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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF GLIBENCLAMIDE

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Abstract:

The present study aimed to formulate and evaluate sustained release matrix tablets of Glibenclamide using different polymeric systems, namely sodium alginate and HPMC, to achieve controlled drug release and improve therapeutic efficacy. Four formulations (F1–F4) were developed and systematically evaluated for pre-compression and post-compression parameters, in vitro drug release behavior, and stability studies.Preformulation studies confirmed the purity and suitability of Glibenclamide through organoleptic evaluation, melting point determination (171–175°C), and solubility analysis. FT-IR studies indicated compatibility between drug and excipients, with no significant interaction observed. The powder blends exhibited good flow properties, ensuring suitability for direct compression. Post-compression evaluations showed that all formulations complied with pharmacopoeial standards for weight variation, hardness, friability, thickness, and drug content uniformity.In vitro dissolution studies demonstrated sustained drug release up to 8 hours for all formulations. Among them, formulation F2 (sodium alginate 50 mg) exhibited the most controlled and desirable release profile, achieving 98.52% drug release within 8 hours. Stability studies conducted under ICH conditions showed no significant changes in physical or chemical properties of the optimized formulation over 3 months, confirming its stability.

Keywords : *Glibenclamide; Sustained release; Matrix tablets; Sodium alginate; HPMC; Direct compression; In vitro release; Stability studies.*

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INTRODUCTION:

Sustained Drug Delivery System

Sustained Drug Delivery Systems (SDDS) are advanced pharmaceutical formulations designed to release a drug at a predetermined rate over an extended period, maintaining therapeutic drug levels in the bloodstream for a prolonged duration. Unlike conventional dosage forms, which often release the drug rapidly and require frequent administration, sustained-release systems aim to reduce dosing frequency, enhance patient compliance, and provide a more consistent therapeutic effect.

The concept of sustained drug delivery emerged from the need to overcome the limitations of conventional oral dosage forms, including rapid absorption and elimination, fluctuations in plasma drug concentration, and poor patient adherence. Frequent dosing of conventional formulations can lead to sub-therapeutic levels or toxic peaks, especially in drugs with a narrow therapeutic index or short biological half-life. SDDS addresses these challenges by controlling the drug release kinetics and maintaining plasma drug concentration within the therapeutic window for longer durations.

Key Features of Sustained Drug Delivery Systems

- Prolonged Drug Release: The drug is released gradually over an extended period, reducing the need for repeated dosing.
- Improved Patient Compliance: Reduced dosing frequency leads to better adherence, especially in chronic conditions.
- Stable Plasma Drug Concentration: Avoids fluctuations associated with conventional dosage forms, minimizing side effects and maximizing efficacy.
- Optimized Therapeutic Effect: Enhances the pharmacological response by maintaining consistent drug levels.

Sustained drug delivery systems can be designed using various formulation strategies, including matrix tablets, coated dosage forms, microspheres, nanoparticles, and osmotic systems. Polymers and other excipients play a crucial role in controlling the release rate, ensuring the drug is available at the desired rate and duration.

In conclusion, SDDS represents a significant advancement in pharmaceutical technology, providing a rational approach to improve therapeutic efficacy, patient compliance, and safety. These systems are particularly valuable for drugs with short half-lives, narrow therapeutic indices, or those intended for long-term therapy, making them a cornerstone of modern drug delivery research.

Advantages of Sustained Drug Delivery Systems

Sustained drug delivery systems offer several benefits over conventional dosage forms, primarily by improving therapeutic outcomes and patient convenience:

1. **Improved Patient Compliance**
   - Reduced dosing frequency minimizes the burden on patients, particularly those requiring chronic therapy, thereby enhancing adherence.
2. **Maintained Therapeutic Drug Levels**
   - Provides a **constant plasma concentration** within the therapeutic window, avoiding peaks (toxicity) and troughs (sub-therapeutic effect).
3. **Reduction in Side Effects**
   - Controlled and gradual release decreases the risk of adverse drug reactions associated with high plasma drug concentrations.
4. **Economic Benefits**
   - Fewer doses reduce the total number of tablets or capsules required, potentially lowering overall treatment costs.
5. **Enhanced Drug Efficacy**
   - Prolonged exposure to the drug can improve pharmacological effect, especially for drugs with short half-lives or narrow therapeutic indices.
6. **Better Disease Management**
   - Sustained drug levels are particularly beneficial for chronic conditions like hypertension, diabetes, or cardiovascular disorders, ensuring continuous therapeutic coverage.
7. **Protection of Drugs**
   - Certain formulations can protect drugs from degradation in the gastrointestinal tract or first-pass metabolism, enhancing bioavailability.

Disadvantages of Sustained Drug Delivery Systems

Despite their advantages, SDDS have some limitations that must be considered during development:

1. **Complex Formulation and Manufacturing**
   - Designing sustained-release systems requires advanced technology, specialized excipients, and precise control over drug release kinetics.
2. **Risk of Dose Dumping**

- Accidental rapid release of the entire drug dose can lead to toxicity, particularly in matrix or coated systems.

3. **Limited to Specific Drugs**
   - Not all drugs are suitable for sustained release; those with very short half-lives, low potency, or narrow absorption windows may be challenging to formulate.
4. **Higher Production Costs**
   - Advanced manufacturing techniques and specialized materials can make SDDS more expensive than conventional dosage forms.
5. **Difficulty in Adjusting Dose**
   - Once formulated, modifying the drug dose is difficult without redesigning the entire delivery system.
6. **Potential for Irritation**
   - Prolonged release in a specific site of the GI tract may cause local irritation or discomfort in sensitive patients.

MATERIALS:

Glibenclamide was procured from Synpharma Research Labs, Sodium alginate, HPMC, Micro crystalline cellulose, Talc and Magnesium Stearate were obtained from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY:

Preparation of Glibenclamide tablets:

Table-1: Formulation Table of Glibenclamide sustained release tablets

S.NO.	INGREDIENTS	F1	F 2	F 3	F 4
1	Glibenclamide	5	5	5	5
2	Sodium alginate	25	50	-	-
3	HPMC	-	-	25	50
4	Microcrystalline Cellulose	165	140	165	140
5	Magnesium stearate	3	3	3	3
6	Talc	2	2	2	2
7	Total Wt.	200	200	200	200

Direct compression technique

Sustained release matrix tablets of Glibenclamide were prepared by direct compression. All the ingredients were passed through 40-mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 200mg using 10mm round flat punches on 8-station rotary tablet machine (Rimek).

Evaluation studies

1. Pre-compression parameters

a) Bulk Density

Bulk density is defined as the mass of powder divided by bulk volume.

It is calculated using the following equation:

Bulk density = weight of sample taken /volume noted

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (v_o) was measured. Then the cylinder was dropped at 2-second intervals onto a hard-wooden surface three times, from a height of one inch. The volume was recorded and the bulk density was calculated.

b) Tap density

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (v_o) was measured. Then the surface was carefully smoothed and the volume was measured. Tap density was calculated by measuring final volume (V_f) after 50 taps on wooden surface from 6 inch height and was expressed in g/cm^3 .

$$\text{Bulk density} = W/V_o$$

$$\text{Tapped density} = W/V_f$$

Where,

V_o = initial volume

V_f = final volume.

Compressibility index and Hauners ratio

The Compressibility index and Hauners ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the compressibility index and Hausner ratio.

The compressibility index and Hausner ratio may be calculated using measured values for bulk density (ρ_{bulk}) and tapped density (ρ_{tapped}) as follows:

$$\text{compressibility index} = \frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}} \times 100$$

$$\text{Hausner ratio} = \frac{\rho_{tapped}}{\rho_{bulk}}$$

Angle of repose

The flow characteristics are measured by angle of repose. Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose.

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$$\tan\theta = h/r$$

$$\theta = \tan^{-1} h/r$$

Where

h = height of pile

r = radius of the base of the pile

θ = angle of repose

Post compression parameters

Weight variation:

Method:

Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more then two of the individual tablet weight deviate from the average weight by more than the percentage shown in Table No 1 and none deviate by more than twice the percentage shown.

Table-2: Percentage deviation allowed under weight variation

Percentage deviation allowed under weight variation test.	
Average weight of tablet (X mg)	**Percentage deviation**
130 mg or less	10
130mg to 324 mg	7.5
more than 324 mg	5

Thickness:

Twenty tablets were randomly selected form each batch and there thickness was measured by using vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated.

Hardness:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets were determined.

Friability:

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Twenty tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were dedusted and reweighed. Compressed tablets should not loose more than 1% of their weight.

The percentage friability was measured using the formula,

$\% F = \{1-(Wo/W)\} \times 100$

Where,

% F = friability in percentage

Wo = Initial weight of tablet

W = weight of tablets after revolution

Content Uniformity:

Randomly select 30 tablets. 10 of these assayed individually. The Tablet pass the test if 9 of the 10 tablets must contain not less than 85% and not more than 115% of the labeled drug content and the 10th tablet may not contain less than 75% and more than 125% of the labeled content. If these conditions are not met, remaining 20 tablets assayed individually and none may fall outside of the 85 to 115% range.

Disintegration time:

The disintegration time of tablets was determined by using Disintegration test apparatus (scientific). Tablets were placed in disintegration test assembly and disc was placed on tablets in each glass tube of

assembly. The assembly was dipped in a vessel containing 900 ml distilled water at 37°C. The time for disappearance of tablet residue above mesh was noted as disintegration time.

In- Vitro Release study:
In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 100 rpm. The dissolution medium consisted of 900 ml of pH 6.8 buffer. Temperature maintained at 37±5.The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. From that 5 ml sample, 1 ml sample was withdrawn and placed in a 10 ml volumetric flask and make the volume with buffer. The diluted samples were assayed at 300 nm against reagent blank.

Stability studies:
The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile. The prepared Matrix tablets of Glibenclamide were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2°c and refrigerator 2-8°c for a period of 90 days.

RESULTS AND DISCUSSION:

EVALUATION STUDIES
Pre compression Parameters

Bulk Density: The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.569-0.574.

Tapped density: The tapped density for the formulated blend was carried out for all formulation and found in the range of 0.612-0.620.

Angle of repose: The angle of repose for the formulated blend was carried out and the results were shown in Table. It concludes that all the formulations blend was found to be in the range of 26^0 to 30^0

Compressibility index: Compressibility index was carried out, it found between 10% to 14.27 % indicating the powder blend have the required flow property for compression.

Hauser ratio: Hauser ratio was carried out, it found between 1.17 to 1.21 indicating the powder blend have the required flow property for compression.

Table-2: Results Of Pre-Compression Parameters Of Tablets

F. No	Bulk density	Tapped density	Compressibility index	Hauser ratio	Angle of repose (0)
F1	0.569	0.612	13.24	1.17	30^0
F2	0.574	0.618	14.23	1.20	28^0
F3	0.563	0.620	13.58	1.19	27^0
F4	0.572	0.605	14.27	1.21	26^0

Post compression parameters
Weight variation:
All the formulated (F1 to F4) tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness:
Tablets mean thickness were uniform in F1 to F4 formulations and were found to be in the range of 2.2 mm to 2.6 mm.

Hardness:
The measured hardness of tablets of each batch ranged between 3.1 to 3.5 kg/cm^2. This ensures good handling characteristics of all batches.

Friability:
The % Friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity:
The percentage of drug content for F1 to F4 was found to be between 84.37 % to 87.38 % of Glibenclamide, it complies with official specifications.

Disintegration Time:
In the presented studies, three different types of in vitro methods of tablet disintegration were used: those where the only factor leading to the disintegration was water wicking into the matrix of the tablet, the tests with water agitation or stirring, and the methods where direct destructive forces were put on the tested tablet, such as grinding or pressing with additional weight. Therefore, disintegration tests showed great variability in the data measured with different methods.

Table-3: Evaluation parameters of Glibenclamide SR tablets

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Disintegration time (min)
F1	200	2.4	3.3	0.27	85.30	17
F2	200	2.6	3.5	0.28	87.38	14
F3	199	2.2	3.1	0.30	86.93	15
F4	201	2.4	3.2	0.26	84.37	19

Dissolution studies

All the 4 formulation of Glibenclamide tablets were subjected to in vitro release studies these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for period of time.

Table-4: Drug release studies of all formulations

Time	F1	F2	F3	F4
0	0	0	0	0
1	18.50	19.67	18.64	17.34
2	27.53	28.10	28.16	28.60
3	35.46	38.16	37.50	37.18
4	53.11	55.10	57.46	56.80
5	65.82	69.49	69.50	68.15
6	74.86	75.82	76.50	77.49
7	82.91	87.91	86.49	84.45
8	94.67	98.52	96.72	93.52

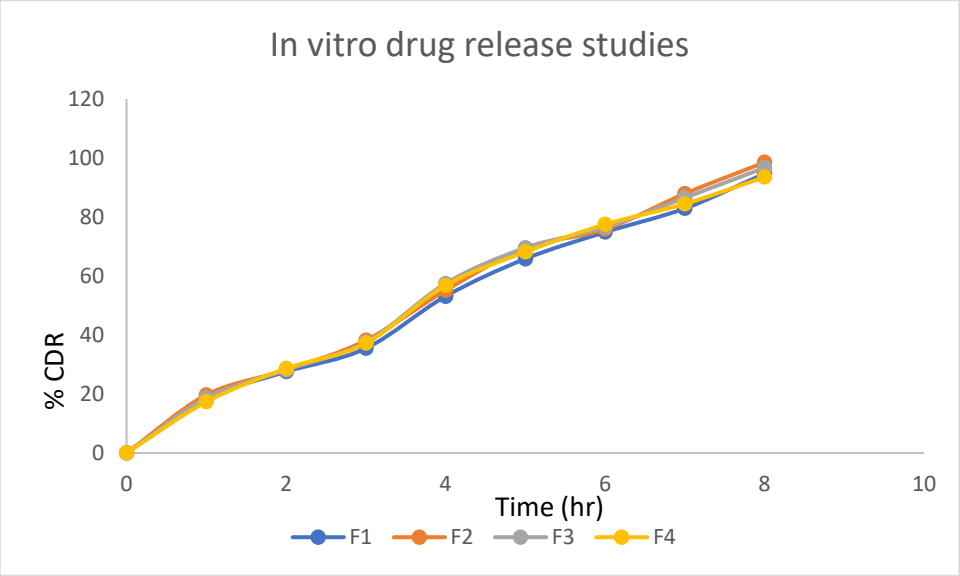


Fig-1: Dissolution Profile of F1 to F4 formulations

Cumulative Drug release of F2 formulation shows 98.52 % within 8 hr better drug release when compared with other formulations.

Stability Study

There was no significant change in physical and chemical properties of the tablets of formulation F-2 after 90 days. Parameters quantified at various time intervals were shown.

Table-5: Stability studies of all formulations

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-2	**25^{0}C/60%RH % Release**	98.52	97.18	96.57	95.10	**Not less than 85 %**
F-2	**30^{0}C/75% RH % Release**	98.52	97.27	96.19	95.22	**Not less than 85 %**
F-2	**40^{0}C/75% RH % Release**	98.52	97.56	96.45	95.48	**Not less than 85 %**

SUMMARY AND CONCLUSION:

In the present study, sustained release matrix tablets of Glibenclamide were successfully formulated and evaluated using different concentrations of polymers such as sodium alginate and HPMC. Four formulations (F1 to F4) were prepared and systematically assessed for pre-compression and post-compression parameters, in vitro drug release, and stability studies.Preformulation studies confirmed the purity and suitability of Glibenclamide for formulation development, as evidenced by organoleptic evaluation, melting point determination (171–175°C), and solubility analysis. The FT-IR studies indicated no significant interaction between the drug and excipients, confirming their compatibility.The pre-compression studies demonstrated good flow properties of the powder blends, as indicated by acceptable values of bulk density, tapped density, angle of repose, Carr's index, and Hausner's ratio, ensuring suitability for direct compression. Post-compression evaluation results showed that all formulations complied with official pharmacopoeial limits for weight variation, hardness, friability, thickness, and drug content uniformity.The in vitro dissolution studies revealed that all formulations exhibited sustained drug release up to 8 hours. Among all formulations, F2 (containing 50 mg sodium alginate) showed the most desirable release profile with 98.52% drug release within 8 hours, indicating better sustained release characteristics compared to other formulations.Stability studies conducted under different ICH recommended conditions showed no significant changes in physical appearance, drug content, or drug release profile of the optimized formulation (F2) over a period of 3 months, confirming its stability and robustness.

CONCLUSION:

It can be concluded that a stable and effective sustained release matrix tablet of Glibenclamide was successfully developed. The optimized formulation (F2) exhibited good physicochemical properties, satisfactory sustained drug release behavior, and stability, making it a promising approach for improving therapeutic efficacy and patient compliance in the management of Type 2 diabetes mellitus.

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