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# Formulation and evaluation of Glipizide Sustained release Anti-Diabetic tablet

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**ABSTRACT: -**

**Background**: - Modification in sustained release system is a newly developed area that has shown good control over the administration of drug by maintaining systemic concentrations.

**Objective**: - The study was conducted to formulate a sustained release tablet of antidiabetic drug, Glipizide, with improvement in patient compliance. Methods: - Sustained release tablet of glipizide was prepared by using different concentration of natural polymers like Glipizide, Lactose Monohydrate, microcrystalline cellulose, Magnesium Stearate, Silicon Dioxide as a release modifier by weight granulation method. The tablets had been analysed by chemical and physical parameters. Drug and polymer interactions had been studied by FT-IR and in vitro drug release had been studied using rotating paddle dissolution apparatus. The release rate had been studied on different models in order to measure their release kinetics.

**Keywords: -** Glipizide antidiabetic, sustained release, natural polymer, wet granulation, drug release, Lactose monohydrate, Microcrystalline cellulose, Magnesium stearate, Silicon dioxide.

## Introduction: -

Glipizide is a medication that is widely used to treat diabetes by boosting the release of insulin. However, the drug also has a number of negative side effects, including nausea, vomiting, heartburn, anorexia, and increased hunger, even when taken orally at regular dosages. It belongs to the class of second-generation sulphonyl urea and is mostly used to treat type II diabetes mellitus. (1,2) Long-Term Release A drug delivery system is one that provides long-term, local or systemic medication delivery. In novel drug delivery system as well as in conventional system, oral drug delivery system is most widely used method. Sustained release dosage forms are the formulations which release the therapeutically active agents for longer period of time at expected rate after its single dose administration. (3,4) Many methods are there to formulate oral sustained released dosage form among which matrix system is most appropriate due to consistency, validation, scale up and cost effective. (5) Oral drug delivery is the most popular approach in both new and traditional drug delivery systems. Since sustained release tablets offer consistent medication release over an extended period of time, they have supplanted traditional dose forms in the modern era. (6) It offers numerous benefits, including as improved patient convenience and compliance, improved medication absorption, and decreased toxicity and expense. Because it targets gastrointestinal physiology4, the oral mode of delivery offers greater flexibility than other routes. (7) Oral route formulations such as sustained release dosage forms can minimize adverse side effects by delivering the medicine directly to the target site, reducing the frequency of doses, and maintaining a steady drug concentration. Sustained release drug delivery systems can be used to administer any medication with a shortened half-life. (8,9) Diabetes mellitus is a chronic metabolic disease that affects a considerable number of people nowadays. It is caused by a lack of insulin and results in hyper-glycemia, or elevated blood glucose levels. In both aqueous and acidic solutions, glipizide is essentially insoluble. (10) The development of sustained release (SR) or controlled release (CR) drug delivery systems has received more attention as a result of the increased costs and problems associated with marketing new pharmacological entities. Predictable and repeatable release rates, longer half-life for short-acting medications, reduced toxicity, a lower dosage needed, improved therapy, and more patient compliance can all be attained using sustained or controlled release delivery systems. The popularity of matrix-type continuous delivery systems can be attributed to their ease of manufacturing. Complex manufacturing processes including coating and pelletization during manufacturing and drug release from the dosage form are not included. The kind and quantity of polymers utilized in the preparation primarily regulate it. A copolymer of acrylic and methacrylic esters, Eudragit RL-100 has a low quaternary ammonium group concentration. The polymers are permeable due to the ammonium groups, which are present as salts. It serves as a tablet diluent, tablet binder, and film farming agent. The applications of ethylene cellulose include coating, flavouring, tablet binder, table filler, and viscosity-increasing. It is a stable, slightly hygroscopic substance that is sensitive to acidic substances but chemically resistant to alkali. Microcrystalline cellulose is a common pharmaceutical aid that is used as a binder or diluent in the production of oral tablets and capsules. It is also excellent for tableting because it possesses lubricating and disintegrating properties. It is a hygroscopic but stable substance. In the production of capsules and tablets, magnesium stearate is utilized as a lubricant at concentrations ranging from 0.25 to 5.0%. A refined hydrated magnesium silicate, talc is used as a lubricant, diluent, anti-cacking agent, and glidant for tablets and capsules. It is frequently employed in the creation of controlled-release products as a dissolution retardant. It can also be used as a powder for dusting. An oral hypo-glycemic medication called glipizide is frequently recommended to

people with type II diabetes. (11) Patients with type II diabetes mellitus are treated with this oral hypo-glycemic medication, which belongs to the second-generation sulfonylurea class-II. (12) It may increase the amount of insulin receptors and stimulate the β cells of the pancreatic islets tissue to secrete more insulin. Following oral dosing, glipizide is well absorbed, 98–99% bound to serum proteins, with urine excreting 80% of its metabolites and faces excreting 10%. (13,14)

Sustained release matrix tablets of Glipizide using HPMC: - Enhancing the solubility of glipizide (BCS Class II) was the goal of the study. The half-life of the oral antidiabetic medication glipizide is comparatively short. The kneading method was used to form the inclusion complex of Glipizide with β-cyclodextrin, and its in-vitro release was assessed. Phase solubility tests were conducted using the Higuchi and Connors method, which was categorized as AL type and distinguished by an apparent 1:1 stability constant. The FTIR spectra of the Glipizide β-CD Complex showed that the Glipizide and Beta Cyclodextrin were compatible. Glipizide β-CD complex dissolution analysis demonstrates a markedly higher drug release compared to pure drug. Microcrystalline cellulose, carboxymethyl cellulose sodium (CMC), and hydroxy propyl methyl cellulose (HPMC) were used to create a matrix Glipizide β-CD complex tablet complex that contained 10 mg of Glipizide. (15) To extend the drug release and enhance patient compliance, the Glipizide matrix tablet was made using a variety of hydrophilic polymers (HPMC in different grades and sodium CMC) in varied ratios as a release retarding agent. The direct compression approach was used to create the matrix tablets. Drug content, hardness, swelling index, thickness, friability, weight variation test, and in vitro release investigations were all performed on the manufactured matrix tablets. The F18 formulation released the medication in a controlled manner for 12 hours, according to the in vitro dissolution research. Formulation F18, which contains a combination of HPMC K100 and E15, releases the medications using zero order kinetics through swelling and diffusion more than any other formulation. In accordance with ICH requirements, stability experiments were conducted for improved formulation F18. Glipizide was found to be stable in matrix tablets after three months of stability tests at 40±2oC and 75±5% relative humidity. (16)

## Aim of the Glipizide Drug: - Formulation and Evaluation of Glipizide Sustained Release Tablet: -

The aim of Glipizide sustained release tablet is to: -

1. Provide prolonged control of blood sugar levels: By releasing Glipizide slowly over an extended period.
2. Improve patient compliance: By reducing the frequency of dosing.
3. Minimize hypo-glycemic episodes: By avoiding peaks and troughs associated with immediate-release formulations.
4. Enhance therapeutic effectiveness: By maintaining a consistent level of Glipizide in the bloodstream. Overall, the aim is to provide effective and convenient management of type 2 diabetes.

### *Objective of the Glipizide Drug: -*

The objective of Glipizide sustained-release tablets is to:

1. Provide effective glycemic control: By maintaining stable blood glucose levels.
2. Improve patient compliance: By reducing dosing frequency.
3. Minimize side effects: Such as hypo-glycemia.
4. Enhance therapeutic outcomes: By providing a consistent and prolonged release of Glipizide. Overall, the objective is to improve the management of type 2 diabetes.

## Material and Methodology: -

The following resources and techniques were employed to produce the formulation and investigate the release augmentation of the antidiabetic medication Glipizide: -

### *Material: -*

### *Preparation of sustained release tablets of Glipizide: -*

All formulations were prepared using the wet granulation process, which involved varying the ratios of each polymer to the medication (drug: polymer, 1:3, 1:4, and 1:5) 26. All components, referred to as medicine, were weighed in precise amounts. Initially, the medication, polymers, and MCC were run through filter number 40. After carefully mixing the necessary amounts of the medication in a mortar, the polymer solution—which was made by dissolving PVP30 (5%) in water—was added to create the granules. To break up the aggregates, the dried granules were subsequently run through mesh sieve number 20. The tablet granules were then compacted into tablets using a tablet-punching equipment equipped with an 8 mm standard concave punch after talc and magnesium stearate27 were added, as indicated in Table. This is a cost-effective and appropriate method for producing tablets. Previously, direct compression was limited to the consolidation of a single compound into a solid mass. Currently, it involves the tablet preparation by compressing a mixture of excipients and the active ingredient. In this technique, it is not necessary to perform wet or dry granulation of the blend. Therefore, this procedure comprises four stages: milling both active and inactive components, mixing the powders, blending them in a mixer, and then lubricating the powder with a suitable lubricant before the final step of compressing the mixture into tablets. The use of varying grades of microcrystalline cellulose and lactose enhances the convenience and suitability of this process. (17)

***Pre-formulation test: -***

Pre- formulation testing's goal is to produce data that will help the formulation create stable and bioavailable dose forms. The likelihood of creating a product that is acceptable, safe, effective, and stable is increased by using pre- formulation parameters.

The Micromeritic properties of the prepared granules were as follows:

**1)Angle of repose: -** [18] The funnel was fixed as part of the funnel and cone technique. The following formula was used to calculate the angle of repose, using r as the conical pile's base radius.

**θ = tan-1 h/r.**

| Angle of Repose | Type of Flow |
|---|---|
| < 25 | Excellent |
| 25-30 | Good |
| 30-40 | Possible |
| >40 | Very Poor |

**2)Hausner`s Ratio: -** Hausner's ratio, which is the ratio of tapped density to bulk density, was associated with inter-particulate friction.

**Hausner's ratio = Tapped density - Bulk density/ Tapped density**

**3)Carr`s index: -**

Bulk and tapped densities can be measured to determine the compressibility index parameter. A material is said to have good flow properties if its values are less than 20%. Carr's Compressibility Index was used to calculate the compressibility index.

**Carr's index % = Tapped density – Bulk density/ Tapped density × 100 Carr's Index**

| **Carr's Index** | **Type of Flow** |
|---|---|
| 5-15 | Excellent |
| 15-18 | Good |
| 18-23 | Fair to possible |
| 23-35 | Poor |
| 35-38 | Very poor |

**4)Tapped Density: -**

An accurately weighed granules of powder was introduced into a 100 ml measuring cylinder. Now the cylinder was allowed to tap at regular interval until no further change in the volume was observed and tapped density was calculated by using the following formula, **Tapped density = weight of the powder / tapped volume of the powder**

**• Evaluation of glipizide sustained release tablet: -**

Tablets underwent an assessment of various properties such as weight variation, hardness, friability, dimensions, thickness, and in-vitro release with differing media.

**1. Weight Variation**

The weight of the tablets is regularly measured to confirm that each tablet contains the appropriate dosage of the drug. The weight variation test outlined by the USP involves individually weighing 20 tablets, calculating the average weight, and comparing each individual weight against the average.

**2)Tablet Hardness**

The durability of tablets against damage during storage, transport, and handling prior to use is influenced by their hardness. The hardness of each tablet batch was evaluated using a Monsanto hardness tester. Hardness was recorded in kg/cm2, with three tablets selected at random for the hardness assessment.

**3)Friability: -**

The Roche friabilator was used to assess friability, with results expressed as a percentage (%). Five tablets from each batch were individually weighed and placed in the friabilator, which was operated for 100 revolutions at a speed of 25 rpm. The tablets were then reweighed, and the percentage of friability for each batch was calculated using the formula, **Friability % = Initial weight – Final weight /Initial weight × 100**.

**4)Thickness: -**

The thickness of the tablet plays a crucial role in ensuring consistent tablet size. A Vernier calliper was used to measure this thickness. The measurements were taken from ten tablets for each formulation. The degree to which each tablet's thickness varied from the standard value by more than ± 5% was evaluated.

**5)Drug content uniformity: -**

The uniformity of drug content in the tablets was evaluated. Twenty tablets were randomly selected, weighed, and then powdered. An amount of powder equivalent to 100 mg of the drug was precisely weighed and dissolved in 100 ml of phosphate buffer at pH 6.8. The solution was thoroughly mixed and subjected to sonication. Any undissolved particles were eliminated by filtering the mixture through Whatman's filter paper No.41. Dilutions were

performed if necessary. The absorbance of the diluted solutions was recorded at 276 nm. The concentration of the drug was determined using the standard curve of glipizide in phosphate buffer at pH 6.8, and the drug content was calculated with the formula provided. **6)In-Vitro Dissolution Study: -**

The paddle method of the USP Dissolution testing device Type II was used to conduct in vitro drug release studies. The device was operated at 37ºC ± 0.5ºC with a rotating speed of 50 rpm in a 900 ml dissolution medium after the tablets were immersed in 0.1 N HCl for the first two hours and pH 6.8 phosphate buffer for the following four hours and pH 7.4 phosphate buffer for the next two hours, respectively. The 5 ml aliquots were taken out every 30 minutes for eight hours, and each time they were replaced with an equal volume of brand-new dissolving media that was kept at the same temperature and analyse for drug release. For every formulation [n=3], the procedure was carried out three times.

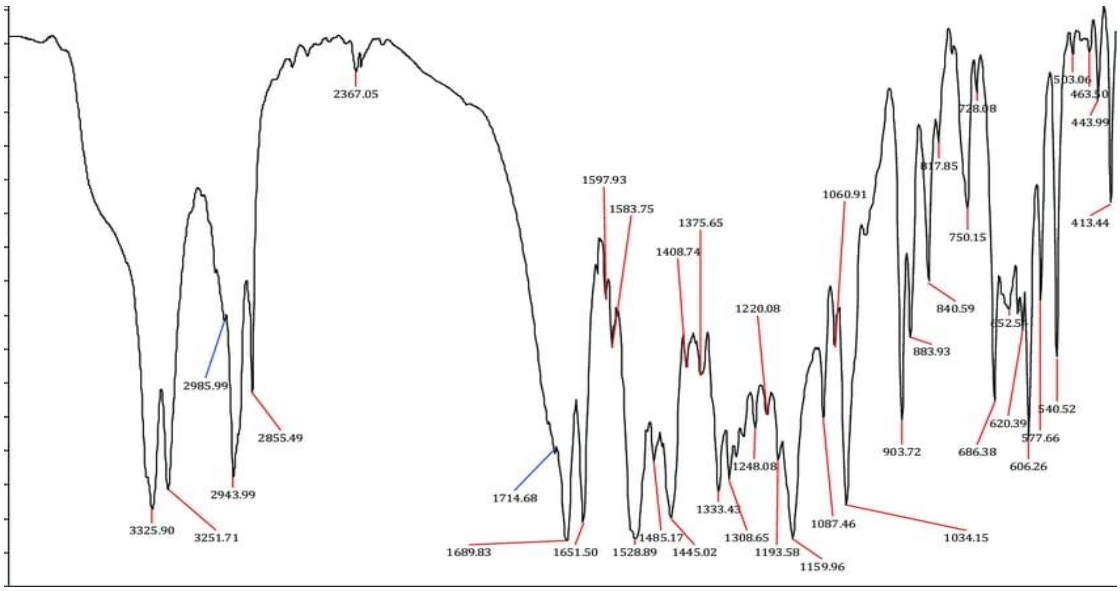
**7)Drug release kinetic study: -**

To explore the release kinetics of in-vitro drug release, data was applied to kinetic models such as Zero order, First order, Higuchi, Korsmeyer-Peppas and Hixson Crowell. BIT-soft 1.12 was used to compute the drug release kinetics. [19]

**• Glipizide sustained release tablet formulation table are as follows: - Formulation Table: - 1**

| Ingredient | F1 | F2 | F3 | F4 | F5 |
|---|---|---|---|---|---|
| Glipizide (API) | 5 mg | 5 mg | 5 mg | 5 mg | 5 mg |
| Crospovidone | 20 mg | 23 mg | 22 mg | 24 mg | 21 mg |
| Magnesium Stearate | 23 mg | 20 mg | 21 mg | 22 mg | 24 mg |
| Talc Powder | 20 mg | 25 mg | 24 mg | 23 mg | 19 mg |
| Lactose | 32 mg | 27 mg | 28 mg | 26 mg | 31 mg |

**FTIR Analysis: -Glipizide tablet: -**




**Conclusion :-**

The formulation and evaluation of Glipizide Sustained Release tablets demonstrated successful development of a stable and effective anti-diabetic formulation, with optimized dissolution profiles and improved patient compliance.

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## Result and Discussion: -

| Sr. No. | Test | Result |
|---|---|---|
| 1 | Colour | White |
| 2 | Odour | Odourless |
| 3 | Taste | Tasteless |
| 4 | Angle of repose | 32.8° C |
| 5 | Bulk Density | 0.25 g/ml |

| | | |
|---|---|---|
| 6 | Tapped Density | 0.7 g/cm$^3$ |
| 7 | Carr's index | 6% |
| 8 | Solubility | Insoluble in Water and alcohol |
| 9 | Melting Point | 208-209°C |

**Table 2: - Pre compressional parameters of Glipizide tablets**

| Formulation code | Angle of repose | Bulk density (gm/ml) | Tapped density (gm/ml) | Carr's index (%) | Hausner's Ratio |
|---|---|---|---|---|---|
| F1 | 23.74 | 0.36 | 0.44 | 18.24 | 1.22 |
| F2 | 25.80 | 0.71 | 0.86 | 17.44 | 1.21 |
| F3 | 28.24 | 0.68 | 0.81 | 16.04 | 1.19 |
| F4 | 24.32 | 0.70 | 0.89 | 21.34 | 1.27 |
| F5 | 24.88 | 0.71 | 0.83 | 14.45 | 1.16 |

**Table 3: - Post compressional parameters of Glipizide tablets**

| Formulation code | Hardness (kg/cm$^2$) ±SD | Thickness(mm) ± SD | Friability (%) | Average weight (gm) ±SD | % Drug content |
|---|---|---|---|---|---|
| F1 | 5.16 ±0.288 | 2.26 ±0.057 | 0.42 | 197.4 ±1.67 | 77.12 |
| F2 | 5.5 ±0.5 | 2.31 ±0.105 | 0.34 | 194.8 ±0.83 | 91.27 |
| F3 | 5.33 ±0.288 | 2.27 ±0.052 | 0.33 | 196.6 ±1.67 | 84.93 |
| F4 | 5.16 ±0.288 | 2.34 ±0.085 | 0.42 | 196.2 ±1.68 | 76.49 |
| F5 | 4.66 ±0.288 | 2.27 ±0.105 | 0.37 | 195.5 ±1.39 | 77.02 |

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