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Advanced Drug Delivery Systems: Formulating and Evaluating Metformin SR Tablets with Fenugreek Seed Mucilage

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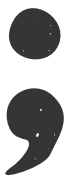

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Preface

This book explores into the innovative formulation of metformin hydrochloride using fenugreek seed mucilage as a natural polymer. It bridges traditional botanical knowledge with modern pharmaceutical science to enhance the effectiveness and patient compliance of metformin, a key treatment for diabetes. The chapters meticulously detail the scientific process from raw material procurement to rigorous post-formulation evaluations, underlining our commitment to improving diabetic care through advanced drug delivery systems. By combining traditional fenugreek uses with contemporary pharmaceutical techniques, we aim to deliver a sustained-release formulation that not only improves bioavailability but also showcases the synergy between nature and technology. This work is designed to guide researchers, clinicians, and students through the development stages, offering insights into natural polymers in drug delivery and inspiring further research in this promising field.

Simanchal Panda

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Chapter 1

Introduction

1. Introduction

Diabetes is a condition characterized by elevated levels of blood glucose, commonly referred to as blood sugar. Glucose serves as the primary energy source for the body, which can produce it internally or obtain it from consumed food. Insulin, a hormone produced by the pancreas, facilitates the entry of glucose into cells for energy production. In individuals with diabetes, the body either produces insufficient or no insulin, or fails to utilize it effectively. As a result, glucose accumulates in the bloodstream instead of being absorbed by cells.

This condition increases the likelihood of complications affecting the eyes, kidneys, nerves, and heart, and is also associated with certain cancers. Proactive measures to prevent or manage diabetes can reduce the risk of these health issues.

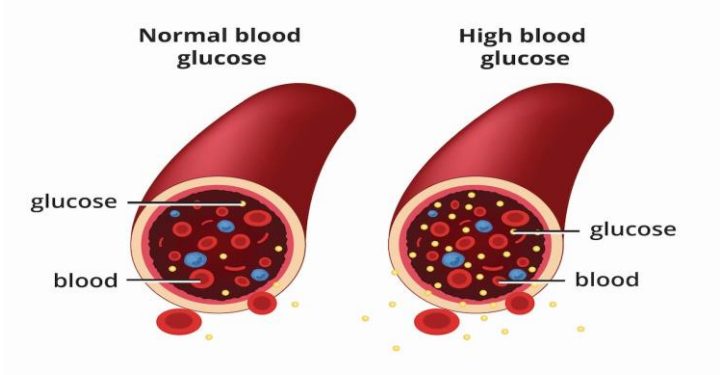

Fig. 1.1 Glucose Levels in Normal and High Blood

The primary forms of diabetes include type 1, type 2, and gestational diabetes.

Type 1 Diabetes

In type 1 diabetes, the body produces little to no insulin due to the immune system attacking and destroying insulin-producing cells in the pancreas. This form is typically diagnosed in children and young adults but can occur at any age. Daily insulin intake is essential for survival in individuals with type 1 diabetes.

Type 2 Diabetes

Type 2 diabetes arises when the body's cells become resistant to insulin, and the pancreas cannot produce enough insulin to maintain normal blood sugar levels. It is the most prevalent form of diabetes and is often linked to risk factors such as obesity, being overweight, or a family history of the disease. While it can develop at any age, including during childhood, adopting a healthier lifestyle—such as weight management—can help delay or prevent its onset.

Gestational Diabetes

Gestational diabetes occurs during pregnancy and usually resolves after childbirth. However, women who experience it are at a higher risk of developing type 2 diabetes later in life. In some cases, diabetes diagnosed during pregnancy may actually be type 2 diabetes.

Prediabetes

Prediabetes is a condition where blood sugar levels are elevated but not high enough for a type 2 diabetes diagnosis. Individuals with prediabetes face an increased risk of developing type 2 diabetes and heart disease compared to those with normal glucose levels.

Other Types of Diabetes

Less common forms include monogenic diabetes, caused by a single gene mutation, and diabetes resulting from pancreas removal or damage due to conditions like cystic fibrosis or pancreatitis.

Modified-Release Dosage Forms

Modified-release drug delivery systems are designed to alter the release profile of medications, addressing the fluctuations in drug concentration seen with conventional dosage forms. These systems aim to maintain therapeutic drug levels in the bloodstream over an extended period or target specific areas in the body. Key terms include:

1. **Modified-Release Dosage Form**: A mechanism that delays drug release (delayed-release), extends its duration (extended-release), or targets specific sites (targeted-release).
2. **Controlled Release**: Drug release occurs at a constant rate, maintaining stable drug concentrations over time.
3. **Delayed Release**: Drug release is postponed rather than immediate.
4. **Sustained Release**: The drug is released gradually, controlled by the delivery system.
5. **Extended Release**: Slow drug release maintains therapeutic levels for 8 to 12 hours.
6. **Prolonged Release**: Drug absorption occurs over a longer period than conventional forms, often with a delayed onset.
7. **Repeat Action**: An initial dose is released shortly after administration, followed by subsequent doses at intervals.

1.2 Oral Sustained-Release Dosage Forms

Sustained-release systems, also known as depot systems, are designed to provide a continuous therapeutic effect by releasing drugs over an extended period after a single

dose. For oral administration, this typically spans hours, while injectable forms can last days to months. These formulations often rely on diffusion, dissolution, or a combination of both to achieve controlled drug release. Factors such as gastrointestinal motility, enzyme activity, and pH levels must be considered during formulation.

1.3 Advantages of Sustained-Release Dosage Forms

1. Enhanced control over drug therapy.
2. Modified rate and extent of drug absorption.
3. Reduced frequency of administration.
4. Improved patient compliance.
5. Convenient drug administration.
6. Optimal drug availability with minimal dosage.
7. Increased safety margin for high-potency drugs.

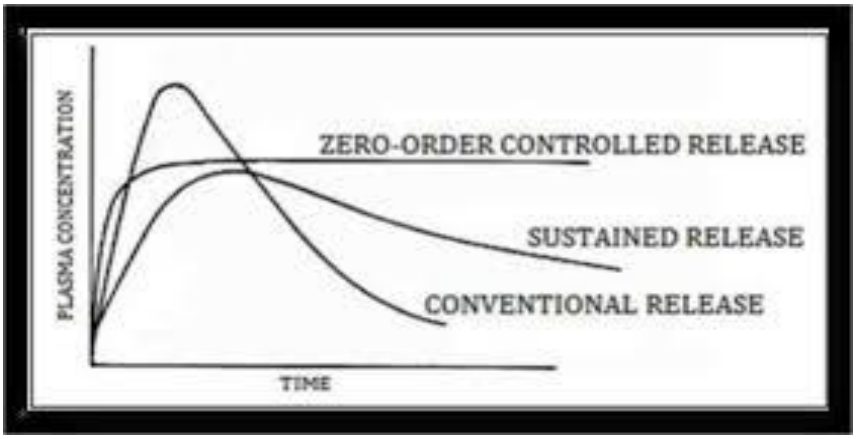

Fig 1.2 Comparison of Drug Release Profiles

1.4 Disadvantages of Sustained-Release Dosage Forms:

1. These formulations do not allow for immediate discontinuation of therapy.
2. There is limited flexibility in adjusting dosages.
3. They are typically designed based on average biological half-life data.
4. They tend to be more expensive than conventional dosage forms.

Metformin (marketed under brand names such as Obimet and Glumetza) is an anti-hyperglycemic agent belonging to the biguanide class. It is the first-line pharmacological treatment for type 2 diabetes. Its mechanism of action involves reducing glucose production in the liver and enhancing insulin sensitivity in body tissues. Often described as an insulin sensitizer, metformin is also utilized in managing polycystic ovary syndrome (PCOS). It is particularly beneficial for obese patients with type 2 diabetes, as it promotes modest weight loss.

Fig 1.3 Pharmaceutical Tablets

Additionally, metformin serves as a second-line treatment for infertility in individuals with PCOS. It is as effective as repaglinide and outperforms other oral medications for type 2 diabetes. By enhancing glucose utilization and reducing glucose production in the presence of insulin, metformin counteracts insulin resistance.

The drug's effects include increased glucose uptake, oxidation, and glycogenesis in muscles, enhanced glucose metabolism to lactate in the intestines, reduced hepatic

gluconeogenesis, and potentially slower intestinal glucose absorption. These effects are generally moderate and do not lead to clinical hypoglycemia or significant weight gain.

Metformin also exhibits anti-hypertriglyceridemic properties and has beneficial effects on haemostasis. The risk of lactic acidosis is minimal if contraindications, particularly renal impairment, are carefully observed.

As a first-line treatment for type 2 diabetes, metformin is taken orally, typically 1 to 3 times daily with meals, which may cause mouth irritation. Common side effects include rapid heartbeat, nausea, vomiting, stomach discomfort, blurred vision, and, in rare cases, lactic acidosis. Some studies have reported severe allergic reactions, such as rashes, swelling (especially of the face, tongue, or throat), and breathing difficulties.

Long-term use of metformin can lead to vitamin B12 deficiency, potentially causing muscle weakness, a sore red tongue, mouth ulcers, and vision problems.

1.5 Materials and Methods

Materials

Metformin hydrochloride was procured from Aarti Drugs. Other materials included Polyvinylpyrrolidone (PVP K-30), Microcrystalline Cellulose (PH101), Xanthan gum (Loba Chemie), and Hydroxypropyl Methylcellulose (Anhui Sunhere Pharmaceutical Excipients Co. Ltd.). Talc and Magnesium Stearate were also obtained from Loba Chemie. All chemicals, solvents, and reagents used were of analytical grade.

1.6 Drug-Excipient Compatibility Study

Understanding the physicochemical properties of the active pharmaceutical ingredient (API), metformin hydrochloride, and assessing its compatibility with excipients is crucial before formulating a prototype. Infrared spectra of the pure drug and drug-polymer mixtures were recorded using a Fourier Transform Infrared (FTIR) spectrophotometer.

The plate method was employed to investigate potential interactions between the drug and polymers. Samples were scanned using KBr plates (IR grade), and transmission spectra were recorded in the wavenumber range of 4000–400 cm^{-1}.

1.7 Excipient Selection Considerations

The selection of excipients for tablet formulation depends on API properties, the manufacturing process, the target formulation, and potential impacts on the final product. Key API properties to consider include:

- Dose
- Particle size
- Flow properties
- Bulk density
- Moisture content
- Hygroscopicity
- Excipient compatibility
- Compactability

The following tables outline potential impacts on tablet formulation and considerations for excipient selection. Data courtesy of Fred Monsuur, Grace, and Pharmaexcipients.com.

1.8 Excipients Used in Tablets

Excipients are inert substances that serve as diluents or vehicles for drugs. They include fillers, binders, disintegrants, lubricants, glidants, flavors, fragrances, and sweeteners. Excipients must meet specific criteria:

- They must be physiologically inert.
- They must be approved by regulatory authorities.

- They must exhibit physicochemical stability.
- They must be free of harmful microorganisms.
- They should not interfere with drug bioavailability.
- They must be commercially available and meet pharmaceutical purity standards.
- They should be cost-effective.
- They must comply with current regulatory requirements.
- Drug-excipient and excipient-excipient interactions must be evaluated during preformulation studies.

1.9 Preparation of Matrix Tablets

Metformin hydrochloride matrix tablets were prepared using the wet granulation method, with Polyvinylpyrrolidone (PVP K30) as the granulating agent. Various formulations were designed using different proportions of hydrophilic polymers, either alone or in combination. The steps involved in granule preparation were as follows:

Step 1: Sifting

Metformin hydrochloride was accurately weighed and sifted through a 60# sieve. Microcrystalline cellulose (PH101), Xanthan gum, and Hydroxypropyl Methylcellulose (HPMC K4M) were also weighed and sifted through a 40# sieve.

Step 2: Dry Mixing

The sifted materials were mixed in a polybag for 30 minutes to achieve a homogeneous blend. Samples were collected to assess loss on drying (LOD) and blend uniformity.

Step 3: Binder Solution Preparation

A binder solution was prepared by dissolving Polyvinylpyrrolidone (PVP K30) in purified water under continuous stirring until a clear, translucent solution was obtained.

Step 4: Wet Mixing

The binder solution is gradually incorporated into the dry blend while continuously mixing until a uniform, cohesive wet mass is formed. The endpoint of granulation is identified through visual observation, focusing on the consistent formation of granules.

Step 5: Wet Sifting

The obtained wet mass is passed through a #10 mesh sieve to ensure the production of uniformly sized particles.

Step 6: Drying

Following wet sifting, the granules are subjected to air drying for 10 minutes. Subsequently, they are placed in a tray dryer set at 50°C until the desired level of moisture content (Loss on Drying, LOD) is achieved.

Step 7: Dry Screening

Once dried, the granules are sifted through a #20 mesh sieve and collected in a container lined with double layers of polyethylene for protection.

Step 8: Lubrication

Pre-measured quantities of talc and magnesium stearate are added to the dried granules. The mixture is then blended thoroughly to achieve a uniform, lubricated powder blend.

Step 9: Compression

The lubricated blend is compressed into tablets using a 10-station single rotary tablet press (Rimek Mini Press, IRM Enterprises Private Limited, Ahmedabad, India) fitted with capsule-shaped punches measuring 19.5 x 9.0 mm. The punches feature a break-line on

one side and a plain surface on the opposite side. A consistent compression force is applied to achieve a tablet hardness of approximately 5–7 kg/cm². After production, all physical parameters are evaluated, and the tablets are stored in airtight containers for future use.

1.10 Pharmacological Properties of FSM (Binder)

Anti-diabetic Effects

- The active constituents of fenugreek, including galactomannan, saponins, trigonelline, diosgenin, and 4-hydroxyisoleucine, have demonstrated significant anti-diabetic properties.
- Various studies have isolated these compounds and documented their ability to regulate blood glucose levels. Fenugreek influences diabetes management through multiple physiological mechanisms, such as enhancing pancreatic β-cell function and inhibiting the enzymatic activities of sucrase and alpha-amylase.
- Extracts rich in fenugreek saponins have exhibited anti-diabetic, hepatoprotective, and lipid-lowering (hypolipidemic) effects.
- Additionally, galactomannan has been shown to reduce 24-hour urinary glucose excretion by 64%, highlighting its protective role against diabetes.

Hepatoprotective Effects

- Liver dysfunctions can be effectively managed with antioxidant supplementation. Fenugreek contains diosgenin, saponins, flavonoids, and polyphenols, all known for their antioxidant, lipid-lowering, and cholesterol-reducing properties.
- Fenugreek enhances lipid metabolism by promoting lipid excretion through feces, thereby reducing hepatic lipid accumulation.

Fig 1.4 Fenugreek Seeds

- It significantly lowers serum levels of total cholesterol, low-density lipoproteins (LDL), very low-density lipoproteins (VLDL), and triglycerides.

Gastroprotective Effects

- Poor dietary habits and lifestyle choices can lead to gastrointestinal issues, including abdominal pain, loss of appetite, nausea, vomiting, gastric ulcers, and peptic ulcers. Fenugreek has been reported to alleviate such conditions effectively.
- Its gastroprotective benefits are attributed to its anti-ulcer, anti-inflammatory, antioxidant, and anti-secretory activities.

Anti-sterility and Anti-fertility Effects

- Fenugreek supports reproductive health by regulating sex hormones, improving sperm viability, enhancing sperm count, and addressing various forms of sexual dysfunction in both men and women. Its bioactive components, particularly steroidal saponins, exhibit anti-sterility and anti-androgenic properties.
- Research indicates that saponins interact with estradiol receptors, modulating estrogen activity in experimental models of ovarian hyperstimulation syndrome.

- Diosgenin promotes reproductive health by stimulating the release of growth hormones from the pituitary gland.
- It also serves as a precursor for synthesizing commercial steroids, including cortisone, pregnenolone, and progesterone. Animal studies have shown that fenugreek extracts can influence sex hormone levels, sperm count, and viability.

Anti-cancer Effects

- Diosgenin, a prominent bioactive compound in fenugreek, exhibits anti-cancer properties. Studies have demonstrated its ability to induce apoptosis in cancer cells.
- It modulates the expression of proteins involved in cell apoptosis, contributing to its anti-cancer efficacy.
- The synergistic action of fenugreek's bioactive components enhances its anti-proliferative potential.
- Experimental evidence suggests that intraperitoneal administration of fenugreek seed extract can inhibit tumor cell growth by up to 70%.
- Fenugreek's cytotoxic effects make it a promising candidate for cancer prevention and treatment strategies.

Chapter 2

Literature survey

This article is reviewed by Kim Rose-Francis, RDN, CDCES, CNSC, LD, et al. (2022)

1. **Fenugreek and Insulin Sensitivity:** A 2018 experimental study suggests that fenugreek can enhance insulin sensitivity by activating insulin signaling pathways in the liver and peripheral tissues at an early stage, thus contributing to reduced blood glucose levels.
2. **Gastrointestinal Impact of Fenugreek:** A 2020 study found that lignin in fenugreek seeds helps delay gastric emptying, which is beneficial for individuals with diabetes who experience rapid gastric emptying. This delay aids in controlling postprandial blood sugar spikes and limits glucose absorption in the intestines.
3. **Fenugreek and Glucose Tolerance:** According to a 2017 study, mice fed fenugreek seeds alongside a high-fat diet demonstrated improved glucose tolerance compared to those not receiving fenugreek. Conversely, mice on a low-fat diet did not exhibit similar improvements.

Kaur Manmeet and Singh Narinder et al. (2016)

This research highlights the positive effects of fenugreek seeds on the glycemic profile of type 2 diabetes mellitus (T2DM) patients. The study indicates that fenugreek can serve as an adjunct therapy with metformin to better manage glycemic and lipid profiles in T2DM.

Shukla Kumar Ajay et al. (2020)

The study explored fenugreek gum as a film-coating polymer using paracetamol as a model drug. Tablets were assessed for parameters like weight uniformity, friability, disintegration time, and dissolution profiles. Fenugreek gum enhanced tablet aesthetics, masked unpleasant tastes, improved stability, and modified drug release properties.

Maryam Hassanzaden Bashtian et al. (2018)

Fenugreek has recently gained prominence as an herbal remedy. Its seeds have demonstrated hypocholesterolemic effects in both human and animal models without any reported toxicological side effects. Additionally, fenugreek has been linked to improved insulin resistance in women with PCOS.

Padmaja Bookya et al. (2018)

Oral drug administration is widely favored for its convenience and ease of production, accounting for 90% of systemic drug effects. However, conventional dosage forms often cause fluctuations in drug concentration, impacting efficacy and side effect risk. The study developed nine formulations of sustained-release matrix tablets using fenugreek seed mucilage, showcasing improved drug delivery, reduced dosing frequency, and enhanced therapeutic effectiveness.

Clifford J. Bailey (2024)

Metformin (dimethyl-biguanide) traces its origins to Galega officinalis, historically used for diabetes treatment. Since 1957, metformin has been the first-line therapy for type 2 diabetes, lowering blood glucose without causing weight gain or hypoglycemia. It offers anti-inflammatory benefits, improved lipid metabolism, and reduced cardiovascular risks. Metformin also aids in prediabetes, pregnancy-related glycemic control, and is often combined with other antidiabetic medications. However, adequate renal function is essential to avoid potential side effects like gastrointestinal discomfort, which can be managed by food intake or extended-release formulations.

Sandeep Chaudhary and Amitabh Kulkarni et al. (2024)

Metformin remains the most prescribed oral antidiabetic agent globally. It reduces blood glucose by decreasing intestinal absorption, inhibiting hepatic glucose production, and enhancing insulin sensitivity. Metformin can be used alone or with other antidiabetics. Despite its efficacy, long-term use may cause lactic acidosis, vitamin B12 deficiency, and gastrointestinal discomfort, especially in patients with renal impairment. Recent studies suggest potential benefits for conditions like PCOS, gestational diabetes, cognitive impairments, and immune-related disorders, though further research is needed.

Kumar Abhishek and Mazumder et al. (2024)

Type 2 diabetes mellitus (T2DM) arises from insulin resistance and declining pancreatic β-cell function. Treatments include insulin secretagogues, biguanides, insulin sensitizers,

alpha-glucosidase inhibitors, incretin mimetics, and SGLT2 inhibitors. Traditional oral formulations face limitations such as frequent dosing and short half-lives. Therefore, novel drug delivery systems are under development to improve therapeutic outcomes.

Davoud Salarbashi and Lavad Bazeli et al. (2019)

This review covers the extraction, chemical composition, and functional properties of fenugreek seed mucilage (FSG). FSG, rich in galactomannan, exhibits excellent solubility and shear-thinning behavior, making it valuable in pharmaceuticals, food, and eco-friendly packaging. Its antioxidant and antifungal activities further enhance its industrial applications.

Balasundaresan M. and Senthil Kumar S.K. et al. (2023)

Polymers play a crucial role in drug delivery systems, with natural polymers gaining popularity for being cost-effective, biodegradable, and biocompatible. This review discusses the use of natural polymers, including fenugreek-derived ones, in modified drug release formulations, highlighting their environmental responsiveness and potential for pharmaceutical innovations.

Muhammed Shabil and Ganesh Bushi et al. (2023)

This systematic review analyzed 14 trials with 894 participants to assess fenugreek's hypoglycemic effects. While fenugreek showed benefits in glycemic control, variability in study quality remains a concern. Given its affordability, more rigorous trials are recommended to validate fenugreek’s role in diabetes management.

Jiwon Kim and Woojeong et al. (2023)

A meta-analysis of 10 studies involving 706 participants evaluated fenugreek’s effectiveness in managing T2DM. Results showed significant reductions in fasting blood glucose, postprandial glucose, and HbA1c levels, along with improved lipid profiles. No severe adverse effects were reported, confirming fenugreek’s safety.

Manjeshwar Shrinath Baliga and Princy Louis Palatty et al. (2017)

Fenugreek has a long history in Ayurvedic medicine for managing diabetes. Both seeds and leaves are effective in reducing hyperglycemia and associated complications. This review consolidates traditional and scientific evidence supporting fenugreek's antidiabetic properties.

Purusottam Mishra and Amit Kumar Shrivastav et al. (2021)

Fenugreek gum, rich in galactomannan, offers significant biopharmaceutical applications due to its solubility, mucoadhesive, and disintegrating properties. It serves as a natural excipient with therapeutic benefits, including antidiabetic, anticancer, anti-inflammatory, and hepatoprotective effects.

Babak Gholamine and Jitendra Malviya et al. (2024)

Medicinal plants like fenugreek are increasingly recognized for managing diabetes due to their natural antioxidants and minimal side effects. This review highlights the efficacy of various herbs, including fenugreek, in lowering blood sugar levels and addressing diabetes-related complications.

Rohini Diwedi and S. Alexander et al. (2011)

Tablets prepared via wet granulation using fenugreek-derived materials exhibited satisfactory pharmaceutical properties. In vitro studies confirmed sustained drug release, particularly for metformin hydrochloride, with optimized formulations maintaining buoyancy and controlled release for up to 8 hours.

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Chapter 3

Research envisaged

3.1 AIM OF THE WORK

The objective of this study is to formulate and develop metformin hydrochloride tablets utilizing fenugreek seed mucilage (FSM) as a natural polymer, aiming to enhance drug delivery efficiency and bioavailability. Fenugreek, due to its inherent polymeric properties, holds potential for improving the controlled release profile of metformin.

The primary goal is to design a formulation that ensures the controlled and sustained release of metformin over an extended duration. This approach is critical for maintaining therapeutic drug levels in the bloodstream, thereby enhancing patient adherence and minimizing dosing frequency.

Furthermore, the study seeks to investigate the applicability of fenugreek seed mucilage as a natural polymer in sustained-release tablet formulations. Natural polymers are increasingly favored in pharmaceutical applications due to their biocompatibility, biodegradability, and low toxicity.

An essential component of this work involves evaluating the safety and biocompatibility of fenugreek seed mucilage within the formulation. Ensuring that the natural polymer does not provoke adverse effects or allergic reactions when administered orally is a key consideration.

Rationale for Selecting FSM as a Natural Polymer:

- Fenugreek seed mucilage is a gelatinous substance naturally occurring in fenugreek seeds, classified as a soluble fiber that forms a viscous, sticky material upon hydration.
- This mucilage exhibits antimicrobial activity and is biologically neutral, with superior water solubility.

- It possesses excellent film-forming capabilities, making it a biodegradable, cost-effective, and environmentally friendly option.
- FSM serves effectively as a carrier in sustained-release drug delivery systems and is readily available.
- Additionally, fenugreek seed mucilage can function in multiple roles within pharmaceutical formulations, such as an emulsifying agent, hydrating agent, thickening agent, gelling agent, and suspending agent.

3.2 PLAN OF WORK

Introduction:

- Comprehensive review of existing literature.

Pre-formulation Studies:

- Characterization of the powdered blend, focusing on the following parameters:
    - Bulk density
    - Tapped density
    - Carr's index
    - Angle of repose
    - Hausner's ratio

Analytical Methods:

- UV-Spectroscopy for drug quantification.
- Fourier Transform Infrared Spectroscopy (FTIR) for identifying chemical interactions.

Formulation Development:

- Preparation of sustained-release metformin hydrochloride tablets using the direct compression method.

Physical Evaluation of Sustained-Release Metformin Hydrochloride Dosage Form:

- Assessment of key physical parameters:
    - Weight variation
    - Friability

- Thickness
- Hardness
- Content uniformity
- In vitro dissolution studies to evaluate the drug release profile.

Chapter 4

Materials and Equipments

4.1 LIST OF MATERIALS

Table 4.1: List of materials

MATERIAL	PROCURED FROM
Metformin Hcl	
Fenugreek seed mucilage	Extracted Powder
Xanthum gum	
HPMC	Himedia Laboratories PVT. LTD.
Magnesium stearate	Loba Chemi PVT. LTD.
Talc	Merck Specialities PVT. LTD.
Isopropyle Alcohol	Thermo Electron LLS India PVT. LTD.

4.2 LIST OF INSTRUMENTS

Table 4.2: List of Instruments

INSTRUMENT	MANUFACTURED BY
Digital weighing balance	WENSAR ISO 9001
UV-VIS Spectrophotometer	UV-1800, Shimadzu
Fourier-Transform Infrared Spectrophotometer (FTIR)	SHIMADZU CORP. 00032
Dissolution Apparatus	Labindia DS 8000+

Friability Apparatus	Electronics India Model 903
Tablet Punching machine	Kembert

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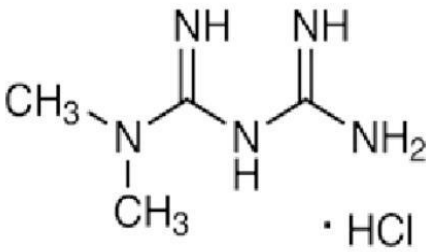
Chapter 5

Drug and Excipient profile

Name: Metformin hydrochloride (MET.HCL)

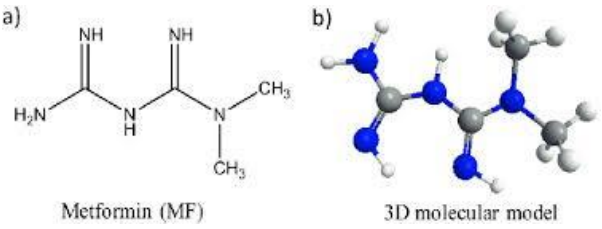
• **Chemical structure:**



Drug entry: Metformin is a biguanide anti-hyperglycemic agent and first-line pharmacotherapy used in the management of type II diabetes.

Metformin is considered an anti-hyperglycemic drug because it lowers blood glucose concentrations in type II diabetes without causing hypoglycemia. It is commonly described as an "insulin sensitizer", leading to a decrease in insulin resistance and a clinically significant reduction of plasma fasting insulin levels. Another well-known benefit of this drug is modest weight loss, making it an effective choice forobese patients type II diabetes.

Structure:



Metformin (MF) 3D molecular model

Chemical safety

Irritant

Molecular Formula:C4H11N5

• **Synonyms :**

- metformin
- 657-24-9
- 1,1-Dimethylbiguanide
- N,N-dimethylimidodicarbonimidic diamide
- Fluamine

• **Molecular Weight:** 165.6 g/mol

• **Physical Description**: Solid

• **Boiling Point:** 224.1ºC at 760 mmHg

• **Melting Point:** 223-226 °C

✓ **Solubility:**Freely soluble

• **Decomposition:** Hazardous decomposition products formed under fire conditions - Carbon oxides, nitrogen oxides(NOx), hydrogen chloride gas.

• **Mechanism of action**: Metformin works by reducing hepatic glucose production and enhancing insulin sensitivity in peripheral tissues. It does not stimulate insulin secretion from the pancreas but improves the efficacy of available insulin.

• **Pharmacokinetics:**

a) Absorption: metformin is absorbed from the gastrointestinal tract, with the peak plasma concentration achieved within 2 hr.

b) Distribution: it does not bind to plasma proteins and has a low distribution into erythrocytes.

c) Metabolism: metformin is not metabolized; it is eliminated unchanged in the urine.

d) Excretion: the renal clearance of metformin is greater then the glomerular filtration rate, indicating tubular secretion

• **Dosage forms**:

Metformin is available in various dosage forms, including immediate-release (IR) tablets, extended-release (ER) tablets, and oral solutions.

• **Dosage and Administration**:

➢ Dosage is individualized based on the patient's response to therapy, renal function, and other factors.

➢ The usual starting dose for adults is 500 mg or 850 mg metformin Hcl two or three times a day with meals.

Adverse effects:

➢ Common side effects include gastrointestinal symptoms such as nausea, vomiting, diarrhea and abdominal discomfort.

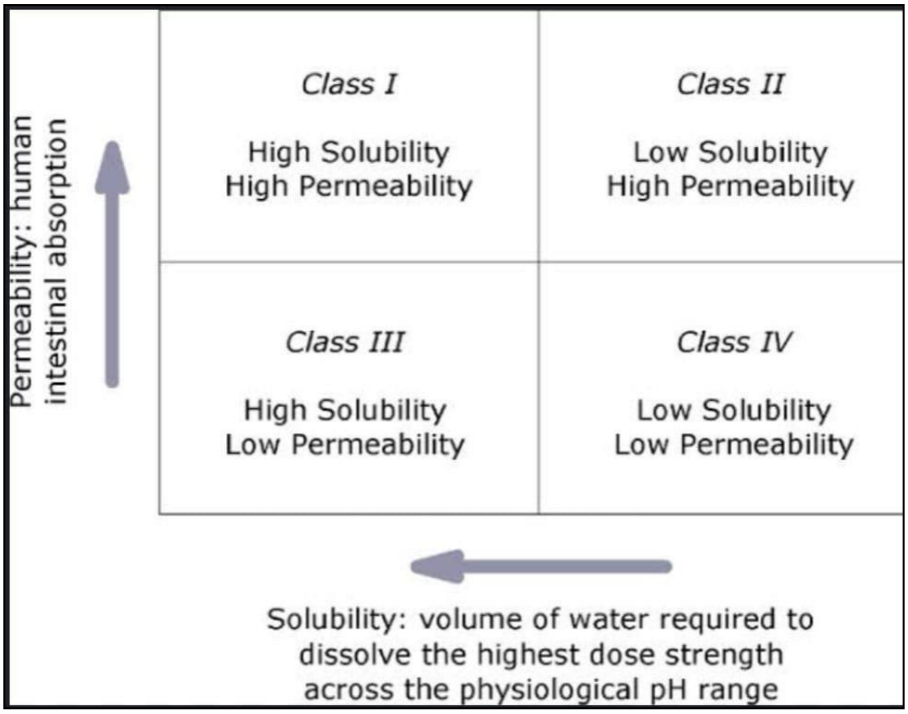
➢ Lactic acidosis is a rare but serious side effect associated with metformin use, particularly in patients with renal impairments.

• **Medicinal benefits:**

➢ Metformin is a biguanide anti-hyperglycemic agents and first line pharmacotherapy used in the management of type-2 diabetes.

➢ Metformin is considered as an anti-hyperglycemic drug because it lowers blood glucose concentrations in type -2 diabetes without causing hypoglycemia.

BCS CLASSIFICATION OF METFORMIN HYDROCHLORIDE:



Class III (High Solubility, Low Permeability): Drugs in this class have high solubility but low permeability. They may face permeability-limited absorption. **Metformin** hydrochloride is an example of a Class III drug.

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Chapter 6

Excipients Profile

• **FENUGREEK,** *Trigonella foenum-graecum*), fragrant herb of the pea family (Fabaceae) and its dried flavorful seeds used as a spice. Native to southern Europe and the Mediterranean region, fenugreek is cultivated in central and southeastern Europe, western Asia, India, and northern Africa.

PLANT AUTHENTICATION: I have cultivated the plant "fenugreek", (trigonella foenum-graecum), and certified by Rajasthan university, jaipur.
The Authentication no. for the specified plant is "RUBL21688".

Fig. 6.1 Fenugreek Seeds and Plant

Physical description of FSM:

Fenugreek (*Trigonella foenum-graecum*) plant.

Fenugreek plants are erect, loosely branched, and less than 1 meter (3 feet) tall with trifoliate light green leaves and small white flowers. The slender pods are up to 15 cm (6

inches) long, curved and beaked, and contain yellow-brown seeds—flat rhomboids characterized by a deep furrow, less than 0.5 cm (0.2 inch) long.

Uses of Trigonella foenum-graecum (Fenugreek) Seed Mucilage:

1. Trigonella foenum-graecum seed gum is utilized as an innovative binder in tablet formulations, contributing to the structural integrity and mechanical strength of tablets.
2. Fenugreek seeds are extensively used in culinary practices as a flavor enhancer and seasoning agent. Additionally, they have been traditionally employed in Iranian folk medicine as a tonic to promote general health.
3. Scientific studies have reported that fenugreek seeds possess glucose-lowering and lipid-lowering properties. They also exhibit antioxidant and anti-inflammatory (antiphlogistic) effects, making them beneficial in managing metabolic disorders.
4. Due to the high viscosity of mucilage produced from fenugreek seeds even at low concentrations, it is considered valuable in pharmaceutical applications, particularly in controlled drug release formulations.
5. The present investigation aims to evaluate the binding properties of fenugreek seed mucilage in tablet production, assessing its effectiveness as a natural polymer binder.
6. Traditionally recognized for aiding digestion, fenugreek seeds have been used internally as an emollient to soothe inflammation within the digestive tract. Externally, they have been applied as poultices to treat conditions like boils and abscesses.

Xanthan Gum:

Xanthan gum powder appears as a free-flowing white to cream-colored substance, soluble in both hot and cold water while remaining insoluble in most organic solvents. Xanthan gum solutions display significantly high viscosity, even at low concentrations, compared to other polysaccharide solutions. This property makes it an effective thickener and stabilizer. Xanthan gum demonstrates pseudoplastic behavior, characterized by a decrease in viscosity under shear stress, but it is not thixotropic. Furthermore, it exhibits remarkable thermal stability, which provides an advantage over other water-soluble polysaccharides. Xanthan gum is tasteless and does not interfere with the flavor profile of food products.

Physical Characteristics:

1. Appearance: Xanthan gum typically appears as a white to off-white, free-flowing fine powder.
2. Solubility: Highly soluble in both hot and cold water, forming viscous solutions at low concentrations.
3. Viscosity: Exhibits pseudoplastic (shear-thinning) behavior, with viscosity decreasing under shear stress, making it suitable for applications requiring stable yet easily spreadable or pumpable consistencies.
4. Stability: Maintains stability over a broad range of temperatures and pH levels. It also retains stability in the presence of salts, acids, and bases.
5. Molecular Weight: Xanthan gum possesses a high molecular weight, typically ranging from 2 to 50 million Daltons.
6. Film-Forming Ability: Capable of forming films, useful in coating applications.
7. Compatibility: Compatible with various hydrocolloids, allowing its combination with other thickeners or stabilizers to achieve desired textures and stability in food and pharmaceutical products.

Uses of Xanthan Gum:

1. Controlled Release Matrix: Functions as a release retardant or matrix-forming agent in tablet formulations. In sustained-release (SR) formulations, it helps regulate the release of active ingredients, such as metformin, by forming a gel matrix that slows down the dissolution rate.
2. Uniform Drug Distribution: Facilitates the uniform distribution of metformin within the tablet matrix, ensuring consistent drug release profiles and meeting required specifications.
3. Improved Stability: Enhances the physical stability of tablet formulations by providing structural integrity and preventing drug degradation or aggregation.
4. Enhanced Bioavailability: May potentially improve the bioavailability of metformin by optimizing dissolution and absorption in the gastrointestinal tract, depending on the specific formulation and excipients used.
5. Compatibility: Exhibits compatibility with common pharmaceutical excipients, aiding in uniform blending and efficient tablet compression.

Hydroxypropylmethylcellulose (HPMC):

HPMC, also known as hydroxypropylmethylcellulose, is widely used as a polymer in the formulation of sustained-release drug products, including metformin. In pharmaceutical

applications, HPMC is valued for its ability to control the drug release rate by forming a gel matrix upon contact with water. This matrix structure slows down drug dissolution, extending its release over time.

Physical Characteristics:

1. Appearance: HPMC typically appears as a white to off-white, odorless, tasteless, free-flowing powder.
2. Solubility: Soluble in cold water, forming clear, viscous solutions. It is insoluble in hot water, but once dissolved in cold water, it can withstand heating without precipitating.
3. Viscosity: Demonstrates pseudoplastic (shear-thinning) behavior. The viscosity varies depending on molecular weight and concentration, allowing flexibility for different applications.
4. Gelation: Exhibits thermal gelation properties. Upon heating, HPMC forms a gel, with the gelation temperature adjustable by modifying hydroxypropyl and methyl substitution levels.
5. Film-Forming Ability: Capable of forming flexible, transparent, and strong films, beneficial in coating applications.
6. Stability: Chemically stable, resistant to microbial degradation, and stable over a pH range of 3 to 11.
7. Thermal Properties: Does not have a defined melting point but decomposes at temperatures above 200°C (392°F).
8. Swelling: Swells in water to form a gel-like structure, enhancing its stabilizing properties in emulsions and suspensions.

Uses of HPMC:

1. Sustained Release: Serves as a polymer matrix in sustained-release metformin formulations. When hydrated, it forms a gel-like matrix that slows drug dissolution in the gastrointestinal tract, maintaining therapeutic drug levels over extended periods.
2. Binder: Acts as a binder in tablet formulations, aiding in the compression of active pharmaceutical ingredients with excipients into tablets of desired shape and size.
3. Film Former: Functions as a film-forming agent in tablet coatings, serving to mask unpleasant tastes, protect from environmental factors, and control drug release profiles.
4. Thickening Agent: In liquid metformin formulations, such as oral suspensions, it acts as a thickener, improving formulation stability.

5. Stabilizer: Helps maintain the physical and chemical stability of metformin formulations during storage and use.

Magnesium Stearate:

Magnesium stearate is commonly employed as an anti-adherent and lubricant in the manufacturing of tablets, capsules, and powders. Its lubricating properties prevent ingredients from sticking to manufacturing equipment during the compression of powders into solid tablets, making it the most frequently used tablet lubricant.

Physical Characteristics:

1. Appearance: Fine, white to off-white powder with a slightly greasy texture.
2. Odor: Typically odorless, with a faint fatty substance-like odor in some cases.
3. Taste: Characteristic, mild taste.
4. Solubility: Practically insoluble in water, ethanol, and ether but soluble in warm alcohol and chloroform.
5. Melting Point: Decomposes at temperatures above 200°C (392°F).
6. Lubrication: Known for excellent lubricating properties, reducing friction during tablet manufacturing.
7. Flowability: Improves the flow properties of powders, facilitating efficient processing.
8. Hydrophobicity: Exhibits hydrophobic characteristics due to fatty acid content, which can influence tablet dissolution rates.
9. Particle Size: Varies from fine to coarse powders, depending on the application.
10. Stability: Stable under normal conditions but reactive with strong oxidizing agents; remains stable across various pH levels.

Uses of Magnesium Stearate:

1. Lubricant: Reduces friction between tablet granules and equipment during compression, ensuring smooth tablet formation.
2. Flow Enhancer: Enhances the flow properties of powdered ingredients, ensuring uniform distribution of active pharmaceutical ingredients and excipients.
3. Tablet Disintegration Control: In SR tablets, aids in controlling disintegration rates, supporting sustained drug release.
4. Compatibility: Compatible with a wide range of pharmaceutical ingredients and excipients without reactive interference.
5. Cost-Effective: An economical excipient, widely used in SR tablet formulations.

Talc:

Talc is utilized in food and pharmaceutical industries as a glidant, cosmetic ingredient, lubricant, and bulking agent. In pharmaceutical applications, it improves powder flow and enhances tablet formation.

Physical Characteristics:

1. Appearance: Typically white to grey, with occasional shades of green, yellow, or brown, featuring a pearly or greasy luster.
2. Texture: Soft, smooth, and soapy to the touch.
3. Hardness: The softest mineral on the Mohs scale, rated at 1.
4. Solubility: Insoluble in water and most acids.
5. Density: Ranges from 2.58 to 2.83 g/cm³, depending on purity.
6. Chemical Inertness: Does not react with most chemicals, enhancing stability in diverse applications.
7. Platy Structure: Layered structure contributing to lubricating properties.
8. Thermal Stability: Stable at temperatures up to 900°C (1652°F).
9. Absorption: Effective at absorbing oils and moisture.
10. Transparency: Ranges from translucent to opaque.

Uses of Talc:

1. Lubricant: Reduces friction during tablet compression.
2. Glidant: Improves powder flow in formulations.
3. Anti-adherent: Prevents tablets from sticking to equipment.
4. Opacifying Agent: Enhances tablet aesthetics.
5. Carrier for Active Ingredients: Acts as an inert filler or carrier in formulations.
6. Powder Flow Improvement: Promotes uniform distribution of ingredients, aiding in consistent drug release.

Isopropyl Alcohol (IPA):

Isopropyl alcohol, also known as isopropanol or 2-propanol, is a colorless, flammable organic compound with a pungent alcoholic odor. It is commonly used as a solvent, disinfectant, and cleaning agent in pharmaceutical manufacturing.

Physical Characteristics:

1. Appearance: Clear, colorless liquid.
2. Odor: Characteristic sharp, alcohol-like scent.
3. Taste: Bitter, though not intended for consumption.
4. Boiling Point: Approximately 82.6°C (180.7°F).
5. Melting Point: Around -89°C (-128°F).
6. Density: Approximately 0.786 g/cm³ at 20°C.
7. Solubility: Miscible with water, ethanol, ether, and chloroform.
8. Viscosity: About 2.43 cP at 20°C.
9. Surface Tension: Around 21.7 dynes/cm at 25°C.
10. Flash Point: 11.7°C (53.1°F) in a closed cup.
11. Refractive Index: Approximately 1.377 at 20°C.
12. Vapor Pressure: Around 44 mmHg at 20°C.
13. Flammability: Highly flammable.
14. Evaporation Rate: Rapid evaporation, useful for cleaning purposes.

Uses of IPA:

1. **Solvent**: Isopropyl alcohol is commonly used as a solvent in the preparation of tablet coatings and in granulation processes. It helps dissolve various coating polymers and aids in the uniform application of coatings onto the tablet cores. For SR tablets, coatings are often applied to control the release rate of the active ingredient over time.
2. **Extraction and Purification**: In some cases, IPA may be used in the extraction or purification processes of certain pharmaceutical ingredients or excipients used in SR tablet formulations. It can help in isolating and purifying active ingredients before they are incorporated into the tablet matrix.
3. **Disinfectant**: IPA is also used as a disinfectant for equipment and surfaces in pharmaceutical manufacturing to maintain sterile conditions and prevent microbial contamination.
4. **Adjustment of Viscosity**: In formulations where viscosity control is critical, IPA can be used to adjust the viscosity of liquid components used in the tablet coating or granulation process. This ensures proper handling and application of these components.
5. **Carrier and Diluent**: In specific formulations, IPA may act as a carrier or diluent for certain excipients or active ingredients. However, this depends on the specific formulation requirements and is less common in SR tablets where Sustained release mechanisms are more crucial.

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Chapter 7

Methodology

➢ **Procurement of chemical into fenugreek seed mucilage**

Method:

• The seed of polymer were washed in water and dried into oven for sufficient temperature in oven, and powdered coarsely with grinder.

• Coursed powder was soaked in distilled water for 10 hour, and then gum was filtered out from the bulk material by using muslin cloth.

• The filterate was precipitate with ethanol several times to compute the extraction process.

• The gum was air dried at 60 degree Celsius, crushed into powdered and collect extraction mucilage, Then package into polythene container for further used.

➢ **Polymer analysis and pre-formulation studies:**
The powder blends of polymers were evaluated before formulations to assess the flow properties of the powder**.**

➢ **Bulk density**: Required amount of powder m was transferred into the measuring cylinder, and apparent volume V0 was measured, bulk density in g per ml is calculated by the formula.

- ✓ Bulk density = m/V0 .

Where m-mass of powder, V0 - apparent volume.

➢ **Tapped density:** After determination of bulk density the measuring cylinder Va volume in ml was measured initially, later the same cylinder was set for 100 tappings on tapped density apparatus and measure the tapped volume finally Vb.

Calculate tapped density in g per ml by the formula.

- ✓ Tapped density = Va/Vb.

Where Va - initial volume, Vb - final tapped volume.

➢ **Carr's index** :It is an indirect method of measuring powder flow from bulk densities to measure bridge strength and stability. Carr's index of each formulation was calculated according to the equation.

- ✓ Carr's index = (Tapped density - bulk density)/tapped density *100.

➢ **Hausner ratio :**It is essential to determine the compressibility strength of powder. It was calculated according to equation.

Hausner ratio = Tapped density/bulk density.

➢ **Angle of repose:** Accurately weighed quantity of powder was transferred into a funnel which was adjusted to a height of 2 cm in such a way that the tip of funnel touches apex of a pile of powder heap. Finally, the height and radius of powder cone were measured using the following equation.

tan θ = h/r ,
θ = tan -1 h/r

Where, θ = Angle of repose, h = Height of heap and r = radius

7.2 Relationship between Angle of Repose (θ) and flow properties

Flowability	Angle of repose
Excellent	<25
Good	25-30
Passable	30-40
Poor	>40

COMPRESSIBILITY INDEX

Compressibility index was determined by the following formula:

- ✓ Compressibility Index= [Tapped density – Bulk density / Tapped density] x100

7.3 Practical Consideration of Compressibility Index

% COMPRESSIBILITY INDEX	FLOW
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very Poor
>40	Very Very Poor

HAUSNER'S RATIO

- ✓ Hausner's ratio was determined by the following formula:

  Hausner's ratio = Tapped Density / Bulk Density

7.4 Practical Consideration of Hausner's Ratio

HAUSNER'S RATIO	FLOW
<1.25	Good
>1.25	Poor
1.25-1.5	Very Poor

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Chapter 8

Analytical Methods

Several analytical techniques are employed to estimate metformin in pharmaceutical formulations and human plasma, including UV Spectroscopy, High-Performance Liquid Chromatography (HPLC), High-Performance Thin-Layer Chromatography (HPTLC), Thin-Layer Chromatography (TLC), Ultra-Performance Liquid Chromatography (UPLC), and Capillary Electrophoresis. Among these, HPLC is the most widely used method for metformin analysis due to its accuracy and reliability. This section compiles recent analytical methods applied in metformin evaluation.

UV Spectroscopy:

The absorption maximum of the test solution is observed within the 200-400 nm range using a UV-Visible Spectrophotometer. Metformin hydrochloride (MET) is received as a gift sample in tablet form, with each film-coated tablet containing 1000 mg of metformin HCl I.P. Analytical-grade methanol, potassium dihydrogen orthophosphate, and sodium hydroxide are procured for the analysis.

A UV spectrophotometer equipped with 1 cm matched quartz cells is used to measure absorbance. An electronic balance is employed for precise weighing. Metformin exhibits a maximum absorbance (λ max) at 234 nm in a water-methanol mixture (60:40). Detection is optimized at 227 nm, suitable for both individual and combined drug analysis.

Concentration Determination:

Using the Lambert-Beer Law, the concentration of metformin in a solution is quantified through UV/VIS spectroscopy. This process involves creating a calibration curve by measuring the absorbance of standard solutions with known

concentrations. This method is applicable for determining concentrations of substances such as DNA, RNA, proteins, carbohydrates, and organic compounds.

Standard Calibration Curve:

- **Preparation of Buffer Solution:** Phosphate buffer with pH 6.8 is prepared by dissolving 13.872 g of potassium dihydrogen phosphate and 35.084 g of disodium hydrogen phosphate in sufficient distilled water to make 1000 ml.
- **Preparation of Dilutions for Standard Curve:** A stock solution is created by dissolving 0.13 g of metformin in 100 ml of phosphate buffer. This stock solution is further diluted to obtain concentrations of 2, 4, 6, 8, and 10 µg/ml. Absorbance of these solutions is measured at 234 nm, and a calibration curve is plotted correlating absorbance with concentration.

Fourier Transform Infrared Spectroscopy (FT-IR):

FT-IR spectroscopy is used to assess the compatibility of metformin with various excipients by analyzing infrared absorption spectra. Any chemical changes resulting from drug-excipient interactions are identified through spectral analysis.

Preparation of Samples:

1. **Preparation of Metformin-Fenugreek Seed Mucilage Granules:** Granules are formulated by blending metformin with fenugreek seed mucilage and excipients like HPMC, xanthan gum, magnesium stearate, and isopropyl alcohol (IPA) using wet granulation techniques.
2. **Sample Preparation for FTIR Analysis:**
    - Select representative granule samples.
    - Grind samples into a fine powder.
    - Prepare small quantities (a few milligrams) for FTIR analysis.
3. **Data Analysis:**
    - **Interpretation of FTIR Spectrum:** Analyze spectra to identify characteristic peaks corresponding to pure metformin, fenugreek seed mucilage, and other excipients.
    - **Diagram:** FTIR spectrum diagram illustrating characteristic peaks.

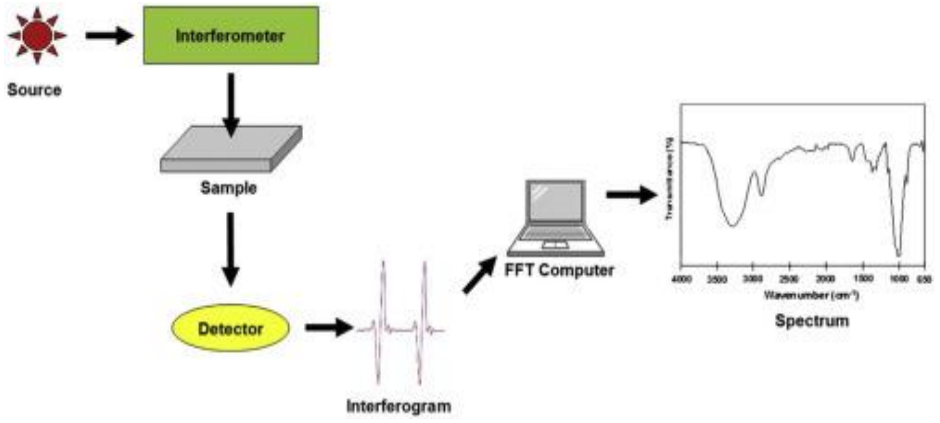

Fig 8.1 Diagram of FTIR

USES OF FT-IR:

1. **Identification and Purity Analysis:** Confirms the identity and purity of metformin hydrochloride, ensuring the substance matches its expected chemical structure.
2. **Formulation Development:** Assists in optimizing metformin formulations, maintaining API stability during processing.
3. **Quality Control:** Ensures batch-to-batch consistency and verifies dosage form uniformity during manufacturing.
4. **Stability Studies:** Monitors chemical stability, degradation products, and API integrity under various storage conditions.
5. **Interaction Studies:** Evaluates drug-excipient interactions, aiding in understanding chemical compatibility.
6. **Bioavailability Studies:** Provides insights into dissolution behavior, influencing drug absorption profiles.

DRUG-EXCIPIENT COMPATIBILITY STUDY:

When formulating dosage forms, it is vital to consider the physical, chemical, and biological properties of both the drug and excipients to ensure stability, efficacy,

aesthetics, ease of administration, and safety. Compatibility studies are particularly critical when introducing new excipients.

Drug-excipient compatibility is assessed using FT-IR spectroscopy to identify potential interactions that may affect the stability and performance of the final product.

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Chapter 9

Formulation

- The conventional wet granulation technique wil be used to prepare matrix tablets, with each tablets containing 500 mg of metformin HCL. The selection of the polymer combination in the composition will be used on the trial preparation of the tablets.
- Each formulation contains 500 mg of the active ingredient, with the total weight of a tablet being 1000 mg. A batch of 5 tablets will be prepared using each formula.
- All the ingredient will go through a 60-mesh sieve. A mixture of all ingredient, with the exception of the glident and lubricant, will be thoroughly mixed to ensure complete phase homogenization.
- Granulation will be done manually with a solution of isopropyl alcohol. The wet masses will be passed through a 12 mesh sieve and the wet granules produced will be first air dried for 10 min and finally at 45-50° in a tray drier for 2 h.
- The granules, once dried, will be sifted through a 16-seive and then lubricated with
- Magnesium staterate. Compression will then take place using tablet punching machine.• Prior to compression, granules will be evaluated for their flow and compressibility characteristics.

Flow chart for metformin SR tablet using FSM as a natural polymer by using wet granulation direct compression method

1- **Preparation of Fenugreek Seed Mucilage** - Collect seeds -> Clean and dry -> Soak in water -> Extract mucilage -> Dry mucilage

2- **Weighing of Ingredients** - Metformin -> Fenugreek mucilage -> Excipients

3- **Mixing of Ingredients** - Mix all ingredients

4- **Wet Granulation Process** - Add fluid -> Knead to wet mass -> Sieve to form granules

5- **Drying of Granules** - Dry granules in oven

6- **Sizing of Granules** - Sieve to uniform size 8. Blending - Blend with lubricants

7- **Compression** - Compress into tablets

Determination of Solubility

A fixed amount of drug + excipient was taken, and then distilled water was added and observes the solubility visually. The same procedure was followed for methanol, ethanol, diethyl formamide, Phosphate buffer pH 6.8, 0.1N HCl.

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Chapter 10

Post Formulation Studies

10.1 Physical evaluation of Tablets:

1. Weight variation
2. Thickness
3. Tablet hardness
4. Friability
5. Content uniformity
6. Swelling index

• **Weight variation**: Ten tablets from each batch will be selected randomly and weighed on a digital balance (Shimadzu, Japan) individual weights will be compared with average weight. The percentage difference in the weight variation should be within the permissible limits.

✓ Weight variation = $\frac{\text{Individual wt. of tab.} - \text{Avg. wt. of tab.}}{\text{Avg. wt. of tab.}}$

10.2 Specification as per IP

Average Weight of Tablet	%Deviation
80 Mg or less	±10
More than 80 Mg less Than 250Mg	±7.5
250 Mg or more	±5

✓ **Thickness:** The thickness of all formulations will determined on screw gauge. Standard deviation values indicate all formulations will be within the range.

• **Tablet hardness**: Hardness of the tablets for shipping or breakage under conditions of storage, transportation, handling depends on hardness which will be determined using Monsanto hardness tester.

• **Friability:** The Friability of five tablets will be determined using Roche friabilator. This device subjects tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at the height of 6 inches in each revolution. Pre-weighed sample of tablets will placed in the friabilator and will be subjected to 100 revolutions dedusted and reweighed.

- ✓ The friability (F) is given by the formula:

$$\text{Friability (\%)} = \frac{(\text{Initial Weight} - \text{Final weight}) \times 100}{\text{Initial weight}}$$

- ✓ Where, W0 is the weight of the tablets before the test.
  W is the weight of the tablet after the test

Content uniformity:

Five tablets will weighed accurately and powdered, powder equivalent to 10 mg of drug will be dissolved in phosphate buffer pH 6.8, filtered using 0.2 um membrane filter. The drug content will be measured by ultraviolet (UV)-spectrophotometer at 233 nm.

Determination of the swelling index: swelling index studies conducted using the vankel dissolution apparatus, no rotation speeds were applied.

Steps :

- Pre-weight the tablet
- Then immersed in 500 m of medium (distiiled water, 6.8 ph buffer solution), Maintain for 8 hr.(37.0 ± 0.5°C).
- The swollen tablets were removed from the solution within 0, 0.5, 2, 4, 6, 8 (hr).
- Immediately wiped with a paper towel to remove surface droplets and weighed.

$$\textbf{Swelling index } S(w) = \frac{W_t - W_o}{W_o}$$

Where W_o is the initial weight of the dry tablet and W_t is the weight of the swollen tablet at time *t.*

***In-vitro* dissolution study**:

An in-vitro release study of tablets was conducted in USP dissolution apparatus Type 2 (paddle). The dissolution test took place with 900 ml of pH 6.8 phosphate buffer at 37 ± 0.5^0C with 50 rpm. At various time intervals, a 5.0 ml sample of the solution was taken from the dissolution apparatus and replaced with intervals, 5.0 ml sample were than filtered at methodology M.pharm (pharmaceutics) school of pharmaceutical sciences, jaipur National university and diluted to an appropriate concentration with pH 6.8 phosphate buffer.

The absorbance of these solutions were measured at 234 nm using a UV-spectrophotometer (SHIMADZU UV-1700). The cumulative percentage drug release was calculated using an equation derived from a standard curve.

Kinetic analysis of dissolution data

The in vitro drug release data will fitted into zero-order, first-order, and Higuchi by employing the method of least squares the mechanism of drug release will compared for all the formulations.

$Mt/M\infty = Ktn$

$Mt/M\infty = b+k2t1/2$

$Mt/M\infty = a+k3t$

In Peppas equation, $Mt/M\infty$ is the fraction of drug released up to time t, K kinetic constant and n is the release exponent indicative of the release mechanism. In Higuchi and zero-order release equations, k1, k2, and k3 are constants s. On the other hand, Higuchi equation expresses a diffuse release mechanism.

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Chapter 11

Result and Discussion

Identification of Drug:

Color: white colored

Odor: Odorless

Taste: Tasteless

Nature: Crystalline powder

Melting point -223-226°C

11.2 Solubility data for Metformin hydrochloride:

S.No	Solvent	solubility
1	Distilled water	Freely soluble
2	Ethanol	Insoluble
3	Methanol	Freely soluble
4	Acetonitrile	Insoluble
5	IPA	Insoluble
6	Buffer ph 4 solution	Freely soluble
7	Buffer ph 7 solution	Freely soluble

11.3 Micromeritic properties of the granules Table:

The results of the Micromeritic properties of the granules are presented in the table:

Formulation NO	Angle of Repose	Bulk Density	Tapped Density	Compressi--bility Index	Hausner Ratio
F1	20.08	0.981	1.076	8.82 (Good)	1.090 (Good)
F2	22.68	0.952	1.092	12.82 (Good)	1.147(Good)

F3	23.64	0.969	1.089	11.01 (Good)	1.123(Good)
F4	21.64	0.941	1.074	12.38 (Good)	1.141(Good)
F5	23.26	0.982	1.090	9.90 (Good)	1.109 (Good)

Angle of repose ranged from **20.08-23.64.** The flow properties of powder blend in all formulations exhibit good flow characteristics.

The Bulk density of various powder mixed blends prepared with different Super disintegrates, was measured by graduated cylinder. The bulk density was found in the range **0.941– 0.982 kg/cm3.**

The Tapped density of various powder mixed blends prepared with different Super disintegrates, was measured by graduated cylinder. The Tapped density was found in the range **1.074-1.092 gm/cm3.**

The Compressibility index of various powder mixed blends, prepared with different super disintegrates, using bulk density and tapped density data,

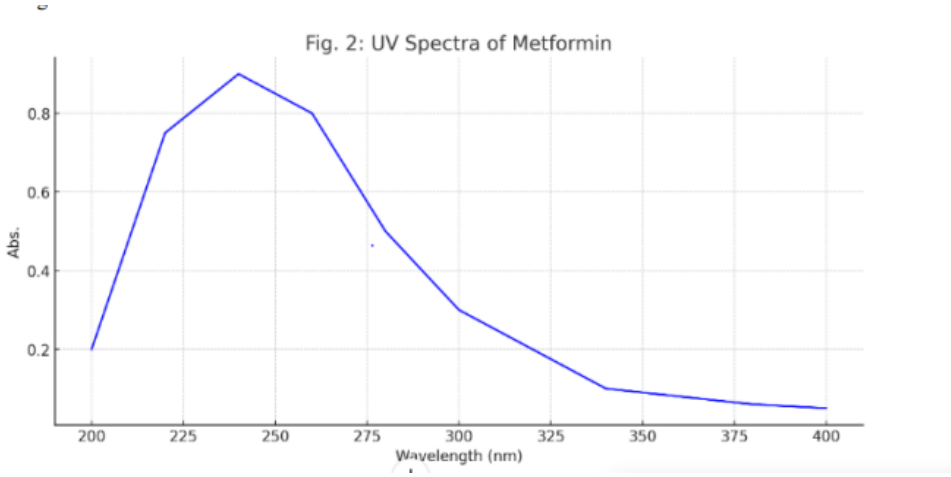
Compressibility index was calculated. It was found in the range **8.82 – 12.82%.**

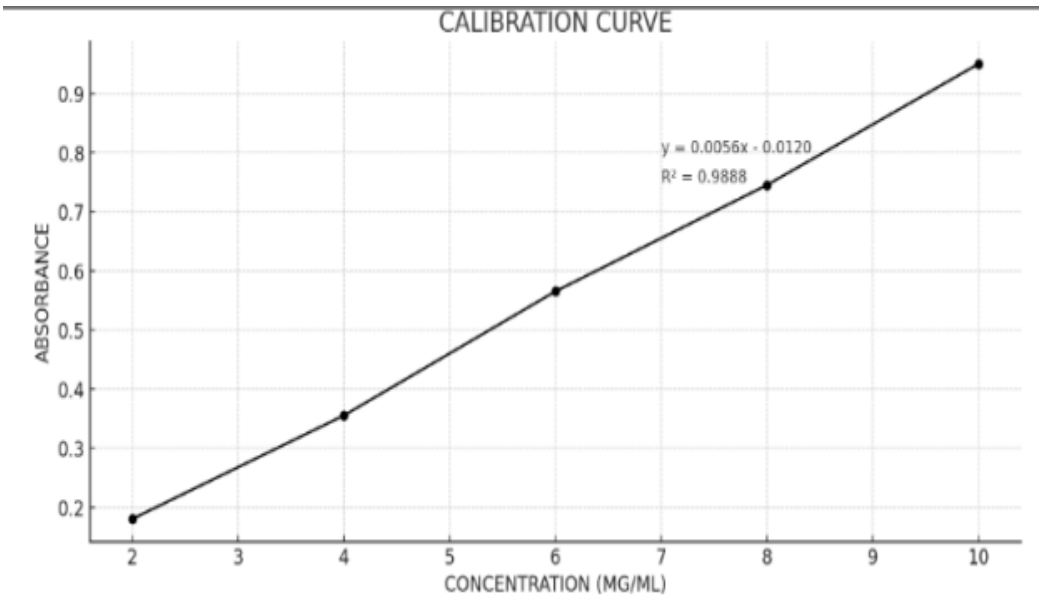
The Hausner's ratio of various powder mixed blends, prepared with different super disintegrates, using bulk density and tapped density data, Hauser's ratio was calculated. It was found in the range **1.090 – 1.147.**

11.4 Standard calibration curve of Metformin Hcl:

S.NO	CONCENTRATION(mcg/ml)	ABSORBANCE
1	2	0.189
2	4	0.355
3	6	0.565
4	8	0.745
5	10	0.95

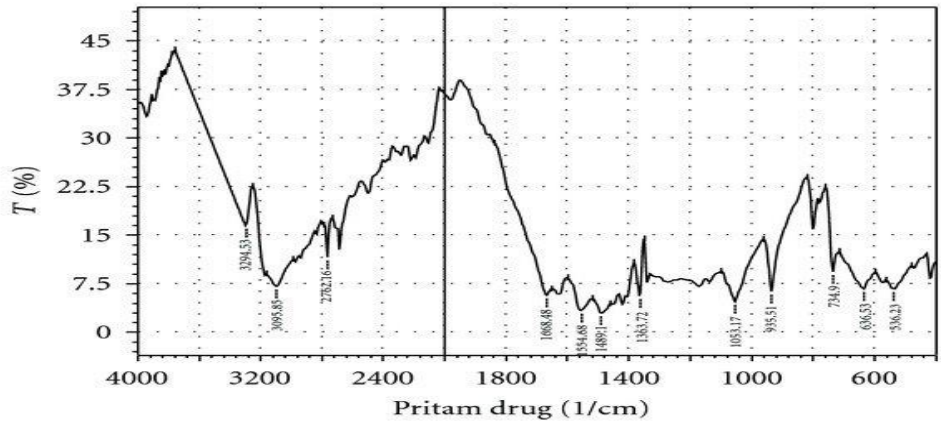
Appropriate volumes of aliquots from standard Metformin stock solution B were transferred to different volumetric flasks of 10 ml capacity. The volume was adjusted to the mark with methanol to obtain concentrations of 2, 4, 6, 8 and 10µg/ml. Absorbance value of each solution against methanol as a blank were measured at 237 nm. From that absorbance value, regression equation and correlation coefficient (r^2) are determined and presented.



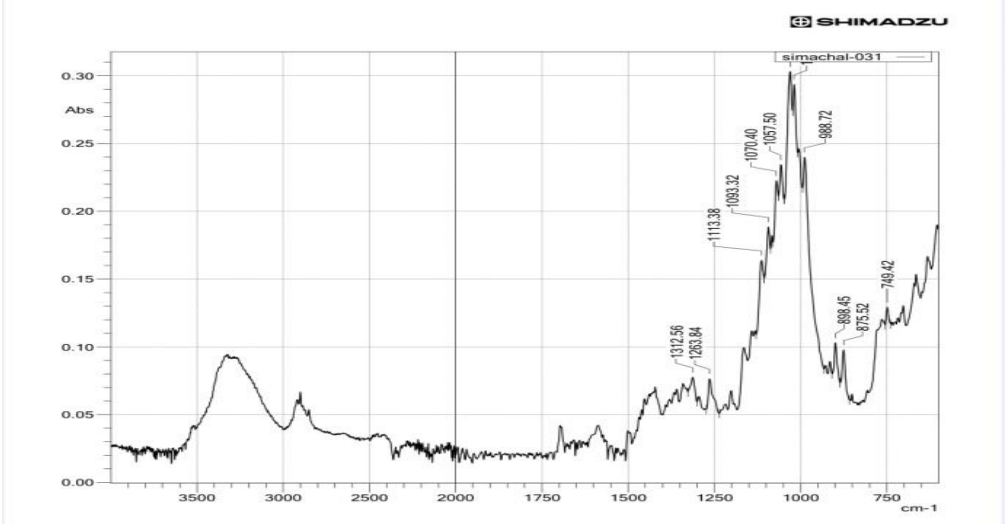


FTIR studies:

INFRA RED SPECTRUM OF PURE METFORMIN HYDROCHLORIDE:

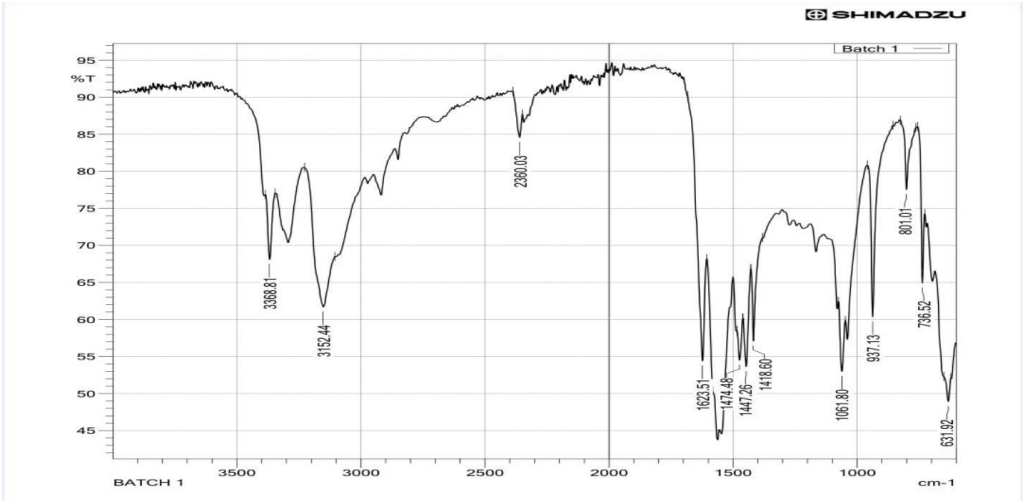


INFRA RED SPECTRUM OF DRUG POLYMER WITHOUT FSM:

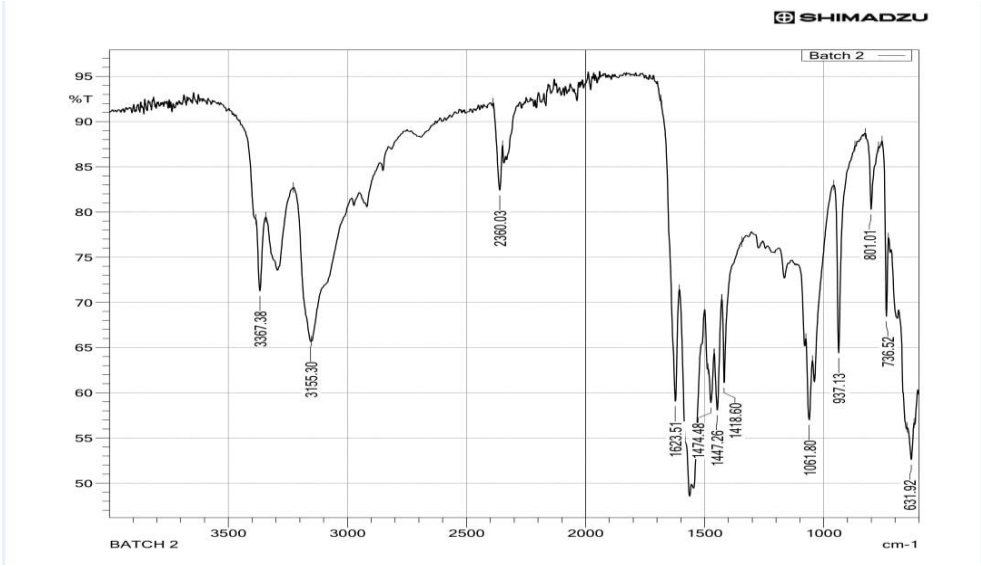


INFRA RED SPECTRUM OF DRUG POLYMER WITH FSM:

Batch-1:



Batch:2



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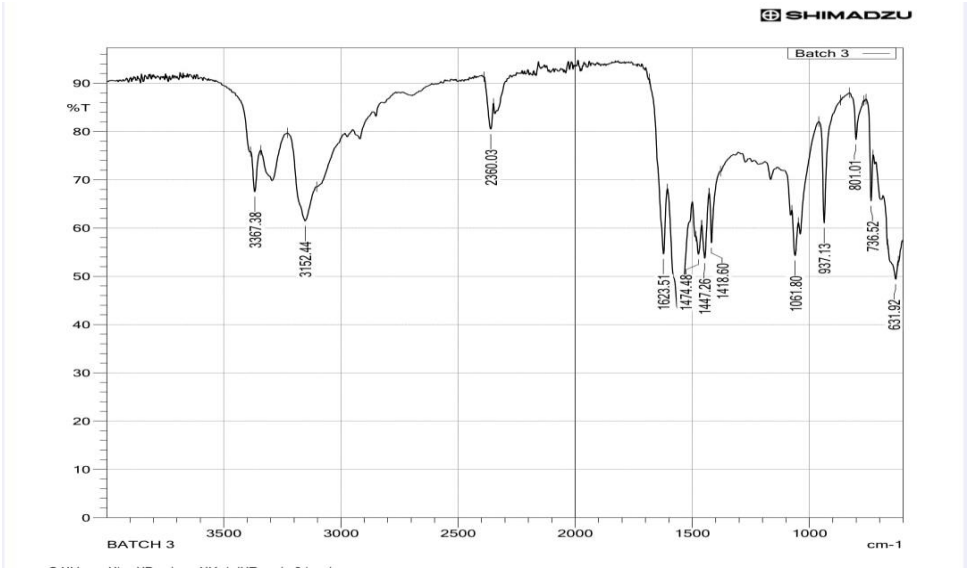

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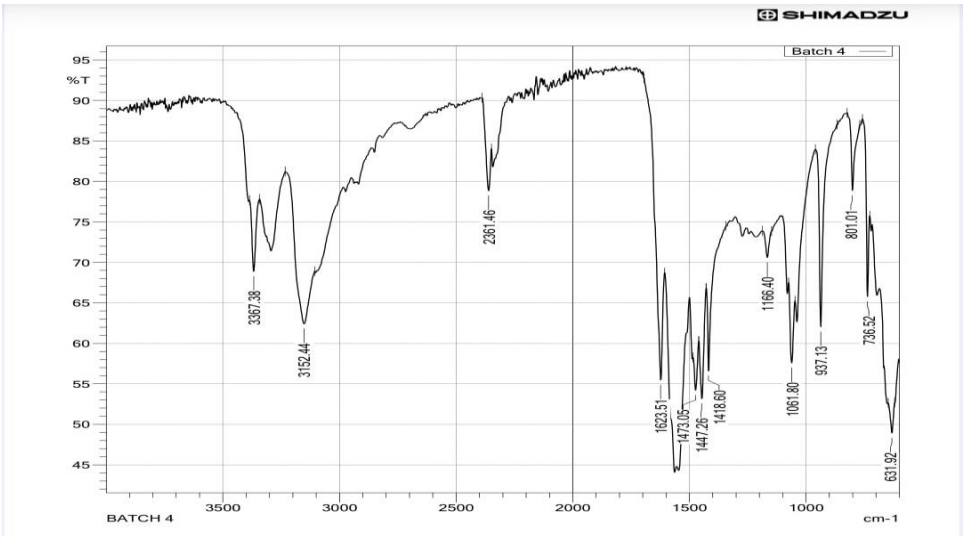

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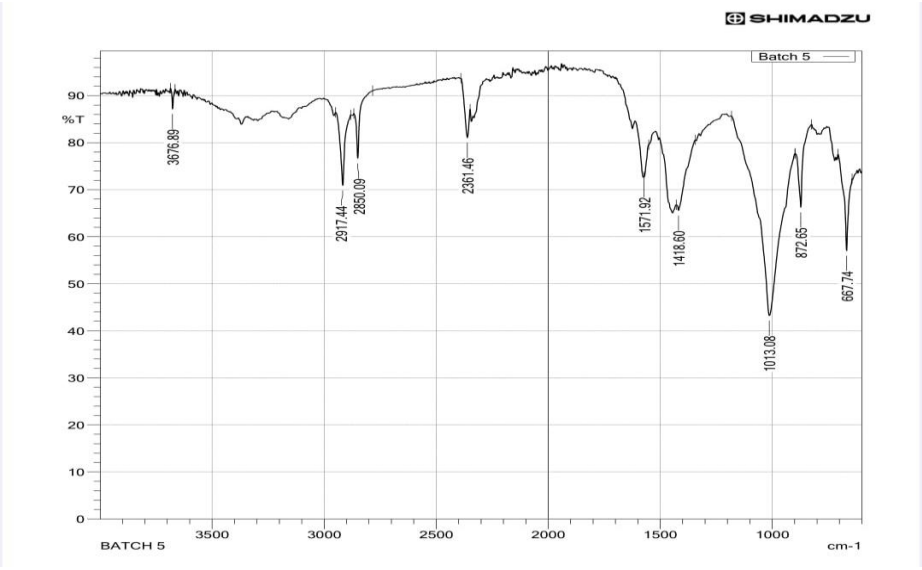
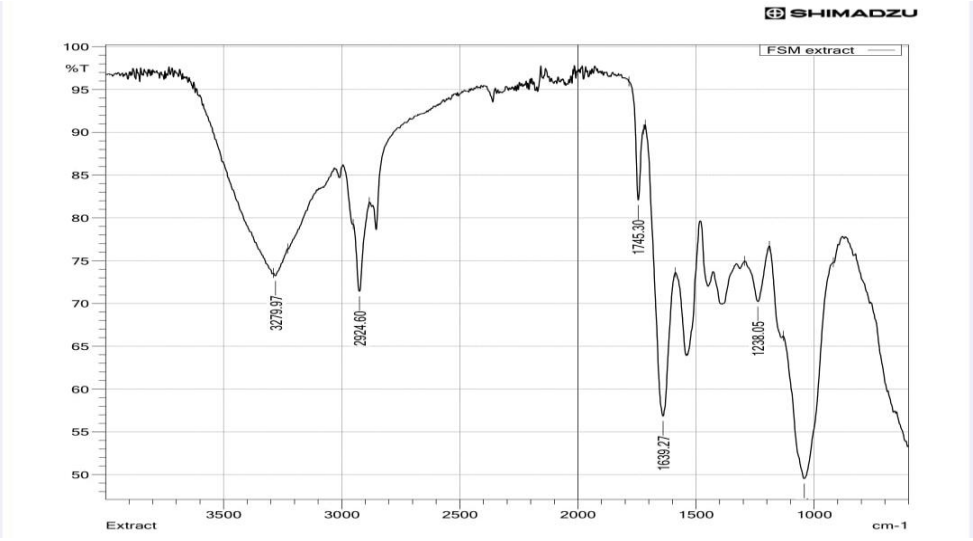
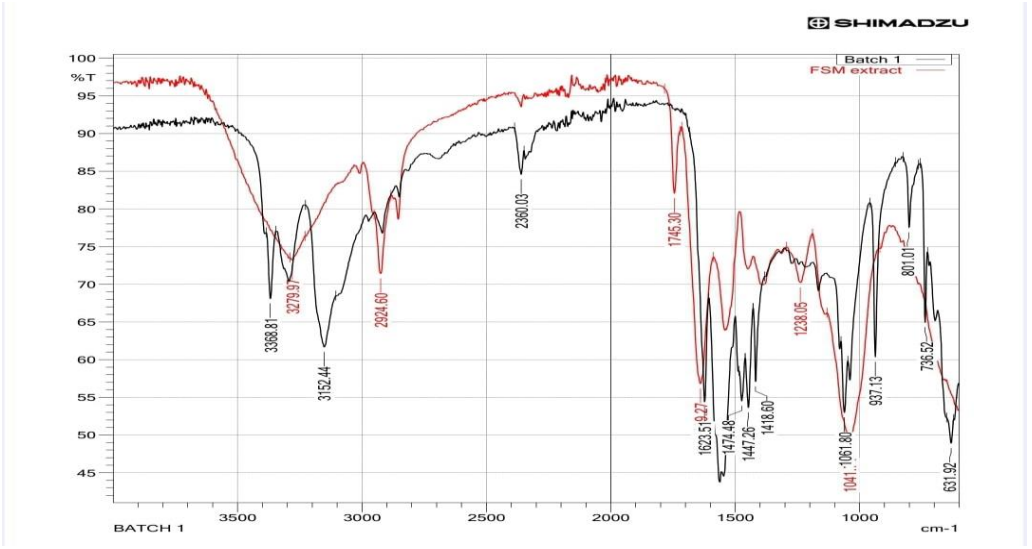


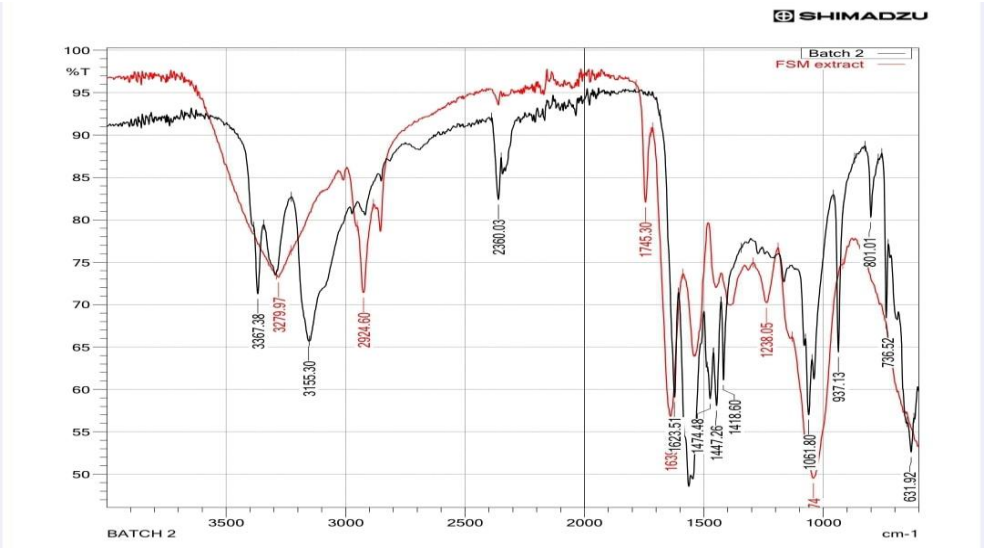
FSM (Extract):



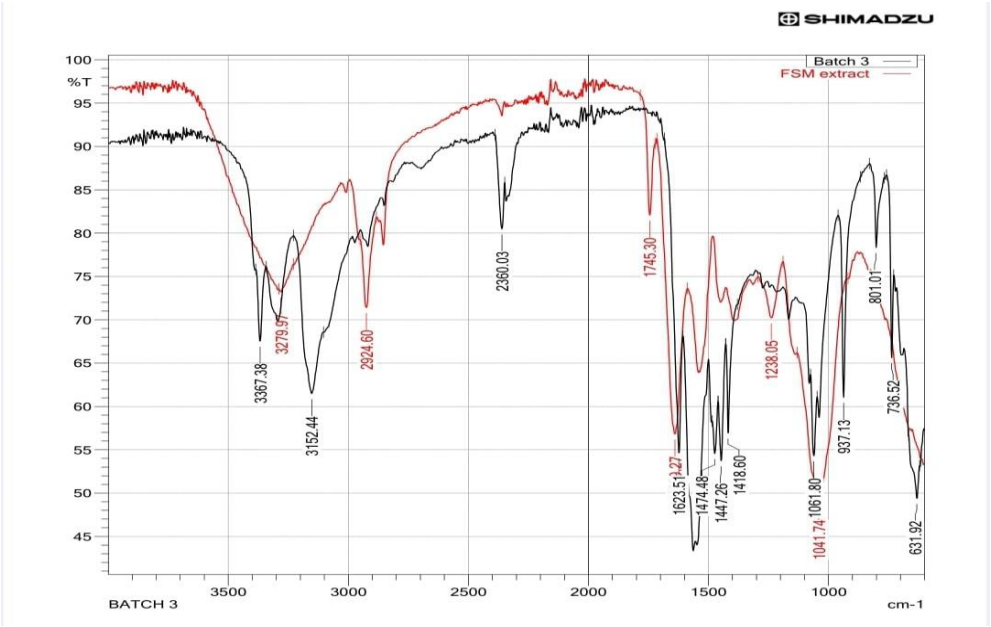
11.7 FSM (Batch-1):



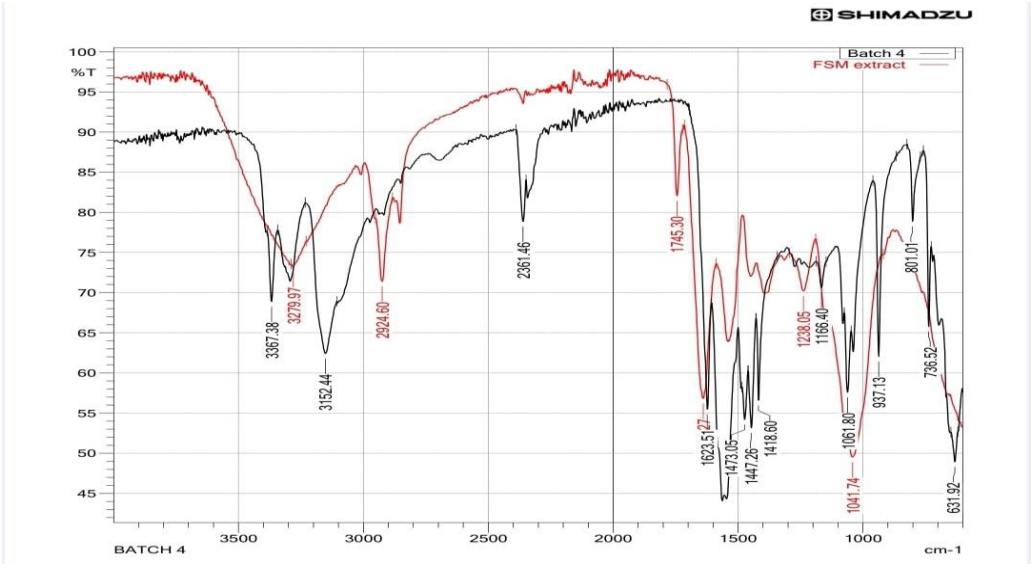
FSM (Batch-2):



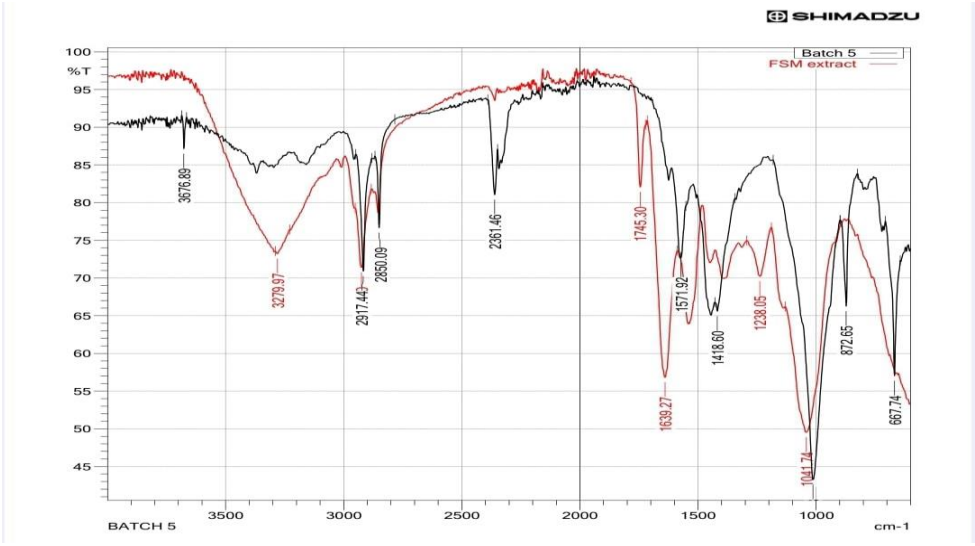
FSM (Batch-3):



FSM (Batch-4):



FSM (Batch-5):



11.5 Manufacturing formula of Metformin hydrochloride:

Sr no	Ingredient	MS1	MS2	MS3	MS4	MS5
1	Metformin Hcl	500	500	500	500	500
2	FSM	50	100	150	200	250
3	HPMC	100	150	200	--	--
4	Xanthun gum	--	--	--	100	150
5	Magnesium sterate	10	10	10	10	10
6	Talc	340	240	140	190	90
7	IPA	Q.S	Q.S	Q.S	Q.S	Q.S
	Total	1000	1000	1000	1000	1000

APPEARANCE OF THE TABLET:

White colored, oval uncoated, molted tablet with plain surface on two side.

11.6 Physical Evaluation of the Metformin SR tablets:

The result of the Physiochemical properties of the prepared tablets was done as per the procedure and presented in the table:

Batch no.	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm2)	Friability (%)	Content uniformity (%)
1	1007 ±5	4.42	6.59	0.271	99.7
2	1002 ±5	4.42	6.59	0.263	99.2
3	1000 ±5	4.41	6.80	0.291	99.6
4	1001 ±5	4.56	7.26	0.300	99.9
5	1001 ±5	4.33	6.33	0.285	99.1

11.7 Swelling indices of matrix tablets of metformin SR hydrochloride:

Formula code	Initial weight (mg)	Final weight (mg)	Swelling index
MS1	1007.45	1354.83	65.8
MS2	1002.92	1373.39	77.6
MS3	1000.63	1468.65	65.4
MS4	1001.81	1489.72	92.6
MS5	1001.60	1488.61	76.7

Evaluation of Metformin SR tablets:

Tablets were prepared using direct compression technique. Since the material was free flowing, tablets were obtained of uniform weight due to uniform die fill tablets were obtained in the range with acceptable weight variations as per pharmacopoeia specifications, less than **5%.**

Tablets were evaluated by using Vernier calliper. The thickness of the tablets was found in the range **4.33-4.41 .**

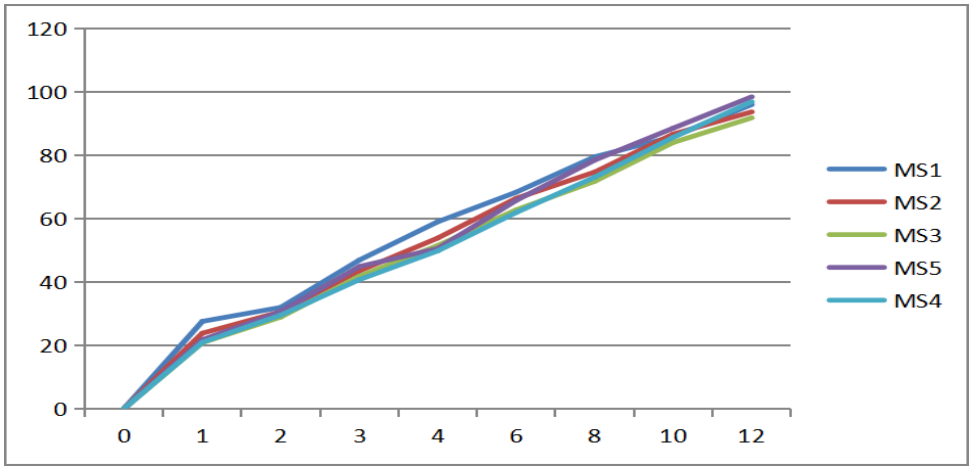
Tablets were evaluated by using Pfizer Hardness tester. Hardness of the tablets was found in the range **6.33 – 7.26 Kg/cm2.** Uniform hardness was obtained due to equal compression force.

Tablets were evaluated by using Roche Friabilator and friability of tablets was observed in the range **0.263 - 0.300.**

Content uniformity of tablets was range in **98-99%.**

11.8 In Vitro Dissolution Profile of METFORMIN SR tablets in pH 6.8 Buffer Solution:

Time in min	**MS1**	**MS2**	**MS3**	**MS4**	**MS5**
0	0	0	0	0	0
1	27.56	23.82	20.85	21.75	20.95
2	31.97	30.58	28.93	30.63	29.54
3	46.88	43.46	41.77	44.86	40.72
4	58.98	53.84	51.48	50.53	49.80
6	68.31	66.37	62.74	65.72	61.91
8	79.47	74.65	71.74	78.43	73.05
10	85.83	86.63	83.99	88.50	85.60
12	95.94	93.64	91.77	96.83	96.51



Time In hours--

In vitro drug release studies were conducted for the formulation using USP dissolution apparatus type-II (paddle), at 50 rpm. The percentage drug release at the end of 30 min was found in the range **90– 98 %.**

11.9 In vitro release kinetic parameter of metformin hydrochloride SR Tablets:

Sr. no.	**Zero order**		**1st order**		**Higuchi**		**Korsmeyer-peppas**		
	r2	**K**	**r2**	**K**	**r2**	**K**	**N**	**r2**	**K**
MS1	0.091	8.67	0.952	-0.28	0.99	25.91	0.636	0.989	23.619
MS2	0.913	8.72	0.931	-0.25	0.991	26.28	0.651	0.995	21.368
MS3	0.900	8.21	0.911	-0.13	0.986	26.16	0.707	0.997	19.102
MS4	0.905	8.10	0.923	-0.21	0.990	26.20	0.644	0.996	20.98
MS5	0.903	8.29	0.915	-0.19	0.985	26.19	0.662	0.998	19.676

DISCUSSION:

The current study involved the preparation of sustained-release tablets of metformin hcl using the wet granulation method due to its feasibility and simplicity. Different formulations were developed by adjusting the polymer amount to investigate the impact of varying polymer concentration on drug release rates. The physical evaluation of the mixed powder indicated its suitability into compression into tablets.

The release profile of the optimized formula fitted best to Korsmeyer-Peppas model with R2 value of 0.995. As the n value for the Korsmeyer-Peppas model was found to be more than 0.5. it follows non- Fickian transport.

The result of dissolution studies as shown and indicate that formula MS1, MS2, MS3, release 46.88, 43.46, 41.77 after 2 hr and 95.94, 93.64, 91.77 after 10 hr. of formulation containing (FSM + HPMC), MS4, MS5, release 44.86, 40.72 after 2 hr. and 96.83, 96.51 drug content release after 10 hr. respectively (FSM +XANTHUM GUM).

Conclusion

The current study focused on achieving sustained delivery of metformin hcl to ensure an efficient and safe therapy by utilizing three polymers: fenugreek seed mucilage, HPMC, and xanthan gum. It belongs to the biguanide class of oral anti-diabetic class medications and is considered initial treatment option for individuals with type -2 diabetes especially for those who are overweight or obese and have normal kidney function.

In conclusion, fenugreek seed mucilage has proven to be an effective binder in the formulation of Metformin SR (sustained release) tablets. The study revealed that fenugreek seed mucilage provides adequate binding properties, ensuring the mechanical strength and integrity of the tablets. Moreover, it facilitates a sustained release profile of Metformin, which is beneficial for maintaining consistent therapeutic drug levels over an extended period, thereby enhancing patient compliance and potentially reducing the frequency of dosing.

Fenugreek seed mucilage is used as the novel binder in the formulation MS1, MS2, MS3, MS4, MS5 at the concentrations of the 5%, 10%, 15% , 20%, 25% respectively.

HPMC is selected as a as a hydrophilic matrix former, creating a gel barrier upon contact with gastric fluids. This gel barrier controls the drug release rate by slowing down the diffusion of Metformin from the tablet. HPMC used in the formulation MS1, MS2, MS3 at the concentration of the 10%, 15%, 20%.

Xanthan Gum swells upon hydration, expanding the matrix and prolonging the drug release duration. Xanthan gum used in the formulation MS4, MS5 at the concentration of the 10%,

Direct Compression method was used to formulate the tablets. All the formulations were showed the acceptable flow properties and the pre compression parameters like Bulk density, Tapped density and Hausner ratio.

The post compression parameters like Hardness, Friability, swelling time, Weight variation, content uniformity values were found to be within the IP limits.

The percentage Drug content of all tablets was found to be between 91.3% - 101.2% of metformin SR , which is within the limit.

Formulation with (FSM + HPMC) was 93.78% and (FSM +XANTHUM GUM) was 96.17% which exhibit the highest drug release.

As the percentage drug release was also found to be increased for these formulation as 95.94, 93.64, 91.77 respectively, from the above result it was found that as the concentration of HPMC increase release kinetic was found to be improved.

And the percentage drug release was also found to be same for to be same form these formulation as 96.8, 96.51 respectively, from the result it was found that as concentration of xanthan gum here is no changes in release kinetics.

Batch no. MS4-MS5 (FSM+ xanthan gum) shows good release kinetics and swelling properties than batch MS1-MS2 (FSM+HPMC).

Batch-MS4 show release kinetic was 96.83 in 12h, weight variation of 1001±5 mg, thickness was 4.56 mm, hardness was 7.26 kg/cm^2 , friability was 0.30% and content uniformity was 99.9 % which satisfy all evaluation parameter for sustained release. Hence, looking at all the satisfactory parameter MS4 Batch selected as the optimized batch.

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