DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF REPAGLINIDE USING PROCESSED ALOEVERA MUCILAGE AS RELEASE MODIFIER.

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ABSTRACT
This study aims to formulate and evaluate sustained-release matrix tablets of *Repaglinide*, an antidiabetic drug, using *processed Aloe vera mucilage* as a natural polymer and release modifier. Aloe vera mucilage is biocompatible, biodegradable, and cost-effective, making it an ideal candidate for modifying drug release. The tablets were prepared using the wet granulation technique, and various concentrations of Aloe vera mucilage were studied. The formulations were evaluated for physical parameters, drug content, in vitro drug release, and kinetic modeling. Results demonstrated that Aloe vera mucilage effectively sustained the release of Repaglinide over 12 hours, indicating its potential as a natural release modifier in controlled drug delivery systems.

INTRODUCTION

Repaglinide is a short-acting oral hypoglycaemic agent used in the management of type 2 diabetes mellitus. Due to its short biological half-life (~1 hour), frequent dosing is required, which can lead to patient non-compliance. Sustained-release formulations can mitigate this issue by maintaining steady plasma drug concentration over an extended period.

Matrix tablets are one of the most widely used dosage forms for sustained drug delivery. Natural polymers such as Aloe vera mucilage have drawn attention due to their safety, sustainability, and favourable gelling properties. Aloe vera mucilage, rich in polysaccharides, exhibits excellent swelling and gel-forming capabilities, making it a suitable matrix-forming agent.

The mechanism of action of repaglinide is as follows:

1. **Stimulation of Insulin Release**: Repaglinide works by stimulating the pancreas to release insulin. It binds to and inhibits ATP-sensitive potassium channels (K_ATP channels) on the pancreatic beta-cell membrane. This inhibition leads to a depolarization of the beta cells.

Calcium Influx: The depolarization of the beta cell membrane triggers the opening of voltage-gated **calcium channels**, allowing calcium ions to enter the cell.

2. **Insulin Secretion**: The increase in intracellular calcium triggers the release of stored insulin from the beta cells into the bloodstream. This insulin release helps lower blood

glucose levels after meals.

3. **Reduction in Blood Glucose**: This insulin release helps to reduce blood glucose levels by facilitating the uptake of glucose by tissues, particularly muscle and adipose tissue.

INTRODUCTIONTODRUGRELEASESYSTEMS

Adrugdeliverysystemshouldbedesignedsuchthatitstaysinstomachandreleases drug in controlled way, after oral administration, inorderto deliver the drugcontinuouslytoitsabsorptionsitesintheGIT.InpresenceofalcoholthesedeliveriesbehavelikeIRproduct. Drug release systems, also known as drug delivery systems or drug delivery mechanisms, are technologies and approaches used to control the release of pharmaceutical drugs into the body in a predetermined and controlled manner. These systems aim to improve the efficacy and safety of drug therapies by optimizing the drug's absorption, distribution, metabolism, and elimination while minimizing side effects. Drug release systems can take various forms, and they are designed based on the specific needs of the drug, the disease or condition being treated, and the desired therapeutic outcomes.

A- Oral Drug Delivery Systems: Oral drug delivery systems are among the most common and convenient ways to administer medications to patients. These systems involve delivering pharmaceutical drugs through the oral route, typically in the form of tablets, capsules, liquids, or other oral dosage forms. They are used for a wide range of drugs, from pain relievers to chronic disease medications. They are designed to deliver drugs through the gastrointestinal (GI) tract, where they are absorbed into the bloodstream. Oral delivery systems are popular because of their convenience, ease of use, and non-invasive nature. However, they face challenges such as limited bioavailability, first-pass metabolism, and gastrointestinal irritation.

- **Immediate-Release Formulations:** These release the drug rapidly upon

ingestion. They are commonly used for drugs that need to be absorbed

quickly.

Characteristics of Immediate-Release (IR) Systems

1. **Rapid Release**:

   Description: The drug is quickly dissolved in the stomach or small intestine after ingestion, leading to a fast onset of therapeutic effects.

   Mechanism: The drug formulation is typically designed to dissolve or disintegrate rapidly once it reaches the stomach or GI tract, without any delay or controlled-release mechanism.

2. **Onset of Action**:

   Quick Absorption: As the drug is rapidly absorbed into the bloodstream, the therapeutic effect is usually seen in a relatively short period (minutes to an hour, depending on the drug).

   Peaks Quickly: Since there's no controlled release, the drug reaches its peak plasma concentration quickly.

3. **No Delay in Drug Release**:

   No Coating or Matrix: Unlike controlled or sustained-release systems, there is no special coating or formulation to delay or control the release. The drug is released immediately once the dosage form dissolves.

Advantages of Immediate-Release Systems

1. **Fast Onset of Action**:

   IR systems are ideal when rapid therapeutic effects are needed, such as for pain relief, acute infections, or emergency situations like seizures. The drug reaches therapeutic levels in the bloodstream quickly, providing relief almost immediately.

2. **Simplicity**:

   These systems are straightforward in terms of formulation and production, making them cheaper to manufacture compared to more complex drug delivery systems.

3. **Convenience**:

   Ease of Use: Patients don't need to worry about specific timing of meals or complex dosing schedules. This makes IR drugs easier to take and increases patient compliance. No need for special equipment or devices, such as infusion pumps, to administer the medication.

4. **Wide Applicability**:

IR formulations are used for a broad range of therapeutic areas, including pain management (e.g., acetaminophen), antibiotics (e.g., amoxicillin), and antihistamines (e.g., loratadine).

Disadvantages of Immediate-Release Systems

1. **Frequent Dosing**:

   Because IR systems release the drug all at once, the drug's effects are typically short-lived. As a result, patients may need to take the medication multiple times a day to maintain effective blood drug levels. This can be inconvenient for patients and may result in reduced adherence to the prescribed treatment regimen.

2. **Fluctuating Drug Levels**:

   Peaks and Troughs: IR systems often cause significant fluctuations in drug levels, leading to peaks (high concentrations of the drug) and troughs (low concentrations). This can increase the risk of side effects or reduce efficacy, especially for drugs with a narrow therapeutic window.

3. **First-Pass Metabolism**:

   Many orally administered drugs undergo **first-pass metabolism** in the liver, meaning a significant portion of the drug is metabolized before it reaches systemic circulation. This can reduce the bioavailability of the drug and may require higher doses or alternative formulations.

4. **Gastrointestinal Side Effects**:

   Some IR formulations, particularly those that dissolve quickly, can irritate the stomach or GI tract, leading to discomfort, nausea, or gastrointestinal upset.

CONCEPTS OF SUSTAINED RELEASE DRUG ANDCERTAINTERMINOLOGIES.

Certainabbreviationscommonlyusedbymanufacturesaresustainedrelease(SR),sustainedaction(SA),prolongedaction(PA),controlledrelease(CD),extendedrelease(ER),timedrelease(TR),andlongacting(LA).Descriptiontoaprolonged therapeuticeffectby constantreleaseof drug tomedicationovera longerperiodafteradministrationofasingledosearedonebytheseterminologies.[11]Thisperiod varyfromdaystomonthsincaseofinjectabledosage.Theproductsbearingdescriptionsdifferin

designandperformance.

Sustainedrelease

Externalenvironmentinwhichthedrugisreleasedsubstantiallyaffectsthereleaseoftheactivea gentofsustainedrelease(SR)dosageformswhichislowerthantheconventionalone.[11]

Sustained release, often referred to as sustained-release drug delivery, is a pharmaceutical concept and technology that involves designing drug formulations to release the active pharmaceutical ingredient (API) over an extended period of time at a controlled rate. This controlled release of the drug is intended to maintain therapeutic drug levels in the bloodstream while minimizing fluctuations and the need for frequent dosing. Here are key aspects of sustained release drug delivery:

1. Controlled Release Profile: Sustained release systems are designed to release the drug gradually and consistently over an extended period, providing a steady supply of the medication to the patient.

2. Dosage Forms: Sustained release formulations can take various forms, including tablets, capsules, transdermal patches, injectables, and implantable devices.

3. Mechanisms for Controlled Release: Sustained release can be achieved through various mechanisms, such as diffusion-controlled release, osmotic-controlled release, matrix systems, and reservoir systems, among others.

4. Advantages:

- Improved patient compliance due to reduced dosing frequency.
- Reduction in peak and trough drug concentrations in the bloodstream.
- Minimization of side effects and improved therapeutic efficacy for some drugs.

5. Applications: Sustained release is used in the treatment of various medical conditions, including chronic pain management, cardiovascular diseases, psychiatric disorders, and diabetes, among others.

6. Formulation Design: The design of sustained release systems involves careful selection of materials, release kinetics, and release-controlling mechanisms. The goal is to ensure that the drug's release aligns with the intended therapeutic objectives.

7. Drug Stability: Sustained release formulations may protect drugs from degradation in the stomach or optimize drug stability over extended periods.

8. Regulatory Considerations: Regulatory agencies, such as the FDA in the United States, have specific guidelines and requirements for the development, testing, and approval of sustained-release drug products.

9. In Vitro and In Vivo Testing: Extensive testing and evaluation are conducted to assess the drug release profile, stability, bioavailability, and therapeutic efficacy of sustained release formulations.

Sustained release drug delivery is a valuable strategy for improving patient compliance and ensuring that drugs are administered in a controlled and predictable manner. It is particularly beneficial for drugs with a narrow therapeutic window or when maintaining steady drug levels is essential for therapeutic effectiveness. Proper formulation design is critical to achieving the desired sustained release profile.

SUSTAINED ACTION

Sustained action" typically refers to the prolonged or continuous effect of a drug or treatment over an extended period. This term is often used in the context of pharmaceuticals and medical treatments to describe the ability of a drug to provide therapeutic effects for an extended duration. Here are some key aspects of sustained action in medicine:

1. Prolonged Therapeutic Effects: Sustained action implies that a drug or treatment continues to produce its intended therapeutic effects over an extended period without the need for frequent dosing or intervention.

2. Dosing Frequency: Drugs with sustained action require less frequent dosing compared to drugs that provide only short-term relief. This can improve patient compliance and reduce the burden of multiple daily doses.

3. Drug Delivery Systems: Sustained action can be achieved through various drug delivery systems, such as sustained-release formulations (e.g., extended-release tablets or patches), depot injections, or long-acting implants.

4. Examples of Sustained-Action Drugs: Some common examples of drugs with sustained action include certain pain medications, contraceptives, psychiatric medications, and treatments for chronic conditions like diabetes and hypertension.

5. Steady Drug Levels: Sustained-action drugs are designed to maintain a relatively constant level of the drug in the bloodstream, which can lead to more stable and consistent therapeutic effects.

6. Improved Quality of Life: For patients with chronic conditions, sustained-action drugs can lead to better disease management, improved symptom control, and an overall improved quality of life.

7. Regulatory Approval: The development and approval of sustained-action drugs involve extensive testing and regulatory considerations to ensure their safety, efficacy, and long-term stability.

In summary, sustained action in the context of pharmaceuticals and medical treatments refers to the ability of a drug to provide therapeutic effects over an extended period with reduced dosing frequency. This approach is essential for managing chronic conditions and improving patient compliance and overall treatment outcomes. Proper formulation design and delivery systems are crucial to achieving sustained action in drug therapy.

PROLONGEDACTION(PA)

Prolonged action (PA)" is a term used in pharmaceutical and medical contexts to describe the extended or prolonged duration of a drug's therapeutic effects. It implies that the drug remains active

in the body for an extended period, leading to prolonged symptom relief or disease management. Here are some key aspects of prolonged action (PA) in medicine:

1. **Extended Duration:** Prolonged action drugs are designed to provide their therapeutic effects over an extended period. This means that patients may experience symptom relief or therapeutic benefits for a longer time compared to drugs with shorter durations of action.
2. **Reduced Dosing Frequency:** PA drugs often require less frequent dosing. Patients may need to take them less frequently throughout the day, which can lead to improved patient compliance and convenience.
3. **Sustained Drug Levels:** These drugs are formulated to maintain consistent and effective drug levels in the bloodstream, which can help manage chronic conditions and maintain therapeutic effects.
4. **Types of Prolonged Action:** PA can be achieved through various drug delivery methods, including extended-release tablets or capsules, depot injections, long-acting implants, and transdermal patches, among others.
5. **Therapeutic Areas:** Prolonged action drugs are used in a wide range of therapeutic areas, including pain management, psychiatric disorders, hormonal therapies, and chronic disease management (e.g., diabetes, hypertension).
6. **Regulatory Approval:** The development and approval of prolonged action drugs involve extensive testing and regulatory considerations to ensure their safety, efficacy, and long-term stability.

In summary, "prolonged action (PA)" in the field of pharmaceuticals and medicine refers to drugs or treatments that have an extended duration of therapeutic effects, reduce the need for frequent dosing, and improve patient convenience and compliance. These drugs are particularly valuable for managing chronic conditions and providing prolonged symptom relief. Proper formulation and drug delivery design are essential to achieve prolonged action in drug therapy.

Longacting(LA)

Long-acting (LA)" is a term used in medicine, particularly in the context of pharmaceuticals and drug formulations, to describe medications or drug delivery systems that provide a prolonged duration of therapeutic effect with a single administration. Long-acting drugs are designed to maintain therapeutic drug levels in the bloodstream or at the site of action over an extended period, thereby reducing the need for frequent dosing. Here are some key aspects of long-acting (LA) medications:

1. Extended Duration of Action: Long-acting medications are formulated to release the drug slowly and continuously, providing therapeutic effects over a longer period compared to immediate-release formulations.

2. Reduced Dosing Frequency: A primary advantage of long-acting medications is the reduction in dosing frequency. Patients typically require fewer administrations, which can improve adherence to treatment regimens and patient convenience.

3. Steady Drug Levels: Long-acting formulations are designed to maintain consistent and therapeutic levels of the drug in the bloodstream, minimizing fluctuations and peak and trough drug concentrations.

4. Types of Long-Acting Formulations: Long-acting medications can take various forms, including extended-release tablets, capsules, patches, injections, and implantable devices.

5. Therapeutic Areas: Long-acting medications are used in various therapeutic areas, including pain management, psychiatric disorders, hormonal therapies, cardiovascular diseases, and chronic disease management, such as diabetes and hypertension.

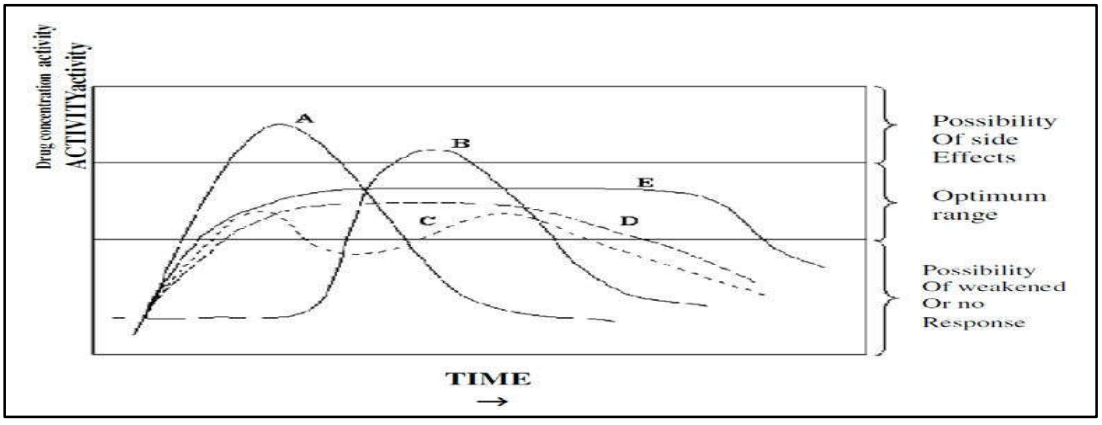
6. Regulatory Considerations: The development and approval of long-acting drug products involve comprehensive testing and regulatory considerations to ensure their safety, efficacy, and long-term stability.

7. Advantages:

- Improved patient compliance due to reduced dosing frequency.
- Enhanced therapeutic efficacy by maintaining steady drug levels.
- Reduction in side effects due to controlled and prolonged drug release.

8. Challenges: Designing long-acting formulations requires careful consideration of the drug's pharmacokinetics, patient needs, and therapeutic goals.

In summary, long-acting (LA) medications are an essential component of pharmaceutical and medical practice, offering a way to deliver drugs with extended duration of action. These formulations improve patient compliance and therapeutic effectiveness, making them particularly valuable for chronic conditions and other situations where consistent and sustained drug delivery is needed. Proper formulation design and drug delivery systems are crucial to achieving the desired long-acting profile for specific therapeutic applications.



prolongationofhalflifeandlongactionofdrug.

Fig.1:Drugrelease{(A)representsImmediaterelease,(B)representsDelayedaction(C)represe ntsRepeataction,(D)representsaProlongedrelease,

Compositionofaloe veraextract

Class	**Compounds**
Anthraquinones/ anthrones	Aloe-emodin,aloetic-acid,anthranol,aloinAandB(orcollectivelyknownasbarbaloin),isobarbaloin,emodin,esterofcinnamicacid
Carbohydrates	Puremannan,acetylatedmannan,acetylatedglucomannan,glucogalactomannan,galactan,galactogalacturan,arabinogalactan,galactoglucoarabinomannan,pecticsubstance,Xylan,cellulose
Chromones	8-*C*-glucosyl-(2'-*O*-cinnamoyl)-7-*O*-methylaloediolA,8-*C*-glucosyl-(*S*)-aloe sol,8-*C*-glucosyl-7-*O*-methyl-(*S*)-aloe sol,8-*C*-glucosyl-7-*O*-methylaloediol,8-*C*-glucosyl-noreugenin,isoaloeresinD,isorabaichromone,neoaloesinA
Enzymes	Alkalinephosphatase,amylase,carboxypeptidase,catalase,cyclooxidase,cyclooxygenase,lipase,oxidase,phosphoenolpyruvatecarboxylase,superoxidedismutase
Inorganiccompounds	Calcium,chlorine,chromium,copper,iron,magnesium,manganese,potassium,phosphorous,sodium,zinc
Miscellaneousincluding organiccompoundsandlipids	Arachidonicacid,γ-linolenicacid,steroids(campestral,cholesterol,β-sitosterol),triglycerides,triterpenoid,gibberellin,lignin,potassiumsorbate,salicylicacid,uricacid
Non-essentialandessential aminoacids	Alanine,arginine,asparticacid,glutamicacid,glycine,histidine,hydroxyproline,isoleucine,leucine,lysine,methionine,phenylalanine,proline,threonine,tyrosine,valine
Proteins	Lectins,lectin-likesubstance
Saccharides	Mannose,glucose,*L*-rhamnose,aldopentose
Vitamins	B1,B2,B6,C,β-carotene,choline,folicacid,α-tocopherol

Anthraquinones are a class of naturally occurring organic compounds characterized by a specific aromatic ring structure called an anthracene ring system. These compounds are widely distributed in nature and can be found in various plants, fungi, and lichens. Anthraquinones have been of interest for their diverse range of properties and applications. Here are some key points about anthraquinones:

1. **Chemical Structure:** Anthraquinones are characterized by a three-ring structure composed of benzene rings. The central ring is an anthracene ring, which contains three benzene rings fused together. Anthraquinones often have various substituents, such as hydroxyl (OH) or carbonyl (C=O) groups, attached to the benzene rings, leading to a wide variety of anthraquinone derivatives.

   Molecular Formula:$C_{14}H_8O_2$

2. **Natural Sources:** Anthraquinones are found in various plants, particularly those belonging to the families Rubiaceae, Polygonaceae, and Fabaceae. Some well-known natural sources of anthraquinones include aloe vera, rhubarb, senna, and cascara sagrada.
3. **Biological and Medicinal Properties:** Anthraquinones are known for their biological activities, including laxative effects. They are often used in over-the-counter laxatives and are responsible for promoting bowel movements. Some anthraquinone derivatives have also shown potential medicinal properties, such as anti-inflammatory, antioxidant, and anticancer effects.
4. **Dye and Pigment:** Anthraquinones have historically been used as dyes and pigments. They produce a range of colors, including red, purple, and blue. Alizarin, an anthraquinone derivative, is a well-known red dye extracted from the roots of the madder plant.
5. **Synthetic Chemistry:** Anthraquinones can be synthesized in the laboratory, and synthetic derivatives are used in various industrial applications, including the production of certain types of dyes, agrochemicals, and pharmaceuticals.
6. **Cultural and Historical Significance:** Anthraquinone-containing dyes have been used for centuries in art, textiles, and cosmetics. The use of natural sources of anthraquinones, like henna, in body art and hair dyeing is a notable example.
7. **Safety Considerations:** While anthraquinones have their uses, particularly in the treatment of constipation, their long-term use as laxatives is not recommended without medical supervision, as it can lead to adverse effects and dependency. Some anthraquinone derivatives can be toxic in high concentrations.

It's important to note that the use of anthraquinone-containing products for medicinal or cosmetic purposes should be done with caution and in accordance with recommended guidelines.

Review of Literature

According to the Version 1 statistics for the Global Status Report 2000 research, published in the World Health Report 2001(2) [1, schizophrenia is the 7th biggest cause of years lost due to disability (YLDs) on a global platform, accounting for 2.8percent of total global YLDs. In previous studies in India, schizophrenia prevalence estimates ranged from 0.1 to 0.35 per 1000 population [2, 3, 4], with prevalence raterangingfrom1.8to3.1per1000population4.The incidence of schizophrenia, however, is uncertain based on current diagnostic classification

Mool A et al. 2017 created a chlorogenic acid (CGA) sustained release floating tablet and optimized its drug release for improved oral bioavailability.Using different quantities of sodium bi carbonate and hydroxyl propyl methylcellulose(HPMC) K15 M Polymer a 32 complete factorial

design was employed to manufacture floating sustained release tablets of CGA.The medication and excipient compatibility was determined using Fourier transform infrared(FTIR) spectroscopy.

Venkateswarlu K et al in 2016 experimented the sustain release matrix tablets of Repaglinide (RPGN) .The USP dissolving equipment type-II was used to conduct in vitro drug release test for 12 hours using 0.1N HCL buffer and pH 6.8 phosphate buffer.

Choudhary M et al 2015 created a formulation of Pioglitazone hydrochloride (HCL) for stretched out time in a zero-order manner.Direct compression approach yields polymer ratios of 1:1,1:2,1:3,1:4 and 1:5 for PAG.

Narenderetal (2013)created the Nislodipine-loaded solid lipid nanoparticulate(ND-SLNs) system, which is made up of a glyceryl tri myristate (dyna san 114) lipid matrix and polymeric non-ionic surfactants. To investigate the effect of formulation factors on the drug delivery system, a Using Design of Experts, a two-factor, five-level central composite design (CCD) was constructed (DOE). The ND-SLNs were generated utilizing a hot homogenization and ultra-sonication technique, with size (Y1), PDI (Y2), and entrapment efficiency (EE) (Y3) as responses and the amount of lipid(X1) and surfactant(X2) as independent factors.

Silvabalan et al.2011 used HPMC , methylcellulose and ethyl cellulose polymers to make and test glipzide-loaded floating tablets. Weight fluctuation, hardness, friability, drug content and release were all investigated.

EXPERIMENTALWORK

Materials

Repaglinide: Natcolabs

Aloe vera mucilage: Local market

Excipients: Microcrystalline cellulose (MCC),

Magnesium stearate, Talc.

METHODOLOGY

Fresh Aloe vera leaves were washed, peeled, and the inner gel was collected. The mucilage was isolated using ethanol precipitation, filtered, and dried in a hot air oven at 40°C. The dried mucilage was powdered and sieved (mesh #80) before use.

Procedure:

Matrix tablets were formulated by **direct compression method** using varying concentrations (5%, 10%, 15%, 20%) of Aloe vera mucilage. MCC was used as diluent. All powders were blended and compressed into tablets using a single-punch tablet machine.

Formulated tablets were evaluated for:

- **Physical parameters:** Thickness, hardness, weight variation, friability
- **Drug content uniformity**
- **Swelling Index**
- **In-vitro Dissolution Studies:** Performed using USP Type II dissolution apparatus in 900 mL phosphate buffer (pH 6.8) at 37±0.5°C for 12 hours. Samples were withdrawn at specific intervals and analyzed using UV-Vis spectrophotometry.

RESULTS

Physical Parameters

All formulations showed acceptable limits for hardness (4–6 kg/cm²), friability (<1%), and uniform drug content (98-102%).

Swelling and Matrix Behaviour

Formulations with higher Aloe vera content showed increased swelling and gel strength, contributing to slower drug release.

Drug Release Kinetics

Release followed non-Fickian (anomalous) diffusion, best fitting the Korsmeyer-Peppas model ($R^2 > 0.98$), indicating both diffusion and erosion mechanisms.

CONCLUSION

Aloe vera mucilage proved to be an effective natural release modifier for the sustained release matrix formulation of Repaglinide. It provides a cost-effective, biodegradable alternative to synthetic polymers. The optimized formulation exhibited prolonged drug release with acceptable physicochemical properties, potentially enhancing patient compliance in diabetes management.

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