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Role of Processed Aloe vera Mucilage in the Formulation of Sustained Release Repaglinide Matrix Tablets.

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ABSTRACT

The present study focuses on the development and evaluation of sustained release matrix tablets of Repaglinide, a short-acting antidiabetic drug, using processed Aloe vera mucilage as a natural release-modifying agent. The primary objective was to extend the drug release profile, reduce dosing frequency, and improve patient compliance. Aloe vera mucilage was extracted, processed, and characterized for its physicochemical properties, including swelling index, viscosity, and compatibility with the drug through FTIR and DSC studies. Matrix tablets were formulated using the wet granulation method with varying concentrations of Aloe vera mucilage and evaluated for pre-compression and post-compression parameters such as hardness, friability, weight variation, drug content, and in vitro drug release. The release data were analyzed using various kinetic models to determine the mechanism of drug release. Among the formulations, the batch containing a higher concentration of Aloe vera mucilage demonstrated a sustained release of Repaglinide over 12 hours, following a non-Fickian diffusion mechanism. Comparative analysis with synthetic polymers revealed that Aloe vera mucilage exhibited comparable or superior release-controlling potential, supporting its use as an effective natural excipient. The study concludes that processed Aloe vera mucilage can be successfully employed as a cost-effective, biocompatible, and efficient release modifier in the formulation of sustained release matrix tablets of Repaglinide.

Keywords: Repaglinide, anti-diabetic drug, Matrix tablets

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INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels resulting from either insufficient insulin production or the body's inability to effectively use insulin. It affects millions of people worldwide and presents a significant public health concern. Management of diabetes typically involves medication, diet, and lifestyle modifications. Repaglinide, a meglitinide-class oral antidiabetic agent, is commonly prescribed to manage diabetes[2]. It stimulates insulin secretion from the pancreas, primarily in response to postprandial glucose levels. However, the rapid absorption and elimination of Repaglinide can lead to fluctuations in blood glucose levels, making it essential to develop sustained release formulations to improve its therapeutic efficacy and patient compliance. Sustained release formulations, such as matrix tablets, are designed to release the active pharmaceutical ingredient (API) slowly and consistently over an extended period, thereby maintaining stable drug levels in the bloodstream[4]. These formulations minimize the need for multiple daily dosing and help to control postprandial hyperglycemia, which is a critical concern in diabetes management. Aloe vera, a succulent plant known for its therapeutic properties, has garnered considerable attention in the field of pharmaceuticals. Aloe vera mucilage, a gel-like substance extracted from the leaves of the aloe vera plant, contains various bioactive compounds with potential pharmaceutical applications. This natural substance has been explored for its use as a release modifier in drug delivery systems. Its ability to form gels, its biocompatibility, and its sustained-release properties make aloe vera mucilage an attractive candidate for use in matrix tablet formulations.

This research aims to develop Repaglinide sustained release matrix tablets using processed aloe vera mucilage as a release modifier. By incorporating aloe vera mucilage into the matrix tablet, we intend to achieve controlled and sustained drug release, thereby optimizing the therapeutic effects of Repaglinide while minimizing the frequency of dosing and the associated side effects[1].

The primary objectives of this study are to design and characterize Repaglinide sustained release matrix tablets, evaluate their in vitro release profiles, and assess their pharmacokinetic behavior in vivo. The results of this research may provide valuable insights into the potential use of aloe vera mucilage as a natural release modifier in oral drug delivery systems, with implications for improved diabetes management and patient well-being. In subsequent sections, we will discuss the materials and methods used in the formulation of Repaglinide sustained release matrix tablets, the results of in vitro and in vivo studies, and the potential impact of this research on diabetes therapy.

Transportation of drug is done through various forms like pills, capsules, tablets, ointments, creams, injectables and aerosols. An immediate release of drug is provided by these types of

drug delivery system, which makes accelerated drug absorption possible resulting the adequate pharmacodynamic effects[3].

Detoriating rate of plasma drug concentration is ascertained after the absorption of drug. Declination of remedial effect is seen if minimum effective plasma concentration (MEC) is achieved prior to declination of plasma drug. To get a desirable sustained therapeutic effect another dose is usually administered before MEC is reached. In order to avoid frequent administration of drug sustained drug release form must be used which will maintain plasma drug concentrations Formulation of a novel drug delivery system / or modified release dosage form has been a matter of primary concern by, pharmaceutical industries and academic laboratories rather than developing a new drug as it is cost effective[2].

In order to get an exaggerated efficiency of the medicine, decrement in after effect and proper remedy in stipulated brief period of time require an adequate pharmacokinetic, pharmacodynamics and biopharmaceutic properties.

Diabetes mellitus is a chronic disease in which enough insulin is not produced by the pancreas or the insulin produced is not used effectively by the body. Blood sugar is regulated by the Insulin hormone. An uncontrolled diabetes leads to hyperglycemia and even causes serious damage to the nerves and blood vessels. Diabetes mellitus, often referred to simply as diabetes, is a chronic medical condition characterized by high levels of glucose (sugar) in the blood. This occurs because the body either does not produce enough insulin, which is a hormone that regulates blood sugar, or it cannot effectively use the insulin it produces. There are several types of diabetes, with the most common being type 1 and type 2 diabetes, as well as gestational diabetes.

Type 1 Diabetes:

This is an autoimmune condition in which the body's immune system attacks and destroys the insulin-producing beta cells in the pancreas. People with type 1 diabetes need to take insulin injections or use an insulin pump to manage their blood sugar levels[5].

Type 2 Diabetes:

This is the most common form of diabetes and is often associated with lifestyle factors like obesity and a lack of physical activity. In type 2 diabetes, the body becomes resistant to insulin, and the pancreas may not produce enough insulin to maintain normal blood sugar levels. Management often involves lifestyle changes, oral medications, and, in some cases, insulin injections[5].

Gestational Diabetes:

This form of diabetes occurs during pregnancy and usually resolves after childbirth. However, women with gestational diabetes have a higher. risk of developing type 2 diabetes later in life[5].

Common symptoms of diabetes include increased thirst, frequent urination, unexplained weight loss, fatigue, and blurred vision. Long-term uncontrolled diabetes can lead to serious complications, such as cardiovascular disease, kidney disease, neuropathy (nerve damage), retinopathy (eye damage), and more.

Managing diabetes typically involves a combination of lifestyle modifications, medication, and regular monitoring of blood sugar levels. A healthy diet, regular exercise, and maintaining a healthy weight are crucial for managing and preventing diabetes, especially type 2 diabetes. It's also important for individuals with diabetes to work closely with healthcare professionals to develop a personalized treatment plan.

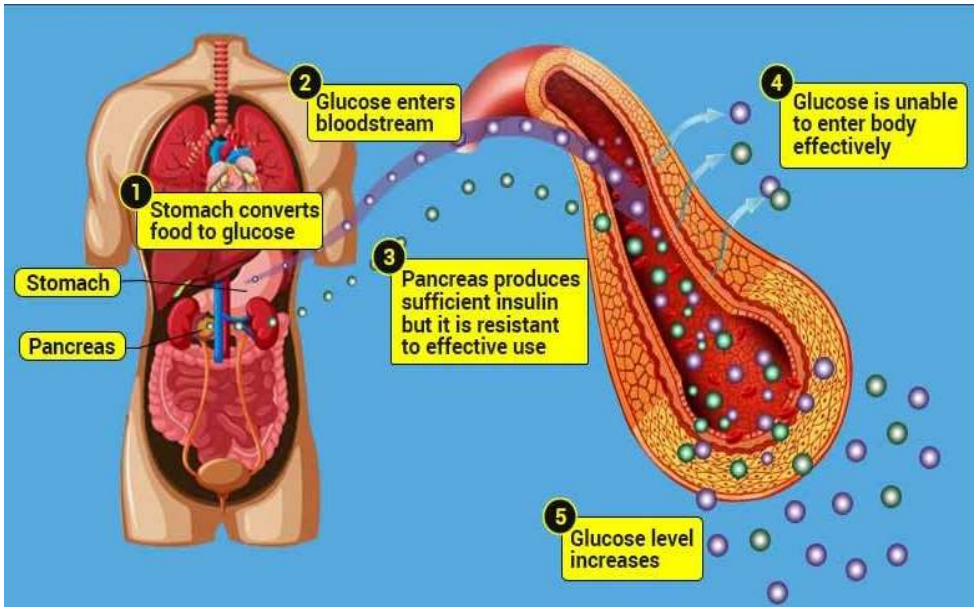

Figure 1: Type 2 Diabetes

Glinides are a new class of short acting insulin secretagogues which are structurally dissimilar to sulfonylurea. They act directly on the pancreatic beta cell and hence stimulate rapid insulin secretion dependent on ambient glucose. The first oral agent of the meglitinide class are Repaglinide which are available for the treatment of type 2 diabetes.[2] These drugs have a mechanism of cell stimulation which makes it different from sulfonylureas[2]. Repaglinide are chemically different from sulfonylurea or any other currently available class of oral hypoglycemic agents. [3] Meal-related blood sugar imbalances are best treated by Repaglinide due to its ability of rapid absorption and clearance. The major advantage of this drug is that it can be used in chronic renal failure. [2]

Repaglinide offers a very short elimination half-life (1hr) and meal-time dosing administration. This quality of Repaglinide makes development of oral controlled release drug challenging, as it not only involves sustaining the drug release but also prolongation of the

presence of the dosage form within the gastrointestinal tract until complete release of drug at the desired period of time.

Currently diagnosed diabetic patients in India are approximately more than 62 million, [2,3] According to a survey done in2000, India was the first ranker in the world for having the highest number (31.7 million) number of people with diabetes mellitus followed by China (20.8 million) and the United States (17.7 million). Due to its devastating impact on global population Diabetes becomes the most challenging disease.

Repaglinide is an oral medication used to manage blood sugar levels in individuals with type 2 diabetes. It belongs to a class of drugs known as meglitinides, which stimulate the release of insulin from the pancreas. Repaglinide is typically prescribed to help lower blood sugar levels in response to meals or when blood sugar is elevated.

COMPOSITION OF ALOEVERA EXTRACT

Class	Compounds
Anthraquinones/ anthrones	Aloe-emodin, aloetic-acid, anthranol, aloin A and B (or collectively known as barbaloin), isobarbaloin, emodin, ester of cinnamic acid
Carbohydrates	Pure mannan, acetylated mannan, acetylated glucomannan, glucogalacto mannan, galactan, galacto galacturan, arabinogalactan, galacto glucoarabinomannan, pectic substance, xylan, cellulose
Chromones	8-*C*-glucosyl-(2'-*O*-cinnamoyl)-7-*O*-methylaloediol A, 8-*C*-glucosyl-(*S*)-aloesol, 8-*C*-glucosyl-7-*O*-methyl-(*S*)- aloesol, 8-*C*-glucosyl-7-*O*-methylaloediol, 8-*C*-glucosyl- noreugenin, isoaloeresin D, isorabaichromone, neoaloesin A
Enzymes	Alkaline phosphatase, amylase, carboxypeptidase, catalase, cyclooxidase, cyclooxygenase, lipase, oxidase, phosphoenolpyruvate carboxylase, superoxide dismutase
Inorganic compounds	Calcium, chlorine, chromium, copper, iron, magnesium, manganese, potassium, phosphorous, sodium, zinc
Miscellaneous including organic compounds and lipids	Arachidonic acid, γ-linolenic acid, steroids (campestrol, cholesterol, β- sitosterol), triglicerides, triterpenoid, gibberillin, lignins, potassium sorbate, salicylic acid, uric acid
Non-essential and essential amino acids	Alanine, arginine, aspartic acid, glutamic acid, glycine, histidine, hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, threonine, tyrosine, valine
Proteins	Lectins, lectin-like substance
Saccharides	Mannose, glucose, *L*-rhamnose, aldopentose
Vitamins	B1, B2, B6, C, β-carotene, choline, folic acid, α- tocopherol

Figure 2: Aloe vera Extract

The study will determine whether processed *Aloe vera* mucilage is effective as a natural, biodegradable, and cost-effective alternative to synthetic polymers in sustained release tablets[7].

Review of Literature

Prevalence of Schizophrenia in Indian Population

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 raterangingfrom1.8to3.1per1000 population [4]. 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 hydroxypropyl 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, methyl cellulose and ethyl cellulose polymers to make and test glipzide-loaded floating tablets. Weight fluctuation, hardness, friability, drug content and release were all investigated.

METHOD

Pre formulation tests were performed primarily to verify the drug's physicochemical properties including its compatible with other excipients. Pre-formulation studies are crucial in the development of sustained-release matrix tablets as they help in understanding the physicochemical properties of the drug, excipients, and their interactions.

Drug or other ingredient selection:

As matrix forming polymers, Methocel K4M, Microcrystalline cellulose K15M, Methocel K 100M, and Xanthan gum were used. As a permeation enhancer and plasticizer, propylene glycol was selected.

Phosphate Buffer, pH6.8 Preparation:

In a 1000 ml volumetric flask, accurately measure 250 ml with 0.2 M potash di-hydrogen phosphates and add 195.5 ml M sodium hydroxide, then add water to make volume up and adjust pH6.8 by 0.2M potash di-hydrogen phosphorus hydroxide.

Permeation studies were used to assess the Aloe vera Mucilage:

Cell of diffusion:

Franz diffusion cells are being used to conduct permeation studies. The donors and receptor compartments are separate in the Franz diffusion cell. The receptors compartment is mm in diameter and holds 15 ml of fluid. A receptor compartment is connected to a collecting tube, enabling for convenient collection of hourly samples during the diffusion process. With the help of a clap, the donor and receptor compartments are held together. The receptor compartment has a total area of 3.83 cm2 which is exposed to a Transdermal patch for diffusion.

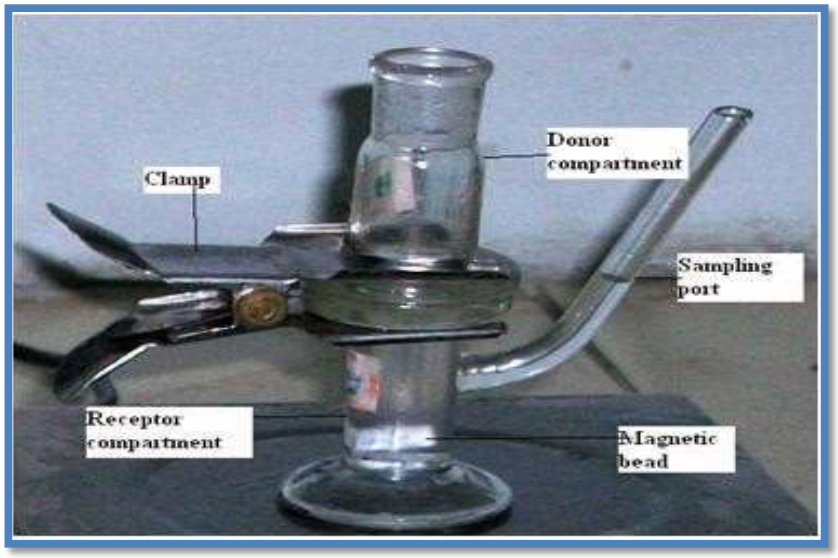

Figure 3: Diffusion cell Franz

Dialysis membrane permeation studies in vitro:

The penetration to Physostigmine, Tacrine, & Repaglinide through aloe vera mucilage via a membrane pores (Hi-Media) with a molecular weight cutoff of 12000 was investigated in vitro. A Franz diffused cells and Transdermal patches were put on top of the membrane. The diffusion cell's receiver compartment were filled using 15.0 ml pH 6.8 as well as the setup was put over a magnetic stirring with a temperature of 370C. At 1, 2, 3, 4, 6, and 12 hours, 3ml samples were removed and replenished from the receiver compartment. They were kept in the fridge until the analysis was completed. A UV-Visible spectrophotometer was used to identify the level of Physostigmine, Tacrine, & Repaglinide in the samples. The drug concentrations were measured at 292 nm, 254 nm, and 250 nm.

Evaluation Parameters:

Dissolution Profile: Drug release at different time intervals (USP Type II Dissolution Test).

Swelling Index: Extent of hydration of mucilage.

Hardness & Friability: Impact on tablet mechanical properties.

Stock solution preparation

10 mg of Nebivolol Hydrochloride was correctly weighed and placed in 100 mL of methanol, resulting in a volume of 100mL. It yielded a concentration of 100 micrograms per milliliter (mcg/mL).

Drug release mechanism:

The drug release mechanism of Aloe Vera mucilage in pharmaceutical formulations, particularly in sustained-release matrix tablets, is primarily controlled by the following mechanisms:

Swelling-Controlled Release

Aloe Vera mucilage absorbs water, swells, and forms a gel-like matrix that modulates drug diffusion. This swelling controls the rate of drug release by forming a barrier that slows down drug diffusion.

Diffusion-Controlled Release

The hydrated mucilage acts as a diffusion barrier, allowing the drug to slowly move through the gel network. The release follows Fickian or non-Fickian diffusion**,** depending on the polymer's swelling behavior.

Erosion-Controlled Release

Over time, the mucilage matrix undergoes surface erosion, leading to a gradual release of the drug. This is significant in hydrophilic matrix systems where the polymer dissolves progressively.

pH-Sensitive Release

Aloe Vera mucilage contains polysaccharides that may exhibit pH-dependent solubility**,** affecting drug release in different parts of the gastrointestinal tract.

Enzymatic Degradation

In some cases, gut enzymes can degrade the mucilage, influencing drug release kinetics

Structure:

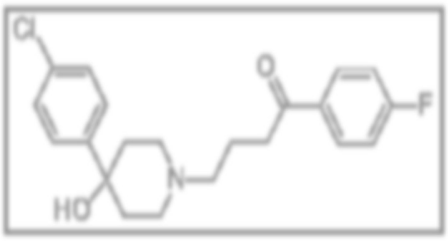

Figure 4: Structure of REPAGLINIDE

IUPAC nomenclature: (S)-2-Ethoxy-4-{2-[(3-methyl-1-(piperidin-2 butyl) carbamoyl] benzoic acid}

Synonyms:(3-P-Fluorobenzoylpropyl)-4-P-chlorophenyl-4-hydroxypiperidine

Solubility:0.39 mg/mL aq 2-hydroxypropyl—cyclodextrin, 45 %

RESULTS AND DISCUSSION

Formulation with 15% w/w Aloe Vera mucilage (AVM-15) showed optimal sustained release profile over 12 hours Drug content uniformity: 98.2-99.7% across all formulations Matrix tablets exhibited good physical parameters: Hardness: 5.5-6.2 kg/cm² Friability: <0.75% Weight variation: within ±5% AVM-15 showed comparable performance to HPMC-based formulation with 97.9% drug release at 12h

Validation of UV spectrophotometric method and preparation of calibration curves

In 0.1 N HCL, aliquots of REPAGLINIDE (0-1 g/ml) were scanned for absorbance. The absorbance spectrum was discovered to be between 0.214 and 0.947. In the above concentration range, these solutions conformed Beer-law Lambert's with a regression of 0.9978. This demonstrates excellent linearity and range. Table shows the recovery and precision results. The intra-day precision & recovery RSD values are low, indicating strong robustness. The proposed UV approach for risperidone was shown to be easy, accurate, exact, and specific, and can also be used for scientific purposes.

Table 1: Standard graph of Repaglinide

(g/ml) Concentration	Absorption(nm)
0	0
0.2	0.214
0.4	0.388
0.6	0.615
0.8	0.788
1	0.947

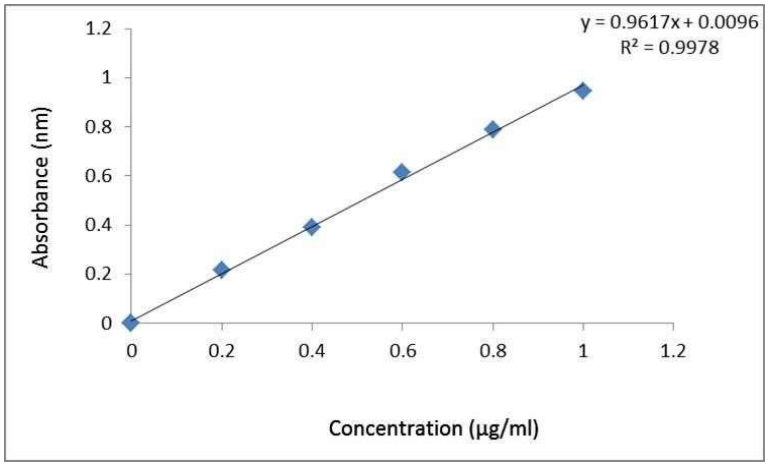

Figure 5: Calibration curve of Repaglinide

CONCLUSION

Successfully developed sustained release matrix tablets of Repaglinide using processed Aloe vera mucilage Optimal drug release profile achieved with 1:4 drug-to-polymer ratio (formulation F5) Release kinetics followed zero-order pattern with non-Fickian diffusion mechanism Natural, biodegradable polymer with excellent release-modifying properties Cost-effective alternative to synthetic polymers like HPMC and Carbopol Demonstrated excellent stability and compatibility with Repaglinide

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