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FORMULATION AND EVALUATION OF GLICLAZIDE CONTROLLED RELEASE TABLETS USING SODIUM ALGINATE, HPMC H4H IN DIFFERENT PROPORTIONS

K.Vinod Kumar*[1], S.Gayatrisai Vishnavi[2], Sravani.P[2], Syed.Sofiya Sulthana[2], Y.Ramya[2]

[1]*Professor, Department of Pharmaceutics, St.Ann's college of Pharmacy, Chirala*
[2]*Department of Pharmaceutics, St.Ann's College of Pharmacy, Chirala*

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***Corresponding Author**
K.Vinod Kumar

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ABSTRACT

Gliclazide is a second-generation sulfonylurea widely used in the management of type 2 diabetes mellitus. It acts by stimulating insulin secretion from pancreatic β-cells through the closure of ATP-sensitive potassium channels, thereby improving glycemic control. In addition to its hypoglycemic effect, gliclazide exhibits beneficial antioxidant and hemovascular properties, which reduce oxidative stress and improve microcirculation. Compared to other sulfonylureas, gliclazide is associated with a lower risk of hypoglycemia and favorable cardiovascular safety. It shows good oral bioavailability and is commonly formulated as immediate-release and modified-release tablets to enhance patient compliance. Due to its efficacy, safety profile, and cost-effectiveness, gliclazide remains an important therapeutic option in the long-term treatment of type 2 diabetes mellitus. Gliclazide is commonly formulated as a modified-release dosage form to provide sustained glycemic control in patients with type 2 diabetes mellitus. Controlled-release formulations maintain steady plasma drug concentrations, thereby reducing fluctuations in blood glucose levels and minimizing the risk of hypoglycemia. The use of hydrophilic polymers such as HPMC and ethyl cellulose enhances drug release modulation and improves patient compliance by reducing dosing frequency. Controlled-release gliclazide tablets demonstrate improved therapeutic outcomes, better tolerability, and enhanced quality of life in diabetic patients. These formulations represent an effective approach for long-term diabetes management.

INTRODUCTION

Controlled release drug delivery systems are advanced pharmaceutical formulations designed to release drugs at a predetermined rate over an extended period. Unlike conventional dosage forms, which often require multiple doses throughout the day, controlled release systems aim to maintain therapeutic drug levels in the bloodstream for prolonged periods. These systems enhance patient compliance, improve therapeutic outcomes, and minimize side effects.

- Consistent Drug Levels: Maintain drug concentrations within the therapeutic window for a longer duration.
- Reduced Dosing Frequency: Improve patient convenience and adherence by reducing the number of doses required.
- Minimized Side Effects: Reduce peak plasma concentrations, which can lead to adverse effects, and trough levels, which can cause therapeutic failure.
- Targeted Delivery: Deliver the drug to a specific site in the body to enhance efficacy and reduces systemic exposure.
- Improved Stability: Protect drugs from degradation (e.g., by gastric acid or enzymes) before reaching the site of action.

Advantages of Controlled Release Systems

- Improved Patient Compliance: Fewer doses reduce the likelihood of missed doses,especially in chronic conditions.
- Optimized Drug Utilization: Steady release reduces wastage and ensures more of thedrug is used effectively.
- Minimized Toxicity: Avoids high peak concentrations that could lead to toxicity.
- Enhanced Convenience: Particularly beneficial for pediatric, geriatric, or non-adherentpopulations.
- Conventional Technique Used in the Preparation of Immediate Release Tablets:
    - Matrix system
    - Reservoir system (coating technique)
    - Wax matrix technique
    - Hydrophilic matrix technique
    - Hydrophobic matrix technique
    - Encapsulation (microencapsulation)
    - Ion-exchange resin technique
    - Osmotic pump technique
    - Film coating technique
    - Multi-particulate system

Differentiating drug delivery systems according to their mechanism of drug release:

Drug delivery systems can be defined as formulations or devices designed to deliver a drug at a predetermined rate, locally or systemically, for a specified period of time by controlling the mechanism of drug release.

1. Diffusion-Controlled Drug Delivery Systems

In diffusion-controlled systems, the drug is released by diffusion through a polymeric membrane or matrix.

Reservoir system: Drug core surrounded by a rate-controlling membrane

Matrix system: Drug dispersed uniformly in a polymer matrix

Example: Matrix tablets using HPMC, ethyl cellulose

2. Dissolution-Controlled Drug Delivery Systems

Drug release occurs as the coating or matrix slowly dissolves in the gastrointestinal fluids.

Coating dissolution system

Matrix dissolution system

Example: Tablets coated with slowly dissolving polymers

3. Osmotically Controlled Drug Delivery Systems

Drug release is controlled by osmotic pressure created by water influx through a semi-permeable membrane.

Push-pull osmotic systems

Elementary osmotic pump

Example: Osmotic tablets

4. Ion-Exchange Controlled Drug Delivery Systems

Drug is bound to an ion-exchange resin and released by exchange with ions present in gastrointestinal fluids.

Example: Resinates used in sustained-release formulations

5. Swelling-Controlled Drug Delivery Systems

Drug release occurs due to swelling of polymers after contact with gastrointestinal fluids, forming a gel layer that controls diffusion.

Example: Hydrophilic matrix systems using HPMC

6. Erosion-Controlled Drug Delivery Systems

Drug release is governed by erosion or degradation of the polymer matrix.

Surface erosion

Bulk erosion

Example: Biodegradable polymer matrices

7. pH-Dependent Drug Delivery Systems

Drug release depends on the pH of the surrounding environment.

Example: Enteric-coated tablets

8. Enzyme-Controlled Drug Delivery Systems

Drug release is triggered by enzymatic degradation of polymers.

Example: Biodegradable systems for targeted delivery.

Solubility:

Gliclazide is practically insoluble in water, sparingly soluble in acetone, and freely soluble in organic solvents such as chloroform and dichloromethane. It shows low aqueous solubility, which classifies it as a poorly water-soluble drug and makes it suitable for modified-release formulations.

Site and Mode of Action:

Gliclazide acts at the pancreatic β-cells of the islets of Langerhans. It works by binding to sulfonylurea receptors (SUR1) on the β-cell membrane, which leads to closure of ATP-sensitive potassium (K^+) channels. This causes membrane depolarization, opening of voltage-gated calcium (Ca^{2+}) channels, and an increase in intracellular calcium, resulting in insulin release. The released insulin lowers blood glucose levels by enhancing glucose uptake in peripheral tissues.

Half-life -10–12 hours.

METHODOLOGY:

Procedure for compression batch

Step-1: Gliclazide, polymer (HPMC/MCC), and other excipients were accurately weighed according to the formulation design.

Step-2: Gliclazide, polymer, diluent, and disintegrant were passed through 40 ASTM sieve to remove lumps and ensure uniform particle size.
Step-3: All the above-sieved materials of Step-2 were transferred into a polybag and blended for 20 minutes at 16 rpm to obtain a uniform mixture.
Step-4: Magnesium stearate and talc were previously passed through 60 ASTM sieve and added to the above blend.
Step-5: The final blend was mixed for 5 minutes to ensure proper lubrication.
Step-6: The lubricated blend was evaluated for pre-compression parameters such as bulk density, tapped density, angle of repose, Carr's index, and Hausner's ratio.
Step-7: The blend was compressed into tablets using a rotary tablet compression machine with suitable punches by adjusting the compression force.
Step-8: The compressed tablets were evaluated for post-compression parameters such as weight variation, hardness, thickness, friability, drug content uniformity, and in-vitro dissolution study.

Sifting of raw materials

(Gliclazide, polymer, diluent, disintegrant)

⬇

Binder preparation

(PVP K-30 dissolved in purified water / IPA)

⬇

Granulation

(Mixing of sifted powders with binder solution in RMG)

⬇

Drying

(Tray dryer / Fluid bed dryer at 40–50 °C)

⬇

Sizing of granules

(Passing dried granules through #20 sieve)

⬇

Lubrication

(Addition of magnesium stearate and talc)

⬇

Compression

(Compression into tablets using rotary tablet press)

⬇

Film coating

(Optional – for protection / modified release)

Table1: Formula for all formulations

S.no	Ingredients	F1	F2	F3	F4	F5	F6
1	Gliclazide	120	120	120	120	120	120
2	Calcium starch	3	-	-	3	-	-
3	Sodium Alginate	6	9	12	-	-	-
4	HPMC H4M	-	-	-	15	30	45
5	MCC	161	161	158	152	140	125
6	Magnesium Stearate	5	5	5	5	5	5
7	Talc	5	5	5	5	5	5

EVALUATION PARAMETERS

Evaluation of powder flow properties

Bulk density
Tapped Density
Carr's compressibility Index
Hausner's Ratio

Evaluation of Tablets

Uniformity of weight

⬇

Thickness

⬇

Hardness

⬇

Friability

⬇

Disintegration

⬇

In-vitro drug dissolution study

⬇

Stability studies

Stability Studies

- **Long-term Stability Testing** 25 °C ± 2 °C / 60% RH ± 5% RH for 12 months
- **Intermediate Stability Testing** 30 °C ± 2 °C / 65% RH ± 5% RH for 12 months
- **Accelerated Stability Testing** 40 °C ± 2 °C / 75% RH ± 5% RH for 6 months

Procedure

Gliclazide controlled release tablets were prepared by the wet granulation method. Accurately weighed quantities of gliclazide, polymer, and other excipients were passed through a #40 mesh sieve and blended uniformly for 10–15 minutes. A binder solution was prepared separately using PVP K30 in purified water and was added slowly to the powder blend to obtain a coherent damp mass. The wet mass was passed through a #16 mesh sieve to form granules, which were then dried in a tray dryer at 50–60 °C until the loss on drying was within acceptable limits. The dried granules were resized through a #20 mesh sieve and lubricated with talc and magnesium stearate for 3–5 minutes. The lubricated granules were finally compressed into tablets using a rotary tablet compression machine. The prepared tablets were evaluated for physical parameters, drug content, and in-vitro dissolution to ensure controlled drug release.

Table 2: Blending properties of different formulations.

Formulation	B.D (gm/ml)	T.D (gm/ml)	C. I (%)	H. R	Property
F1	0.71	0.81	12.34	1.14	Fair
F2	0.72	0.82	12.19	1.13	Fair
F3	0.74	0.85	12.94	1.15	Fair
F4	0.75	0.86	12.79	1.14	Fair
F5	0.76	0.87	12.64	1.14	Fair
F6	0.78	0.88	11.36	1.13	Passable

Table 3: Physical evaluation (film coated tablets)

Formulation	Avg. Weight (Mean±SD)	Hardness (kg/cm^2)	Disintegration time (min'sec")
F1	414±4.43	7.6±0.2	8'54"
F2	412±3.74	7.8±0.2	8'48"
F3	409±3.85	7.8±0.3	8'52"
F4	413±3.87	8.1±0.4	9'02"
F5	411±4.45	8.2±0.2	9'26"
F6	413±4.26	7.9±0.3	12'43"

Table 4: in-vitro dissolute on profile of Gliclazide

Time(min)	Innovator	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0	0
5	18	14	16	15	13	12	10
10	32	24	28	26	23	21	18
15	48	38	42	40	36	34	30
20	62	52	56	54	50	48	46
30	78	68	72	70	66	64	59
45	90	82	86	84	80	79	74
60	98	94	96	95	92	92	88

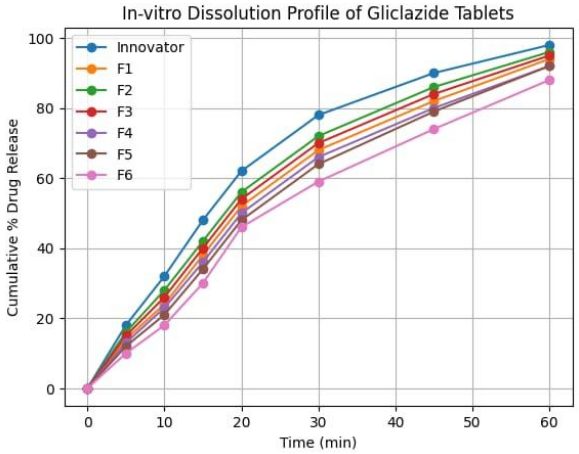

Fig no.1: Dissolution of Gliclazide in OGD media

Table 5: stability condition % assay result of F5 and F6

Stability Condition	Description	F9 Amlodipine Besylate	F10 Amlodipine Besylate
Room temperature initial	white film coated tablets	99.6	99.4
40° C /75% RH (1 month)	Light white colored film coated tablets	98.8	98.5
40° C /75% RH (2 months)	Light white colored film coated tablets	97.9	97.6

Table 6: in - vitro dissolution profile of Gliclazide in optimized formulation F5at 40°C and 75% RH

Time (min)	Innovator	1 month	2 months
0	0	0	0
5	18	17	15
10	48	46	44
15	72	70	68
20	88	86	84
30	96	95	93
45	99	98	97
60	99	98	97

DISCUSSION

Scanning of drug

The standard calibration curve of Gliclazide was obtained by plotting Absorbance v/s. Concentration.The pure drug Gliclazide was scanned over a range 226-232 nm to determine its λmax. The peak was observed at the 226 nm for Gliclazide The obtained results Conforms the identification of Gliclazidein ethanol and distilled water.

Standard calibration curve of Gliclazide:

The standard calibration curve was found to be linear in the concentration range of 2,4,6,8and 10 µg/ml(Beer's range) at 226 nm.

Pre compression parameters

The Gliclazide tablets were prepared direct compression method. Before compression the powder is evaluated for angle of repose, bulk density, tapped density, Hausner's ratio and compressibility index The bulk density of the powder was found to be 0.43 gm/cm3, while the tapped density was found tobe Trail-1: 0.55 g/cm3, Trail-2: 0.58g/cm3, Trail-3: 0.60g/cm3.The flow characteristics of the powder were assessed by determining their angle of repose and Carr's Index. The Hausner's ratio value 1.25indicates excellent flow property. The low values of compressibility 13% signify good and fine flowability. The angle of repose of the formulation was 20-31 also indicate the good& fair flow ability of the prepared powder. This shows that the powder had smooth flow properties ensuring homogenous filling of the die cavity during the compression of tablets.

Post Compression

The tablets were prepared by direct compression method. The tablets were evaluated for their hardness, diameter, thickness, friability; disintegration and in vitro drug release. The Optimized formula was F5.F5 formulation has hardness- 4.90 kg/cm2, thickness-3.96mm, friability 0.125 %, drug content9.85mg and it has 92.8 mg cumulative drug released in 9 hours as a best contolled drug release and it follows the zero-order drug release profile. The stability studies were carried out at 40 0C / 75% RH for all the selected formulations up to 30 days. The tablets were analyzed for drug content uniformity, hardness, drug content and friability up to 30 days. These formulations showed not much variation inany parameters.

SUMMARY AND CONCLUSION

- The present works involves formulation and development and optimization and in-vitro evaluation of controlled release tablets of Gliclazide. With fixed dose.
- Under pre-formulation studies API (Active pharmaceutical ingredients) Charecterizations and drug excipient compatability studies caried out
- The polymers and other excipients were selected based on the satisfying results produced during drug excipients compatibility studies develop the Final formulation the final suitable formulation was achieved by the direct compression method.
- The combination of polymers that is sodium alginate, HPMC for Gliclazide given controlled release.
- The results reveal that the formulation F1 has met the objective of controlled release for over a period of 12 hours.
- The formulation F1 has met the desired invivo & inviyro correlation limits as for USP.

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CONFLICT OF INTEREST

Not declared

INFORMED CONSENT AND ETHICAL STATEMENT

Not applicable

AUTHOR CONTRIBUTIONS

All authors are contributed equally.

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