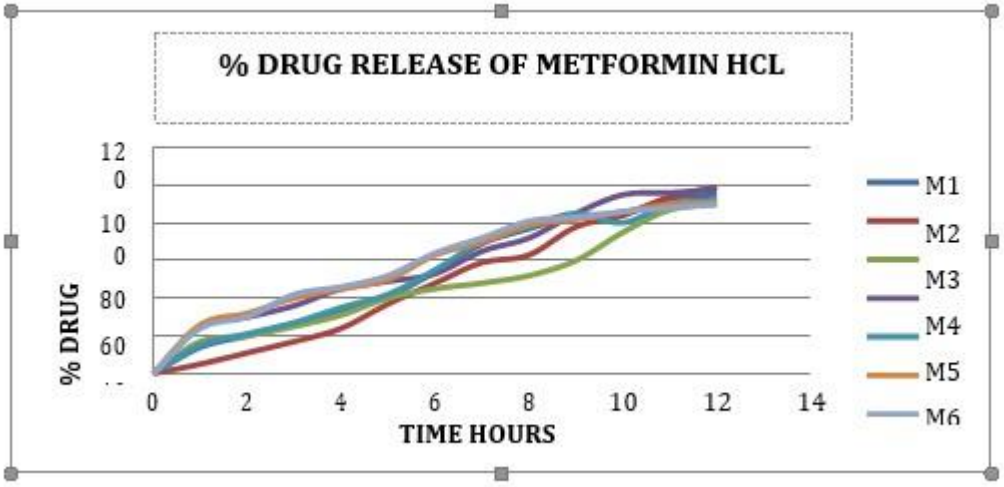
DISSOLUTION STUDIES:
The results of this test depend on the solubility of the active substance. It is conducted only on the finished products as the procedure involved in time consuming. Dissolution rate has direct relevance in the performance of dosage especially to predict rate and extend of drug absorption or bioavailability. Usually apparatus type 2(basket type) is used for partially water soluble drugs, while type 1(paddle type) is employed in the evaluation of tablets containing poorly water soluble drugs. The results are plotted as concentration vs. time. This test has greater importance in the evaluation of the sustained and controlled release products

In vitro dissolution studies of the sustained-release layer containing Metformin hydrochloride
All the formulations subjected to *in vitro* dissolution studies revealed that tablets containing release modifiers exhibited sustained release of Metformin hydrochloride and Gliclazide. The dissolution profile of formulations containing Metformin hydrochloride was represented in fig. The dissolution profile of Metformin hydrochloride formulation revealed that M1-M4 formulations released the drug completely by the end of 12 h, which is probably due to faster dissolution of the highly water-soluble drug from the core and its diffusion out of the matrix forming the pores for the entry of solvent molecules. A suitable sustained-release formulation should release the required amount of drug in the initial hour, followed by slow release. Formulation M4 (30% HPMC K100M) exhibited the slowest dissolution profile which was consistent with USP specification. In contrast, the release of Metformin hydrochloride from formulation M5-M7 prepared using polio WSR coagulant was extended up to 24 h. Batch M7 prepared by direct compression method using polio WSR coagulant (25%) exhibited a good drug release profile. Data of comparison of formulations M4 and M7 with innovator by similarity and dissimilarity factor represented in table 8 reveals that M7 is the promising batch and selected as the best formulation for further studies.

Table 8: Comparison of formulations with innovator by similarity and dissimilarity factor

Time(HRS)	M1	M2	M3	M4	M5	M6	M7
0	0	0	0	0	0	0	0
1	14	25	17	5	15	26	24
2	20	30	20	11	21	32	30
3	26	36	25	17	27	40	42
4	34	45	31	24	35	45	46
5	41	49	40	37	42	50	52
6	54	53	45	48	55	63	64

7	69	65	48	59	70	70	72
8	77	72	52	63	78	79	81
9	84	85	60	78	85	82	83
10	85	95	75	84	80	86	86
11	93	96	87	94	90	90	88
12	95	98	90	99	92	91	90



Sustained-release layer containing Gliclazide

The dissolution profile of Gliclazide formulations was represented in fig. All Formulations displayed a cumulative release of nearly 84 in 40 minutes where 40% of polymers HPMC K4M and K15M were employed. In contrast, the formulation G4 exhibited a better-controlled release profile of 99.8% at 24 h as represented in fig.

TIME	G1	G2	G3	G4	G5	G6	G7
0	0	0	0	0	0	0	0
5	21	36	10	37	18	28	22
10	27	45	15	42	23	31	30
15	35	54	20	53	30	42	36
20	42	68	30	66	38	58	45
25	55	82	37	72	53	62	57
30	65	82	50	87	72	70	62
35	73	82	66	96	78	76	73
40	82	83	84	99	82	80	81

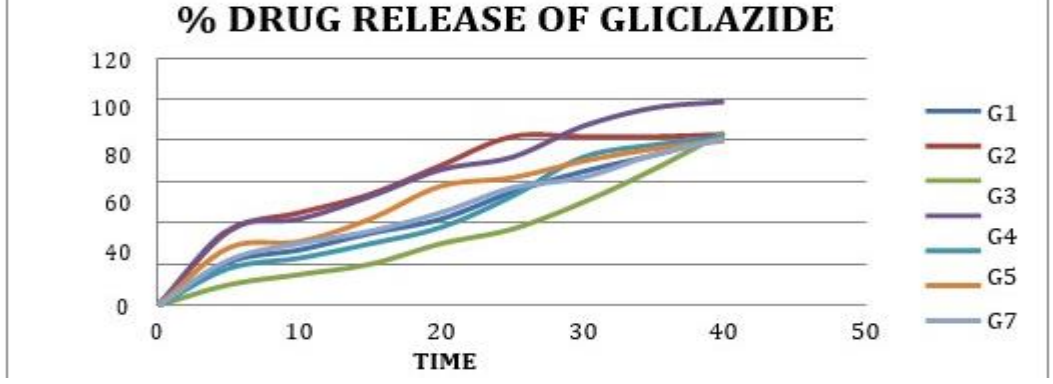


Fig. 5: *in vitro* dissolution profile of Gliclazide formulation G1-G7

Here, the polymer HPMC K100M showed a better rate of retardant ability than the above two variants at a lesser concentration. The hydration rate of HPMC increases with an increase in the Hydroxyl Propel content and the solubility of HPMC are pH-independent. The water- repelling property of higher variants of HPMC retarded the drug release from the matrix by preventing the penetration of solvent molecules. HPMC K100M was judiciously selected in preparation due to its profound ability to form a strong viscous gel on contact with aqueous media, which helps in controlling the delivery of highly water-soluble drugs.

Drug-incipient interaction study

The compatibility of the pure drug with its recipients on physical observation exhibited no interaction; therefore, the recipients were selected for formulation. The distinctive melting points were observed for Metformin hydrochloride at 224 °C and Gliclazide at 182 °C and no evident melting point changes were noted indicating overall compatibility.

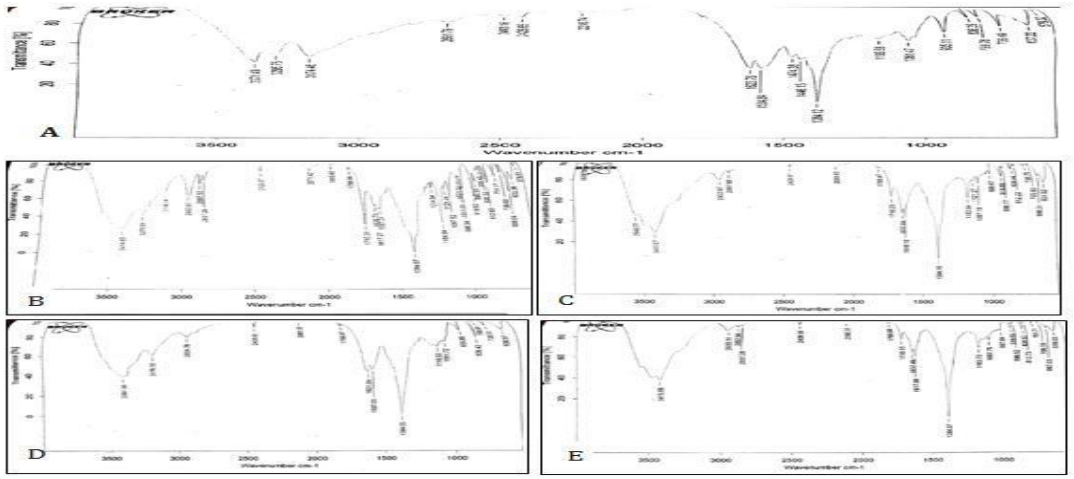
FT-IR spectroscopy

The FT-IR spectrum of Metformin hydrochloride and Gliclazide in formulations was as shown in fig. 3C. FT-IR studies revealed that Metformin hydrochloride showed two typical bands at 3371 and 3296/cm due to N-H primary stretching vibrations and a band at 3174/cm due to N-H secondary stretching, and characteristics bands at 624 and 1584/cm assigned to C=N stretching. No significant shifts of reduction in the intensity of the FT-IR bands of Metformin hydrochloride were observed which indicates the absence of drug-drug interaction and drug-polymer interaction between Metformin hydrochloride and Polio WSR coagulant.

Hence, these two drugs were selected for the development of sustained-release bilayered tablets and polio WSR coagulant was selected as a release-retarding agent. An IR spectrum of pure Gliclazide shows two characteristic peaks. A peak at 3414.85 cm^{-1} due to NH group and another peak at 1636.79 cm^{-1} due to C=O as observed in fig. 3B showing no interaction indicating overall compatibility with the polymer HPMC K100M and recipients.

Characterization of powder blend

The results of the pre compression parameters such as bulk density, tapped density angle of repose, Hauser's ratio and compressibility index of all batches of SR blend containing Metformin hydrochloride and Gliclazide exhibited good characteristics. All the formulations showed good compressibility and flow properties than pure drugs. The recompression values of Metformin hydrochloride and Gliclazide blend were indicated in table 3 and table 4 respectively.



CONCLUSION

The diffusion-controlled bilayered tablets of Metformin hydrochloride and Gliclazide were successfully developed using the lesser concentration of HPMC K 100M as retardant polymers. *In vitro* release profiles revealed that 99% of the Metformin hydrochloride and 99% Gliclazide were released from the final optimized formulation at the end of 12 hours and 40 minutes. The drug release follows first order and is diffusion controlled. Therefore, the designed formulation offers improved patient compliance and convenience with better postprandial hyperglycaemic control with once-a-day dosing. The sustained release of the drug up to 12h regulates ant diabetic activity round the clock with minimal side effects.

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