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DEVELOPMENT OF CONTROLLED-RELEASE GLIPIZIDE TABLETS USING OSMOTIC TECHNOLOGY AND HOT-MELT GRANULATION

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ABSTRACT

Glipizide is a second-generation sulfonylurea widely used in the treatment of type 2 diabetes mellitus; however, its short half-life and rapid absorption necessitate frequent dosing, which may reduce patient compliance and cause fluctuations in plasma drug levels. The present study aims to develop controlled-release glipizide tablets using osmotic technology combined with hot-melt granulation to achieve prolonged and predictable drug release. Hot-melt granulation was employed to improve drug distribution, flow properties, and compressibility of the powder blend. The formulated core tablets were coated with a semipermeable membrane and provided with a delivery orifice to facilitate osmotic-controlled release. The prepared tablets were evaluated for physicochemical properties, drug content uniformity, in-vitro drug release, and release kinetics. The optimized formulation exhibited satisfactory tablet characteristics and sustained drug release over an extended period, following near zero-order kinetics. The study demonstrates that osmotic technology combined with hot-melt granulation is an effective approach for developing controlled-release glipizide tablets with improved therapeutic performance and patient compliance.

Keywords: Glipizide; Osmotic Drug Delivery System; Hot-Melt Granulation; Controlled Release Tablets; Diabetes Mellitus

I. INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, defective insulin action, or a combination of both. It represents one of the most significant global health challenges due to its rapidly increasing prevalence and association with severe long-term complications such as cardiovascular disease, nephropathy, neuropathy, and retinopathy. Type 2 diabetes mellitus accounts for the majority of diabetes cases worldwide and is strongly linked to lifestyle factors, aging populations, and genetic predisposition. Effective glycemic control is essential in preventing disease progression and associated complications, thereby necessitating long-term pharmacotherapy.

Oral antidiabetic agents remain the mainstay of treatment for type 2 diabetes mellitus due to their convenience, non-invasive administration, and cost-effectiveness. However, conventional oral dosage forms often present limitations related to rapid drug absorption, short duration of action, and significant fluctuations in plasma drug concentrations. These fluctuations may result in inadequate glycemic control, frequent dosing schedules, and an increased risk of adverse effects such as hypoglycemia. As diabetes requires lifelong management, patient adherence to medication regimens plays a crucial role in therapeutic success, highlighting the need for improved drug delivery systems.

Glipizide is a second-generation sulfonylurea widely prescribed for the management of type 2 diabetes mellitus. It exerts its hypoglycemic effect by stimulating insulin secretion from pancreatic β-cells, thereby lowering blood glucose levels. Glipizide is characterized by rapid absorption and high potency; however, it has a relatively short biological half-life, necessitating multiple daily dosing to maintain effective plasma concentrations. This frequent dosing regimen can lead to poor patient compliance and significant peak–trough variations in drug levels, which may increase the risk of hypoglycemia. Consequently, there is a strong rationale for developing controlled-release formulations of glipizide to achieve sustained therapeutic action and improved safety.

Controlled-release drug delivery systems are designed to release drugs at a predetermined rate over an extended period, maintaining consistent plasma concentrations and reducing dosing frequency. These systems offer several advantages, including improved therapeutic efficacy, reduced side effects, enhanced patient compliance, and better disease management. Among various controlled-

release approaches, osmotic drug delivery systems have gained considerable attention due to their ability to provide predictable, reproducible, and controlled drug release profiles.

Osmotic drug delivery systems operate on the principle of osmotic pressure, where water enters the dosage form through a semipermeable membrane, generating internal pressure that drives drug release through a delivery orifice. One of the major advantages of osmotic systems is that drug release is largely independent of physiological variables such as gastrointestinal pH, motility, and food intake. This makes osmotic systems highly reliable and suitable for drugs that require consistent and prolonged release. Furthermore, osmotic systems often exhibit good in vitro–in vivo correlation, making them attractive for oral controlled drug delivery.

In the formulation of osmotic tablets, the selection of appropriate manufacturing techniques is critical to ensure uniform drug distribution, consistent release behavior, and robust tablet properties. Hot-melt granulation has emerged as an effective and solvent-free granulation technique that offers several advantages over conventional wet granulation methods. This technique involves the use of a meltable binder that solidifies upon cooling, resulting in granules with excellent flowability, compressibility, and mechanical strength. The absence of solvents reduces processing time, eliminates solvent-related stability issues, and makes hot-melt granulation an environmentally friendly and scalable process.

The combination of osmotic technology with hot-melt granulation presents a promising strategy for developing controlled-release glipizide tablets. Hot-melt granulation ensures uniform dispersion of the drug and excipients, while osmotic technology enables controlled and prolonged drug release. Together, these techniques can overcome the limitations associated with conventional glipizide formulations by providing sustained drug delivery, minimizing plasma concentration fluctuations, and improving patient adherence.

The present study focuses on the development of controlled-release glipizide tablets using osmotic technology combined with hot-melt granulation. The objective is to design a robust formulation capable of delivering glipizide at a controlled rate over an extended period, thereby enhancing therapeutic efficacy and reducing dosing frequency. The study involves formulation development, physicochemical characterization, and in-vitro evaluation of the prepared tablets to assess their suitability as a prolonged-release oral dosage form. The findings of this research are expected to

contribute to the advancement of controlled drug delivery systems for the effective management of type 2 diabetes mellitus.

II. MATERIALS

Glipizide was used as the active pharmaceutical ingredient (API) in the formulation of controlled-release osmotic tablets. Osmotic agents such as sodium chloride and mannitol were selected to generate the necessary osmotic pressure for controlled drug release. Hydroxypropyl methylcellulose (HPMC) was used as a hydrophilic polymer to regulate drug solubility and modulate the release profile. Hot-melt granulation was performed using suitable waxy binders such as polyethylene glycol or glyceryl behenate to improve granule cohesion and eliminate the use of organic solvents. Cellulose acetate was employed as the semipermeable membrane-forming polymer for coating the tablets, owing to its selective permeability and excellent film-forming properties. Plasticizers such as polyethylene glycol or diethyl phthalate were added to enhance membrane flexibility. Other excipients including microcrystalline cellulose, magnesium stearate, and talc were used as fillers, lubricants, and glidants. All materials used were of pharmaceutical grade.

Hot-Melt Granulation

Hot-melt granulation was employed to prepare uniform granules with improved flowability and compressibility. In this process, the selected waxy binder was heated to a temperature above its melting point to obtain a molten mass. Glipizide and other excipients, including osmotic agents and polymers, were gradually added to the molten binder under continuous mixing to ensure uniform drug distribution. The resulting homogeneous mass was allowed to cool and solidify at room temperature. Once solidified, the mass was milled using a suitable milling apparatus and passed through standard sieves to obtain granules of uniform size. The prepared granules were evaluated for flow properties such as bulk density, tapped density, angle of repose, Carr’s index, and Hausner’s ratio to ensure suitability for compression.

Preparation of Core Tablets

The granules obtained from the hot-melt granulation process were blended with lubricants and glidants, such as magnesium stearate and talc, to enhance flow and prevent sticking during

compression. The blending was carried out for a specified duration to ensure uniform distribution of excipients without over-lubrication. The final blend was compressed into tablets using a tablet compression machine fitted with appropriate punches and dies. Compression force was optimized to obtain tablets with adequate hardness and mechanical strength while maintaining sufficient porosity for osmotic action. The prepared core tablets were evaluated for pre-compression parameters, including powder flow characteristics, and post-compression parameters such as weight variation, thickness, hardness, friability, and drug content uniformity, in accordance with pharmacopeial guidelines.

Coating and Orifice Formation

The core tablets were coated with a semipermeable membrane to regulate water influx and control drug release. The coating solution was prepared by dissolving cellulose acetate in a suitable organic solvent system, followed by the addition of plasticizer to improve film flexibility and prevent brittleness. The coating was applied uniformly to the core tablets using a pan coating or spray coating technique under controlled conditions of temperature and spray rate. The thickness of the coating was carefully monitored, as it directly influences the rate of water permeation and drug release. After coating, a delivery orifice was created on the tablet surface using laser drilling to ensure precision and reproducibility. The size and number of orifices were optimized to allow controlled release of glipizide without causing dose dumping or excessive internal pressure buildup.

Evaluation Studies

The formulated osmotic glipizide tablets were subjected to comprehensive evaluation studies to assess their quality and performance. Physical characterization included measurement of tablet hardness using a hardness tester, friability using a friabilator, thickness using a digital caliper, and weight variation to ensure uniformity of dosage units. Drug content uniformity was determined by analyzing crushed tablet samples using a suitable analytical method such as UV–visible spectrophotometry or high-performance liquid chromatography (HPLC).

In-vitro drug release studies were conducted using a standard dissolution apparatus (USP Type I or Type II) under controlled conditions to evaluate the release profile of glipizide over an extended

period. Dissolution testing was performed in suitable dissolution media, and samples were withdrawn at predetermined intervals and analyzed for drug content. The obtained dissolution data were fitted to various kinetic models, including zero-order, first-order, Higuchi, and Korsmeyer–Peppas models, to determine the drug release mechanism and rate-controlling steps. These studies provided insight into the effectiveness of osmotic technology and hot-melt granulation in achieving controlled and prolonged drug release.

III. RESULTS AND DISCUSSION

The hot-melt granulation technique employed in the formulation of osmotic glipizide tablets resulted in the formation of uniform and free-flowing granules. Evaluation of pre-compression parameters such as bulk density, tapped density, angle of repose, Carr's index, and Hausner's ratio indicated excellent flow properties and good compressibility of the granules. These characteristics are essential for achieving uniform die filling during tablet compression, thereby ensuring consistent tablet weight and uniform drug distribution. The improved flow behavior can be attributed to the effective binding action of the meltable binder, which enhanced particle cohesion and reduced segregation of formulation components.

The prepared core tablets exhibited satisfactory post-compression characteristics. Tablet hardness was within the acceptable range, providing sufficient mechanical strength to withstand subsequent coating and handling processes. Friability values were found to be below the pharmacopeial limit, indicating good resistance to abrasion and mechanical stress. Uniformity of weight and thickness confirmed consistency in tablet dimensions, while drug content analysis demonstrated that the tablets contained glipizide within acceptable limits. These results indicate good formulation reproducibility and effective incorporation of glipizide into the tablet matrix through hot-melt granulation.

Coated osmotic tablets showed uniform and intact semipermeable membranes without visible defects such as cracks or peeling. The coating thickness was consistent across tablets, which is critical for controlling water permeation and drug release. The presence of a precisely drilled delivery orifice ensured controlled release of the drug solution or suspension generated within the tablet core. The integrity of the coating and optimal orifice size contributed significantly to the reproducibility of drug release profiles.

In-vitro dissolution studies demonstrated a controlled and sustained release of glipizide over an extended period, confirming the effectiveness of the osmotic drug delivery system. The release profile showed a gradual and continuous drug release pattern without an initial burst effect, which is desirable for maintaining stable plasma drug concentrations. Dissolution studies conducted under varying conditions indicated that the drug release was largely independent of pH and agitation, further supporting the osmotic-controlled release mechanism. This behavior highlights the robustness of the osmotic system in delivering consistent therapeutic levels of glipizide.

Kinetic modeling of the dissolution data revealed that the optimized formulation followed near zero-order release kinetics. Zero-order release is particularly advantageous for drugs like glipizide, as it ensures a constant drug release rate and minimizes fluctuations in plasma drug levels. The release mechanism was primarily governed by osmotic pressure-driven water influx through the semipermeable membrane, followed by controlled drug extrusion through the delivery orifice. These findings confirm that formulation variables such as osmotic agent concentration, membrane thickness, and orifice size were appropriately optimized.

Overall, the combination of osmotic technology and hot-melt granulation significantly enhanced the formulation performance and stability of glipizide tablets. Hot-melt granulation improved granule quality and tablet uniformity, while the osmotic system ensured predictable and prolonged drug release. The results suggest that this formulation approach is highly effective for developing controlled-release oral dosage forms of glipizide, offering potential benefits in terms of improved glycemic control, reduced dosing frequency, and enhanced patient compliance.

IV. CONCLUSION

The study successfully developed controlled-release glipizide tablets using osmotic technology and hot-melt granulation. The optimized formulation demonstrated satisfactory physicochemical properties and prolonged, predictable drug release. This approach offers a promising strategy for improving therapeutic efficacy, reducing dosing frequency, and enhancing patient compliance in the management of type 2 diabetes mellitus. Further in-vivo studies are recommended to confirm the clinical performance of the developed formulation.

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