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Design, Development and Evaluation of Natural Polymer-Based Matrix Systems for the Controlled Delivery of Repaglinide in Diabetes Management

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyper-glycemia resulting from defects in insulin secretion, insulin action, or both. Oral antidiabetic drugs remain the cornerstone of therapy for type 2 diabetes mellitus; however, conventional immediate-release formulations often suffer from short biological half-lives, frequent dosing requirements, fluctuating plasma drug concentrations, and reduced patient compliance. Repaglinide, a meglitinide class antidiabetic drug, exhibits rapid onset of action and a short elimination half-life, necessitating multiple daily dosing prior to meals. These pharmacokinetic limitations make repaglinide a suitable candidate for controlled drug delivery systems.

The present research focuses on the design, development, and evaluation of natural polymer-based matrix tablets of repaglinide aimed at achieving sustained and controlled drug release, thereby improving therapeutic efficacy and patient adherence. Matrix tablets were formulated using natural polymers such as guar gum, xanthan gum, and other biodegradable polysaccharides, selected for their biocompatibility, safety, and cost-effectiveness. Tablets were prepared by wet granulation/direct compression techniques and evaluated for pre-compression and post-compression parameters, including flow properties, hardness, friability, weight variation, drug content, and in-vitro dissolution behavior.

In-vitro drug release studies were conducted using USP dissolution apparatus, and release kinetics were analyzed using zero-order, first-order, Higuchi, and Korsmeyer-Peppas models to elucidate the drug release mechanism. Stability studies were performed under accelerated conditions to assess formulation robustness. The optimized formulation demonstrated sustained drug release over an extended period with acceptable physicochemical properties, following diffusion-controlled and anomalous transport mechanisms. This study concludes that natural polymer-based matrix systems offer a promising approach for controlled oral delivery of repaglinide in diabetes management.

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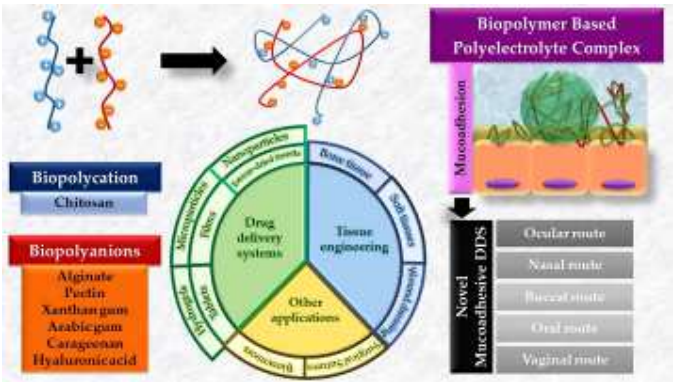


KEYWORDS: *Repaglinide, Controlled release, Matrix tablets, Natural polymers, Diabetes mellitus, Sustained drug delivery.*

1. INTRODUCTION

1.1. Controlled Drug Delivery Systems

Controlled drug delivery systems (CDDS) represent one of the most significant advancements in pharmaceutical formulation science, designed to deliver therapeutic agents at a predetermined rate for a specified period of time. Unlike conventional dosage forms, which release the drug immediately after administration, controlled release systems maintain drug concentrations within the therapeutic window, minimizing peaks and troughs in plasma levels.

The primary objectives of controlled drug delivery systems include:

- Prolongation of drug action
- Reduction in dosing frequency
- Improvement in patient compliance
- Minimization of adverse effects
- Optimization of therapeutic efficacy

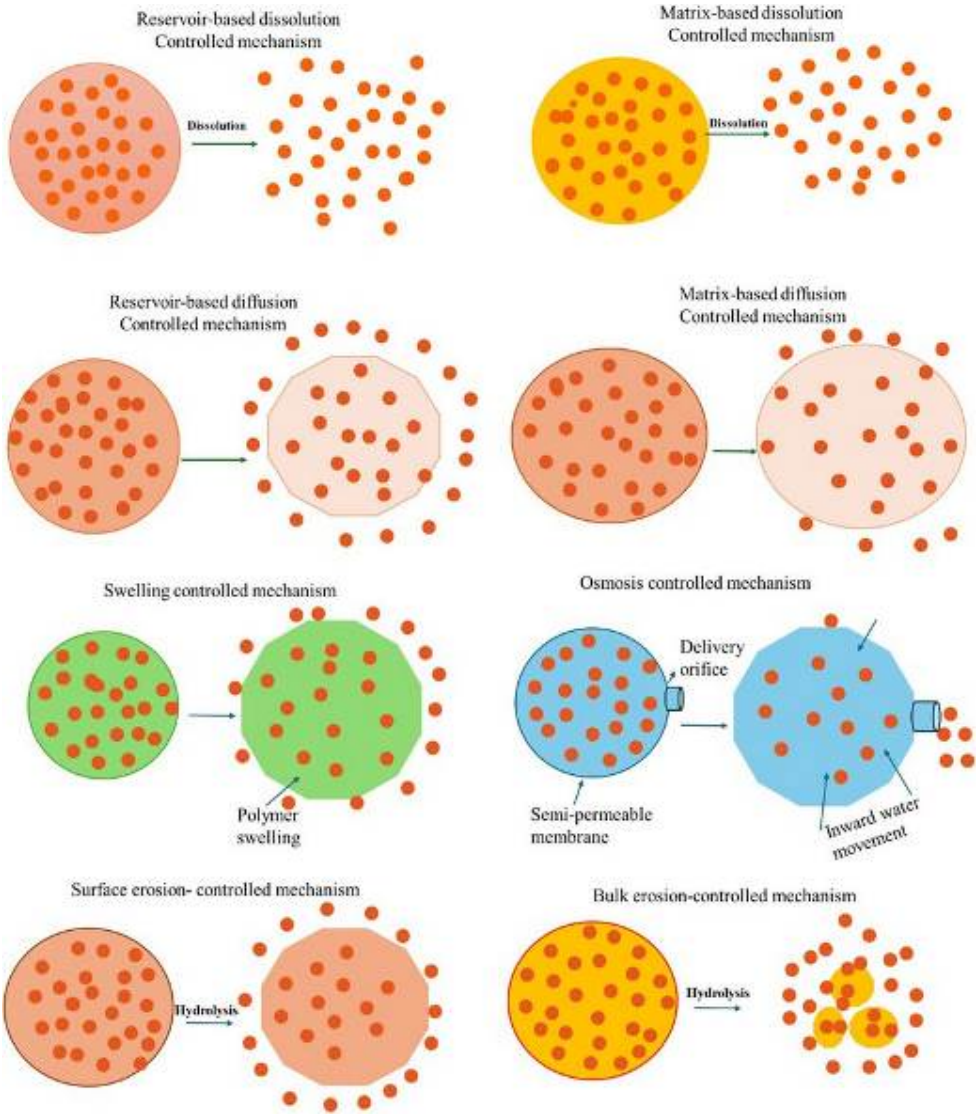


Figure 1. Schematic representation of controlled drug delivery systems (CDDS) showing maintenance of plasma drug concentration within the therapeutic window over an extended period, in contrast to immediate-release dosage forms that exhibit pronounced peaks and troughs.

Controlled release systems are particularly beneficial in the management of chronic diseases such as diabetes mellitus, hypertension, cardiovascular disorders, and neurological conditions, where long-term pharmacotherapy is required.

1.2. Classification of Modified Release Drug Delivery Systems

Modified release dosage forms are broadly classified into:

1.2.1. Sustained Release Systems

These systems are designed to slowly release the drug over an extended period, maintaining a relatively constant drug concentration in systemic circulation. Sustained release does not necessarily imply a constant release rate but aims to prolong drug availability.

1.2.2. Controlled Release Systems

Controlled release formulations release the drug at a predetermined, predictable rate, ideally following zero-order kinetics. These systems provide greater control over plasma drug concentrations.

1.2.3. Extended Release Systems

Extended release formulations allow a reduction in dosing frequency, often by approximately two-fold compared to immediate-release products.

1.2.4. Delayed Release Systems

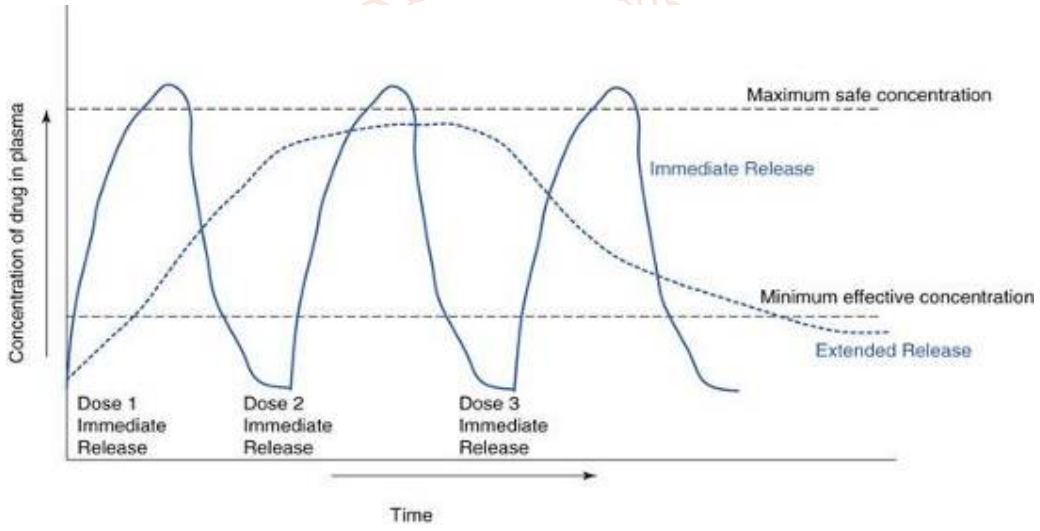
These formulations delay drug release until the dosage form reaches a specific site in the gastrointestinal tract, such as enteric-coated tablets.

1.3. Oral Controlled Drug Delivery Systems

The oral route remains the most preferred route of drug administration due to its convenience, patient acceptability, safety, and cost-effectiveness. Oral controlled drug delivery systems aim to overcome limitations associated with conventional oral dosage forms, such as:

- Short half-life of drugs
- Poor bioavailability
- Frequent dosing
- Gastrointestinal side effects

Among various oral controlled release systems, **matrix tablets** are the most widely investigated and commercially successful due to their simplicity of formulation, ease of manufacturing, and reliability.



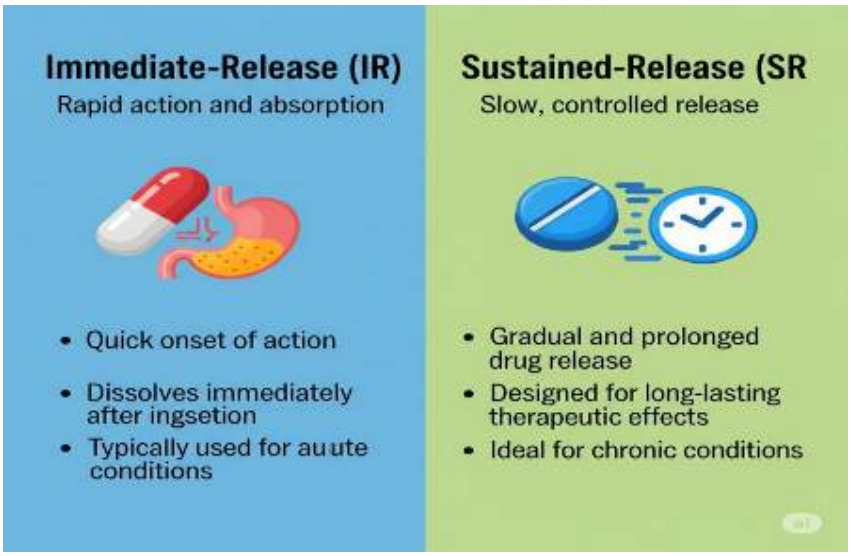


Figure 2. Colourful classification of modified release drug delivery systems, including sustained release, controlled release, extended release, and delayed release formulations, based on drug release pattern and site of action.

1.4. Matrix Tablets as Controlled Release Systems

Matrix tablets consist of a drug uniformly dispersed within a polymeric matrix that controls drug release through diffusion, erosion, or a combination of both mechanisms. Unlike reservoir systems, matrix systems eliminate the risk of dose dumping, making them safer for oral administration.

Drug release from matrix systems is influenced by:

- Nature and concentration of polymer
- Drug solubility
- Particle size
- Matrix porosity
- Degree of swelling and erosion

Matrix systems follow Fick's laws of diffusion, and drug release kinetics are often described using Higuchi, Korsmeyer-Peppas, or zero-order models.

1.5. Natural Polymers in Controlled Drug Delivery

Natural polymers have gained considerable attention in pharmaceutical research due to their:

- Biodegradability
- Biocompatibility
- Non-toxicity
- Low cost
- Renewable nature

Examples include guar gum, xanthan gum, alginates, pectin, chitosan, and starch derivatives. These polymers form hydrophilic matrices that swell upon contact with gastrointestinal fluids, creating a gel barrier that controls drug diffusion.

Compared to synthetic polymers, natural polymers offer improved safety profiles and are environmentally sustainable, making them ideal candidates for oral controlled release formulations.

1.6. Diabetes Mellitus

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels due to impaired insulin secretion, insulin resistance, or both. Type 2 diabetes mellitus accounts for approximately 90-95% of all diabetes cases and is often associated with obesity, sedentary lifestyle, and genetic predisposition.

Long-term uncontrolled diabetes leads to serious complications, including:

- Cardiovascular disease
- Neuropathy
- Nephropathy
- Retinopathy

Effective glycemic control through pharmacotherapy is essential to prevent these complications.

1.7. Repaglinide: Drug Profile

Repaglinide is a short-acting oral hypoglycemic agent belonging to the meglitinide class. It stimulates insulin release from pancreatic β-cells by closing ATP-dependent potassium channels, resulting in calcium influx and insulin secretion.

Pharmacokinetic limitations of repaglinide include:

- Short biological half-life (~1 hour)
- Rapid hepatic metabolism
- Requirement of multiple daily dosing

These characteristics make repaglinide an excellent candidate for controlled release formulation to improve patient compliance and therapeutic outcomes.

1.8. Rationale of the Study

Despite the clinical effectiveness of repaglinide, its short duration of action necessitates frequent dosing, which may reduce patient adherence. Developing a **natural polymer-based controlled release matrix tablet** can:

- Sustain drug release
- Reduce dosing frequency
- Minimize plasma level fluctuations
- Enhance patient compliance

Therefore, the present study aims to design and evaluate natural polymer-based matrix tablets of repaglinide for effective diabetes management.

2. Aim and Objectives

Aim

To design, develop, and evaluate natural polymer-based matrix systems for the controlled delivery of repaglinide in diabetes management.

Objectives

1. To formulate controlled release matrix tablets of repaglinide using natural polymers
2. To evaluate pre-compression and post-compression parameters
3. To study in-vitro drug release behavior
4. To analyze drug release kinetics and mechanism
5. To perform stability studies on optimized formulation

3. Materials and Methods

3.1. Materials

Repaglinide was obtained as a gift sample from a reputed pharmaceutical manufacturer and used as the active pharmaceutical ingredient (API). Natural polymers such as guar gum, xanthan gum, and other polysaccharide-based excipients were selected as matrix-forming agents. Microcrystalline cellulose (MCC) was used as a diluent, polyvinyl pyrrolidone (PVP K-30) as a binder, magnesium stearate as a

lubricant, and talc as a glidant. All chemicals and reagents used were of analytical grade.

Purified water was used throughout the study. All materials were stored under appropriate conditions as recommended by the manufacturers.

3.2. Preformulation Studies

Preformulation studies were conducted to understand the physicochemical properties of repaglinide and to assess its compatibility with selected excipients. These studies are critical for successful formulation development.

3.2.1. Organoleptic Properties

The drug sample was evaluated for color, odor, and appearance. Repaglinide appeared as a white to off-white crystalline powder with no characteristic odor, confirming its purity and suitability for formulation.

3.2.2. Determination of Melting Point

The melting point of repaglinide was determined using the capillary method. A small quantity of the drug was filled into a capillary tube sealed at one end and placed in a melting point apparatus. The temperature at which the drug started melting and completely liquefied was recorded.

3.2.3. Solubility Studies

Solubility studies of repaglinide were conducted in various solvents including distilled water, 0.1 N hydrochloric acid (pH 1.2), phosphate buffer (pH 6.8), methanol, and ethanol. An excess amount of drug was added to each solvent and shaken at room temperature for 24 hours. The solutions were filtered, and the drug concentration was determined spectrophotometrically.

3.2.4. Determination of λmax

A stock solution of repaglinide was prepared in methanol. The solution was scanned in a UV-visible spectrophotometer between 200-400 nm to determine the wavelength of maximum absorbance (λmax). The identified λmax was used for further quantitative analysis.

3.2.5. Preparation of Calibration Curve

A calibration curve of repaglinide was prepared in phosphate buffer pH 6.8. Serial dilutions were made from the stock solution to obtain concentrations within the Beer-Lambert's law range. Absorbance values were measured at λmax, and a standard calibration curve was plotted between concentration and absorbance.

3.2.6. Drug-Excipient Compatibility Studies

Compatibility between repaglinide and selected polymers was evaluated using Fourier Transform Infrared Spectroscopy (FTIR). Physical mixtures of drug and excipients were prepared in a 1:1 ratio and analyzed in the range of 4000-400 cm^{-1}. The spectra were compared with the pure drug spectrum to identify any significant shifts or disappearance of characteristic peaks, indicating potential interactions.

3.3. Formulation Design of Matrix Tablets

Matrix tablets of repaglinide were formulated using different concentrations of natural polymers to study their effect on drug release behavior. The polymers were selected based on their swelling, gel-forming, and release-retarding properties.

3.3.1. Selection of Polymers

Natural polymers such as guar gum and xanthan gum were selected due to their hydrophilic nature, biodegradability, and ability to form gel matrices upon hydration. These polymers control drug release primarily through swelling and diffusion mechanisms.

3.3.2. Method of Preparation

Matrix tablets were prepared by the **wet granulation method**, which offers improved content uniformity and flow properties compared to direct compression.

Procedure:

1. Repaglinide and polymer were accurately weighed and passed through a #60 sieve.
2. The drug and excipients were mixed uniformly in a mortar.
3. PVP K-30 solution in isopropyl alcohol was used as a granulating agent.
4. The wet mass was passed through a #16 sieve to form granules.
5. Granules were dried at 40-45 °C until optimal moisture content was achieved.
6. Dried granules were passed through a #20 sieve.
7. Magnesium stearate and talc were added and mixed gently.
8. The final blend was compressed into tablets using a rotary tablet compression machine.

3.4. Evaluation of Granules (Pre-Compression Parameters)

Granules were evaluated for flow and compressibility properties to ensure uniform die filling and consistent tablet weight.

3.4.1. Bulk Density

Bulk density was determined by pouring a known weight of granules into a graduated cylinder and measuring the initial volume.

Bulk Density=Bulk volume/Weight of granules

3.4.2. Tapped Density

Tapped density was measured by tapping the cylinder containing granules until a constant volume was achieved.

Tapped Density=Tapped volume/ Weight of granules

3.4.3. Carr's Compressibility Index

Carr's index was calculated to assess flowability.

Carr's Index=Tapped Density- Bulk Density×100/ Tapped Density

3.4.4. Hausner's Ratio

Hausner's ratio was calculated as an indicator of interparticle friction.

Hausner's Ratio=Bulk Density/Tapped Density

3.4.5. Angle of Repose

The angle of repose was determined using the fixed funnel method to evaluate flow properties.

$\tan\theta = rh$

Where *h* is the height and *r* is the radius of the heap.

3.5. Evaluation of Matrix Tablets (Post-Compression Parameters)

3.5.1. Physical Appearance

Tablets were visually inspected for color uniformity, surface texture, and absence of defects such as cracks or capping.

3.5.2. Weight Variation Test

Twenty tablets were randomly selected and weighed individually. The average weight was calculated, and percentage deviation was determined according to pharmacopeial standards.

3.5.3. Thickness

Tablet thickness was measured using a digital vernier caliper, and the mean thickness was calculated.

3.5.4. Hardness Test

Tablet hardness was determined using a Monsanto hardness tester. Adequate hardness is essential to withstand mechanical stress during handling.

3.5.5. Friability Test

Friability was evaluated using a Roche friabilator. Tablets were rotated at 25 rpm for 4 minutes, and percentage weight loss was calculated.

3.5.6. Drug Content Uniformity

Tablets were crushed, and an accurately weighed quantity equivalent to one tablet was dissolved in phosphate buffer pH 6.8. The solution was filtered, diluted, and analyzed spectrophotometrically.

3.6. In-Vitro Dissolution Studies

In-vitro drug release studies were carried out using USP Dissolution Apparatus Type II (Paddle method). Dissolution medium consisted of phosphate buffer pH 6.8 maintained at 37 ± 0.5 °C with a paddle speed of 50 rpm. Samples were withdrawn at predetermined intervals, filtered, and analyzed for drug content.

3.7. Drug Release Kinetics

The dissolution data were fitted into various kinetic models including:

- Zero-order model
- First-order model
- Higuchi model
- Korsmeyer-Peppas model

To determine the mechanism of drug release.

4. Results and Discussion

4.1. Preformulation Studies

4.1.1. Organoleptic Properties

Repaglinide was found to be a white to off-white crystalline powder with no characteristic odor. The uniform appearance and absence of discoloration or odor indicated acceptable purity and stability of the drug sample. These observations were consistent with official literature reports and confirmed the suitability of the drug for formulation development.

4.1.2. Melting Point Determination

The melting point of repaglinide was found to be within the reported literature range, indicating the crystalline nature of the drug and confirming its identity. The sharp melting point further suggested the absence of significant impurities and validated the integrity of the API used in the study.

4.1.3. Solubility Studies

Solubility studies revealed that repaglinide is poorly soluble in distilled water but showed comparatively higher solubility in organic solvents such as methanol and ethanol. In aqueous buffers, the drug exhibited limited solubility, which supports the rationale for developing a controlled release formulation. Poor aqueous solubility combined with short biological half-life makes repaglinide an ideal candidate for matrix-based sustained release systems, where drug diffusion can be effectively controlled by polymeric matrices.

4.1.4. Determination of λmax and Calibration Curve

The UV-visible spectrophotometric analysis showed that repaglinide exhibited maximum absorbance (λmax) at a characteristic wavelength in phosphate buffer pH 6.8. The calibration curve demonstrated a linear relationship between absorbance and concentration over the selected range, with a correlation coefficient (R^2) close to unity. This confirmed compliance with Beer-Lambert's law and validated the analytical method for quantitative estimation of repaglinide in dissolution and drug content studies.

4.1.5. Drug-Excipient Compatibility Studies (FTIR Analysis)

FTIR spectra of pure repaglinide showed characteristic peaks corresponding to functional groups such as carbonyl (C=O), amide (N-H), and aromatic stretching vibrations. The FTIR spectra of

physical mixtures of repaglinide with selected natural polymers exhibited all the characteristic peaks of the drug without significant shifts, disappearance, or formation of new peaks. This indicated the absence of chemical interactions between repaglinide and excipients, confirming compatibility and stability of the formulation components.

4.2. Evaluation of Granules (Pre-Compression Parameters)

Pre-compression evaluation is critical to ensure uniform die filling and reproducibility during tablet compression.

4.2.1. Bulk Density and Tapped Density

The bulk density and tapped density values of all granule formulations were found to be within acceptable ranges. The relatively small difference between bulk and tapped densities indicated good packing ability of the granules and minimal interparticle void spaces.

4.2.2. Carr's Compressibility Index and Hausner's Ratio

Carr's index values for all formulations were found to be below 20%, and Hausner's ratio values were less than 1.25, indicating good flow properties. These results suggest that the granules possessed adequate compressibility and flow characteristics suitable for tablet compression without problems such as weight variation or segregation.

4.2.3. Angle of Repose

The angle of repose for all formulations was found to be within the range indicative of good flowability. The improved flow behavior can be attributed to uniform granule size distribution and the presence of glidants such as talc. Good flow properties ensured consistent tablet weight and uniform drug distribution.

4.3. Evaluation of Matrix Tablets (Post-Compression Parameters)

4.3.1. Physical Appearance

All formulated matrix tablets were uniform in color, smooth-surfaced, and free from visible defects such as cracks, capping, or lamination. The absence of physical defects indicated appropriate formulation composition and optimized compression force.

4.3.2. Weight Variation

Weight variation studies showed that all formulations complied with pharmacopeial limits. The minimal variation in tablet weight indicated uniform die filling and consistent flow of granules during compression, which is essential for dose uniformity.

4.3.3. Thickness and Hardness

Tablet thickness was found to be uniform across all batches, indicating consistency in compression parameters. Hardness values were within the acceptable range, providing sufficient mechanical strength to withstand handling and transportation while allowing adequate matrix hydration during dissolution studies.

4.3.4. Friability

Friability values for all formulations were less than 1%, which is within acceptable pharmacopeial limits. This indicated good mechanical integrity of the tablets and confirmed the effectiveness of the binder and compression process.

4.3.5. Drug Content Uniformity

Drug content analysis revealed that all formulations contained repaglinide within acceptable limits of the labeled claim. Uniform drug distribution throughout the matrix tablets demonstrated effective blending and granulation processes.

4.4. In-Vitro Dissolution Studies

In-vitro dissolution studies were conducted to evaluate the drug release behavior of repaglinide from natural polymer-based matrix tablets. Dissolution profiles showed a clear influence of polymer type and concentration on drug release patterns.

Formulations containing lower concentrations of natural polymers exhibited faster initial drug release due to rapid hydration and weaker gel barrier formation. In contrast, formulations with higher polymer concentrations showed prolonged drug release owing to increased matrix swelling, gel strength, and diffusion path length.

The swelling of hydrophilic natural polymers resulted in the formation of a viscous gel layer around the tablet, which acted as a diffusion barrier and controlled the release of repaglinide. This mechanism effectively reduced burst release and maintained sustained drug release over an extended period.

4.5. Effect of Polymer Concentration on Drug Release

An increase in polymer concentration resulted in a significant decrease in the drug release rate. This can be attributed to enhanced gel layer thickness and reduced matrix porosity, which slowed down the diffusion of drug molecules from the hydrated matrix.

Natural polymers such as guar gum and xanthan gum demonstrated excellent release-retarding properties due to their high swelling index and gel-forming ability. These findings highlight the potential of natural polymers as effective and safe alternatives to synthetic polymers in controlled drug delivery systems.

4.6. Drug Release Kinetic Modeling

To elucidate the mechanism of drug release, dissolution data were fitted to various kinetic models.

4.6.1. Zero-Order Kinetics

Some formulations exhibited a near-linear release profile, indicating zero-order release kinetics. This suggests a constant drug release rate over time, which is ideal for maintaining steady plasma drug levels.

4.6.2. First-Order Kinetics

Formulations with lower polymer content followed first-order release kinetics, where the release rate depended on the concentration of the drug remaining in the matrix.

4.6.3. Higuchi Model

Most formulations showed good correlation with the Higuchi model, indicating that drug release was predominantly diffusion-controlled. This is characteristic of hydrophilic matrix systems where drug diffusion occurs through a swollen polymeric network.

4.6.4. Korsmeyer-Peppas Model

The release exponent (n) values obtained from the Korsmeyer-Peppas model ranged between 0.45 and 0.89, indicating anomalous (non-Fickian) transport. This suggests that drug release was governed by a combination of diffusion and polymer relaxation/erosion mechanisms.

4.7. Accelerated Stability Studies

The optimized formulation was subjected to accelerated stability studies as per ICH guidelines. No significant changes were observed in physical appearance, hardness, drug content, or dissolution profile over the study period. These results confirmed the stability and robustness of the developed matrix tablets.

5. Conclusion

The present study successfully demonstrated the formulation and evaluation of natural polymer-based matrix tablets of repaglinide for controlled drug delivery in diabetes management. The developed formulations exhibited acceptable physicochemical properties, sustained drug release behavior, and stability under accelerated conditions. Natural polymers proved to be effective release-controlling agents, offering a safe, biodegradable, and economical alternative to synthetic polymers.

6. Future Scope

Further studies involving in-vivo pharmacokinetic evaluation, bioavailability assessment, and scale-up studies are recommended to establish the clinical relevance and commercial feasibility of the developed formulation.

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