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COMPREHENSIVE RESEARCH ON: PRE-FORMULATION STUDIES OF METFORMIN TABLET AND COMPARATIVE STUDY OF MEDICATIONS OF DIABETES MELLITUS WITH METFORMIN TABLET

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ABSTRACT
Metformin is a first-line oral antihyperglycemic agent widely prescribed for managing type 2 diabetes mellitus (T2DM), due to its proven safety, efficacy, and cost-effectiveness. This research article provides a comprehensive review of essential pre-formulation studies for developing an optimized metformin tablet. Key parameters such as solubility, polymorphism, particle size distribution, pH-dependent stability, hygroscopic nature, and excipient compatibility are evaluated to support robust formulation, improved bioavailability, and consistent therapeutic outcomes. These studies also inform manufacturing and storage decisions. Additionally, the article presents a comparative analysis of commonly used antidiabetic drugs – including sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors, thiazolidinediones, GLP-1 receptor agonists, and insulin therapies – based on their mechanisms, efficacy, side effects, cardiovascular benefits, cost, and patient adherence. Data were gathered from literature and clinical surveys across hospitals and pharmacies. Findings reaffirm metformin's central role in T2DM treatment while highlighting the importance of alternative or combination therapies when needed. The study emphasizes the value of pre-formulation and comparative drug profiling in optimizing personalized treatment strategies and enhancing patient outcomes.

KEYWORDS: *Diabetes Mellitus, Pre Formulation Studies, Metformin Tablet, Survey of Medications of Dibaties Mellatus*

INTRODUCTION
Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia due to insufficient insulin secretion, resistance, or both. The condition has been documented in medical literature for over 3,000 years, with references found in ancient Egyptian and Indian texts. Historically, diabetes was diagnosed based on symptoms like excessive thirst and frequent urination. In the 19th and 20th centuries, advancements in biochemistry led to the discovery of insulin, transforming diabetes management. Despite insulin therapy, oral hypoglycemic agents like Metformin emerged as cornerstones in type 2 diabetes treatment. Today, Metformin remains the first-line therapy, but formulation challenges necessitate extensive pre-formulation studies.

1.1 Diabetes in India
India has the largest number of diabetic individuals, earning the title of the "diabetes capital of the world." According to the Diabetes Atlas 2006, published by the InternationalDiabetes Federation, the number of people with diabetes in India, currently around 40.9 million, is expected to rise to 69.9 million by 2025 unless urgent preventive measures are taken.

Globally, diabetes is a growing concern. Recent estimates suggest that approximately 285 million people (6.6%) in the 20–79 age group had diabetes in 2010. By 2030, this number is expected to rise to 438 million (7.8%) of the adult population. According to Wild et al., the global prevalence of diabetes is projected to double from 171 million in 2000 to 366 million by 2030, with India experiencing the highest increase. By 2030, diabetes mellitus may affect up to 79.4 million individuals in India, while China (42.3 million) and the United States (30.3 million) will also see significant rises in cases.

One of the key factors contributing to this high prevalence in India is the "Asian Indian Phenotype," which refers to unique clinical and biochemical abnormalities in Indians. These include increased insulin resistance, greater abdominal adiposity (higher waist circumference despite a lower body mass index), lower adiponectin, and higher high-sensitive C-reactive protein levels.

1.2 Pre-Formulation Studies
Pre-formulation studies of tablets are a critical phase in drug development, providing essential data to design a stable, effective, and manufacturable dosage form. These studies focus on the physicochemical properties of the active pharmaceutical ingredient (API) and excipients to ensure compatibility, stability, and optimal drug delivery. Key evaluations include solubility studies, as poor solubility can impact bioavailability, and pKa determination, which influences drug ionization and absorption. Polymorphism analysis is essential to identify different crystalline forms that may affect stability and dissolution rates.

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Hygroscopicity testing helps assess moisture sensitivity, preventing degradation during storage.

Excipient compatibility studies ensure that the API does not interact negatively with binders, fillers, disintegrants, or lubricants used in tablet formulation. Differential scanning calorimetry (DSC) and Fourier-transform infrared spectroscopy (FTIR) are commonly used to detect interactions. Powder flow properties, such as bulk density, tapped density, angle of repose, and compressibility index, are evaluated to ensure uniformity in tablet compression. Particle size distribution analysis is also crucial, as it affects dissolution rates, blend uniformity, and tablet strength.

Mechanical properties like hardness, friability, and disintegration time are assessed to optimize the tablet formulation. Additionally, pre-formulation studies investigate wetting properties and surface morphology to predict dissolution behavior. Advanced techniques such as X-ray diffraction (XRD) and thermal analysis (TGA) help understand the structural and thermal stability of the drug. These studies collectively guide the selection of the best formulation strategy, reducing development time and ensuring regulatory compliance for a high-quality, stable tablet dosage form.

2.GOALS AND OBJECTIVES OF PRE-FORMULATION STUDIES

Goals of Pre-Formulation Studies

The primary goal of pre-formulation studies is to generate critical information about Metformin's physicochemical and mechanical properties to ensure successful formulation. These studies help in identifying potential challenges and optimizing drug delivery strategies.

• To assess the solubility and dissolution behavior of Metformin in different media.
• To evaluate the flow properties and compressibility for tablet formulation.
• To determine the stability profile of Metformin under various environmental conditions.
• To study drug-excipient compatibility for selecting suitable excipients.
• To investigate the hygroscopic nature and moisture sensitivity of Metformin.
• To analyze the polymorphic forms and their impact on bioavailability.
• To establish pre-formulation data that aids in dosage form design and quality control.

Objectives of Pre-Formulation Studies:h

The objectives of pre-formulation studies are to systematically evaluate various physicochemical properties of Metformin, ensuring the development of a stable and bioavailable tablet formulation.

• To determine the pKa, partition coefficient, and solubility profile of Metformin.
• To analyze the particle size distribution and micromeritic properties.
• To perform thermal analysis (DSC, TGA) to assess thermal stability.
• To conduct forced degradation studies to understand the degradation pathways.
• To investigate the effect of humidity and temperature on drug stability.
• To optimize excipient selection through drug-excipient interaction studies.
• To ensure reproducibility in formulation by defining critical formulation parameters.

2.1 Pre-Formulation Studies of Metformin

1.Solubility Studies

Solubility plays a crucial role in drug absorption and bioavailability. Metformin is highly soluble in water but poorly soluble in non-polar solvents. This impacts its formulation approach, requiring modifications such as salt formation or complexation.

Solvent/Medium	Solubility (mg/mL)	Observation
Water	300 mg/mL	Highly soluble
Ethanol (95%)	0.02 mg/mL	Practically insoluble
Methanol	1.5 mg/mL	Slightly soluble
0.1 N HCl	200 mg/mL	Highly soluble
pH 6.8 Phosphate Buffer	50 mg/mL	Moderately soluble
Chloroform	Insoluble	Not suitable for extraction

2.Micromeritics Studies

Micromeritic properties such as density, flow properties, and compressibility impact the manufacturing process. Poor flowability can lead to inconsistent tablet weight and content uniformity.

Bulk Density	0.45 g/cm³	Affects dose uniformity
Tapped Density	0.65 g/cm³	Indicates powder packing ability
Carr's Index	30%	Poor flowability; requires glidants
Angle of Repose	34°	Moderate flowability
Hausner Ratio	1.44	Indicates cohesive powder

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3.Hygroscopicity Studies
Metformin is hygroscopic, meaning it absorbs moisture from the environment, which can affect its stability. Studies are conducted under different humidity conditions to evaluate its moisture uptake.

4.Polymorphic Studies
Metformin exists in different crystalline forms. Polymorphic variations can affect solubility, stability, and bioavailability. X-ray diffraction (XRD) and differential scanning calorimetry (DSC) are commonly used for polymorph characterization.

5.Thermal Analysis
Thermal properties of Metformin are analyzed using Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA). DSC determines melting point and heat of fusion, while TGA assesses thermal stability by measuring weight loss at different temperatures.

6.Drug-Excipient Compatibility Studies
Compatibility studies ensure that excipients do not interact with Metformin, leading to degradation. Fourier Transform Infrared Spectroscopy (FTIR), DSC, and isothermal stress testing (IST) are used to detect potential incompatibilities.

7.pKa and Partition Coefficient
Metformin has a pKa of 12.4, indicating it remains ionized under physiological pH conditions. Its partition coefficient (log P) is -1.43, signifying poor lipid solubility, which impacts its permeability and absorption.

8.Compression Properties
Compression studies evaluate how well Metformin forms tablets. Key parameters include tabletability (ability to form a compact tablet), compactibility (relationship between pressure and strength), and elasticity (deformation behavior).

9.Stability Studies
Stability testing determines the shelf life and degradation pathways of Metformin. Forced degradation studies expose the drug to extreme conditions to assess stability.

Accelerated Stability (40°C, 75% RH)	6 months	No Significant Degradation
Long-Term Stability (25°C, 60% RH)	12 months	Stable Formulation
Forced Degradation (Acid Hydrolysis)	24 hours in 1N HCl	Partial Degradation Observed
Forced Degradation (Oxidation)	24 hours in 3% H_2O_2	Minor Degradation Detected

10.Dissolution Test
Objective:-To evaluate the dissolution profile of Metformin tablets using a dissolution test apparatus to ensure consistent drug release for optimal therapeutic efficacy.

2.3 Materials and Methods

1. Dissolution Apparatus: USP Type II (Paddle)
2. Dissolution Medium: 900 mL of 0.1N HCl (pH 1.2) for the first 2 hours, followed by phosphate buffer (pH 6.8) for the remaining time.
3. Temperature: Maintained at 37 ± 0.5°C
4. Rotation Speed: 50 rpm
5. Sampling Intervals: 5, 10, 15, 30, 45, and 60 minutes
6. Analysis Method: UV-Visible Spectrophotometry at 233 nm
7. Tablet Strength: 500 mg Metformin Hydrochloride

Results

Time (minutes)	% Drug Release (Mean ± SD)
5	20.5 ± 1.2%
10	38.9 ± 1.5%
15	55.3 ± 1.8%
30	75.8 ± 2.1%
45	89.7 ± 2.3%
60	98.4 ± 1.9%

Discussion
The dissolution profile of the Metformin tablets followed a typical immediate-release pattern, with over 80% drug release within 45 minutes, complying with USP specifications. The release rate was within the acceptable limits, indicating good formulation quality and appropriate excipient selection. The absence of lag time or slow dissolution suggests proper tablet disintegration and drug solubilization.

2.4 Conclusion
The pre-formulation dissolution test confirms that the Metformin tablet meets the pharmacopeial dissolution criteria, ensuring its bioavailability and therapeutic efficacy. Further studies, including stability and in vivo bioequivalence, can be conducted to validate long-term performance

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Fig.Dissolution Test of Tablate



Fig. Fribility Test of Tablate

11.Friability test of Metformin Tablet

The friability test of Metformin tablets assesses their ability to withstand mechanical stress during handling and transportation. Typically, 10–20 tablets are weighed, placed in a friabilator, and rotated at 25 rpm for 4 minutes (100 revolutions). After the run, tablets are dusted and reweighed. The percentage weight loss is calculated using the formula:

Friability (%) = [(Initial weight – Final weight) / Initial weight] × 100.

According to pharmacopeial standards, the friability should not exceed 1.0%, and the tablets should remain intact without significant cracks or breaks.

12.Disintegration Test of Tablet

The disintegration test of a metformin tablet is performed to determine how quickly the tablet breaks down into smaller particles when placed in a liquid medium, simulating conditions in the stomach. In this test, a metformin tablet is placed in a disintegration test apparatus containing 900 ml of water maintained at a temperature of 37±2°C. The basket rack in the apparatus moves up and down to mimic the movement in the digestive system. According to USP standards, the tablet should disintegrate completely within 30 minutes. This test ensures that the tablet dissolves properly in the body for effective absorption and therapeutic action.



3. Physicians often choose metformin as the first-line treatment for type 2 diabetes for several interrelated reasons:

1. Proven Efficacy and Mechanism of ActionReduces Hepatic Gluconeogenesis: Metformin decreases the liver's production of glucose, addressing one of the core problems in type 2 diabetes.
2. Improves Insulin Sensitivity: It enhances the body's responsiveness to insulin, which helps lower blood sugar levels without overstimulating insulin secretion.

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3. Favorable Safety Profile

Low Risk of Hypoglycemia: Unlike some other diabetes medications (e.g., sulfonylureas), metformin does not typically cause low blood sugar because it does not boost insulin release directly.

Weight Neutrality: Metformin is generally weight neutral and can even promote modest weight loss, which is beneficial for many patients with type 2 diabetes who are often overweight or obese.

4. Long-Term Benefits and Cost-Effectiveness

Cardiovascular Benefits: Studies have shown that metformin may help reduce cardiovascular risks, a significant concern in diabetic populations.

Extensive Track Record: With decades of use, its long-term efficacy and safety are well documented.

Affordability: Metformin is generally inexpensive compared to newer diabetes medications, making it accessible for a broad patient base.

5. Clinical Guidelines Endorsement
6. Standard of Care: Major guidelines, including those from the American Diabetes Association, recommend metformin as the first-line therapy for type 2 diabetes, provided there are no contraindications (like significant renal impairment or a risk of lactic acidosis).

In summary, the combination of its effective mechanism, strong safety profile, additional cardiovascular benefits, and cost-effectiveness makes metformin a preferred option over many other antidiabetic drugs for most patients with type 2 diabetes.

- Metformin's prominence in the management of type 2 diabetes mellitus is attributed to its favorable clinical profile and the extensive research conducted during its preformulation phase, which has optimized its therapeutic efficacy.



Fig. Visit Of Physician for Survey of Medications Used in Dibaties Mellatus

3.1 Clinical Advantages of Metformin According to physicians

Efficacy and Safety: Metformin effectively lowers blood glucose levels without causing significant hypoglycemia. Additionally, it is associated with weight neutrality or modest weight loss, which is beneficial for overweight or obese patients.

Cardiovascular Benefits: Long-term studies, such as the UK Prospective Diabetes Study (UKPDS), have demonstrated that metformin not only improves glycemic control but also reduces the risk of cardiovascular events, making it a preferred choice for patients with type 2 diabetes.

Cost-Effectiveness: Being an older medication, metformin is generally more affordable than many newer antidiabetic agents, increasing its accessibility to a broader patient population.

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3.2 Survey of Patient Suffering from Diabetes Mellitus About medications of dibaties mellatus

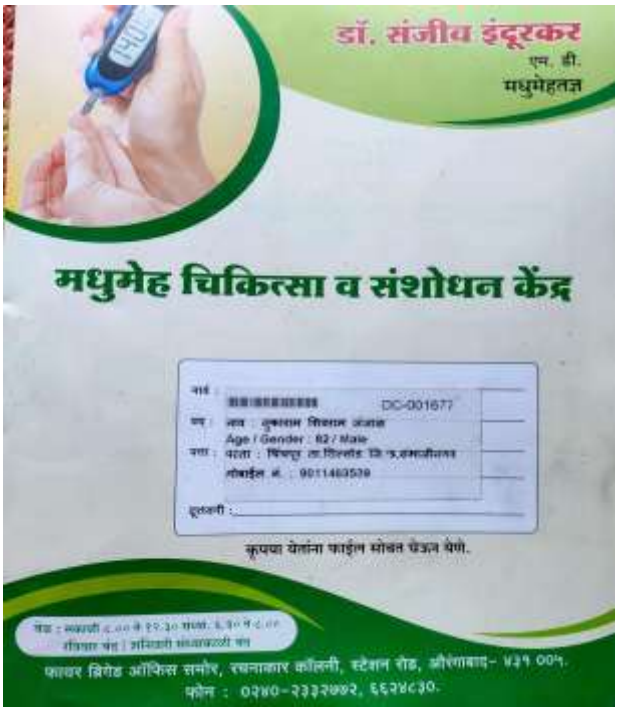


Fig. Patient file of medications report

Diabetes Treatment and Research Center" (Madhumeh Chikitsa va Sanshodhan Kendra) led by Dr. Sanjeev Indurkar, here's a general survey of medications used in Diabetes Mellitus:

1.Overview

This image represents a medical file for a patient named **Tukaram Shivram Janjal**, aged 82, from Sambhajinagar (Aurangabad), Maharashtra, visiting a diabetes specialist. The document suggests that the patient is receiving treatment specifically for diabetes mellitus (commonly known as Type 2 Diabetes in elderly patients)

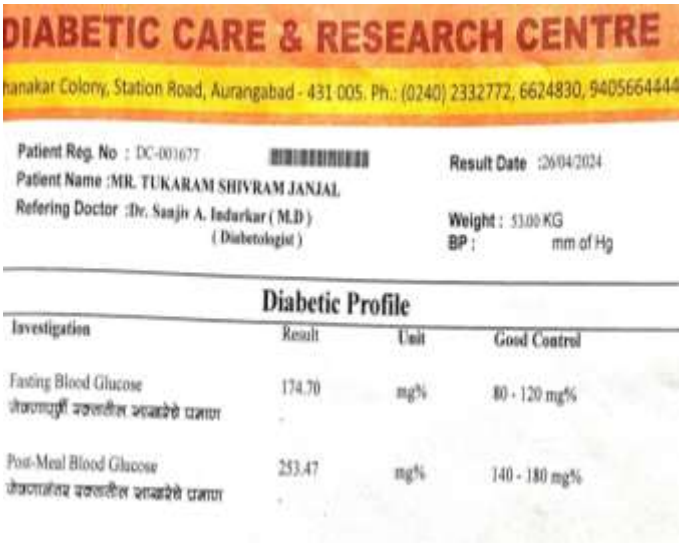
The patient file of Mr. Tukaram Shivram Janjal, 82 years old, documents his treatment for Type 2 Diabetes Mellitus under Dr. Sanjeev Indurkar at Madhumeh Chikitsa Va Sanshodhan Kendra, Aurangabad. It includes prescriptions, blood glucose reports, billing records, and patient history. His management plan involves insulin therapy (Lupisulin 30/70) and oral medications like Glucophage XR (Metformin), Linanext 5, and Cylex 60 XR to control fasting and postprandial blood sugar levels. The file highlights continuous monitoring, regular follow-ups, and a structured approach to diabetes care.

This patient file belongs to Mr. Tukaram Shivram Janjal, an 82-year-old male resident of Shivpur, Taluka Phulambri, District Chhatrapati Sambhajinagar. The file has been maintained under the supervision of Dr. Sanjeev Indurkar, an MD specializing in Diabetes (Madhumeh Tantra), at the Madhumeh Chikitsa Va Sanshodhan Kendra in Aurangabad. It contains comprehensive details of the patient's history of Type 2 Diabetes Mellitus, including medical prescriptions, blood glucose test reports, and related billing documents. The records show regular monitoring of fasting and postprandial blood sugar levels, alongside prescribed medications such as insulin therapy (Lupisulin 30/70), oral antidiabetic agents like Glucophage XR (Metformin), Linanext 5, and Cylex 60 XR. These interventions are aimed at controlling blood sugar levels and preventing diabetic complications. The file also outlines the patient's personal information, contact details, and historical progression of diabetes management. It reflects a systematic approach to diabetes care through medical supervision, regular testing, and consistent follow-u

3.4 Elevated Blood Glucose Levels Indicate Poor Diabetes Control**

The diabetic test report for Mr. Tukaram Shivram Janjal reveals significantly high fasting (174.70 mg%) and post-meal (253.47 mg%) blood glucose levels, both exceeding the recommended ranges (80–120 mg% and 140–180 mg%, respectively), indicating poor glycemic control. The absence of blood pressure data and the patient's low weight (53 kg) further highlight potential health risks, such as malnutrition or uncontrolled diabetes complications. Immediate medical intervention, including medication adjustment, dietary modifications, and additional tests like H bA1c and lipid profiling, is essential to mitigate long-term risks such as neuropathy and cardiovascular disease. Collaboration with the referring diabetologist, Dr. Sanjiv A. Indurkar, is critical for effective management.

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DIABETIC CARE & RESEARCH CENTRE

hanakar Colony, Station Road, Aurangabad - 431 005. Ph.: (0240) 2332772, 6624830, 9405664444

Patient Reg. No : DC-001677 [redacted] Result Date :26/04/2024
Patient Name :MR. TUKARAM SHIVRAM JANJAL
Refering Doctor :Dr. Sanjiv A. Indurkar (M.D) Weight : 53.00 KG
(Diabetologist) BP : mm of Hg

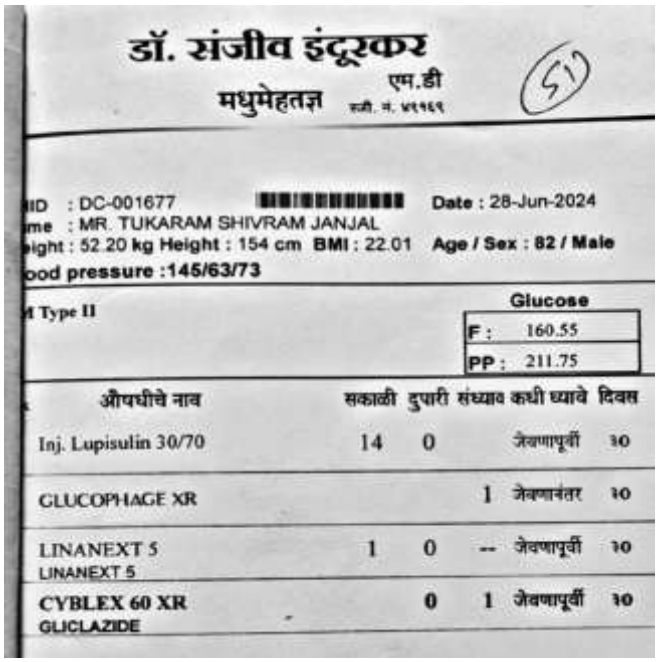
Diabetic Profile

Investigation	Result	Unit	Good Control
Fasting Blood Glucose जेवणापूर्वी घ्यावयाचे प्रमाण	174.70	mg%	80 - 120 mg%
Post-Meal Blood Glucose जेवणानंतर घ्यावयाचे प्रमाण	253.47	mg%	140 - 180 mg%

Fig. Blood Glucose Test reports .

3.5. "Comprehensive Overview of Metformin (Glucophage XR) and other medications Therapy in Type 2 Diabetes"

Mr. Tukaram Shivram Janjal, an 82-year-old male patient under the care of Dr. Sanjeev Indurkar, has been diagnosed with Type 2 Diabetes Mellitus, with fasting blood sugar at 160.55 mg/dL and postprandial sugar at 211.75 mg/dL, both above normal ranges. Among the prescribed medications, Glucophage XR (Metformin Hydrochloride) plays a central role in managing his condition. Glucophage XR belongs to the Biguanide class of anti-diabetic drugs and works by reducing glucose production in the liver, enhancing insulin sensitivity in muscles, and slightly decreasing glucose absorption from the intestines. It is prescribed once daily after breakfast for 30 days, ensuring steady blood sugar control throughout the day with fewergastrointestinal side effects compared to regular Metformin. Importantly, Metformin helps regulate blood sugar without causing hypoglycemia when used alone and even supports weight management. Though mild stomach upset or diarrhea can occur initially, the extended-release formulation minimizes these issues. Very rarely, serious complications like lactic acidosis may occur, requiring careful monitoring, especially of kidney function. Overall, Glucophage XR is crucial for Mr. Janjal's long-term diabetes management, aiming to lower his glucose levels effectively and prevent future complications like kidney damage, neuropathy, and retinopathy.



डॉ. संजीव इंदूरकर
मधुमेहतज्ञ एम.डी
रजी. नं. ४१९६९

51

ID : DC-001677 [redacted] Date : 28-Jun-2024
me : MR. TUKARAM SHIVRAM JANJAL
ight : 52.20 kg Height : 154 cm BMI : 22.01 Age / Sex : 82 / Male
ood pressure :145/63/73

M Type II

Glucose	
F :	160.55
PP :	211.75

औषधीचे नाव	सकाळी	दुपारी	संध्याव	कधी घ्यावे	दिवस
Inj. Lupisulin 30/70	14	0		जेवणापूर्वी	10
GLUCOPHAGE XR			1	जेवणानंतर	10
LINANEXT 5 LINANEXT 5	1	0	--	जेवणापूर्वी	10
CYBLEX 60 XR GLICLAZIDE		0	1	जेवणापूर्वी	10

Fig. Prescription of Medications of Dibaties

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1. Commonly Used Medications in Diabetes Mellitus:

A. Oral Medications (Tablets):

These are generally prescribed in early to moderate stages of Type 2 diabetes.

1. Metformin

First-line therapy.

Reduces glucose production in the liver and improves insulin sensitivity.

Usually well-tolerated with minimal risk of hypoglycemia.

2. Sulfonylureas (e.g., Glimepiride, Glibenclamide)

Stimulate insulin secretion from the pancreas.

Risk of low blood sugar, especially in elderly patients.

3. DPP-4 Inhibitors (e.g., Sitagliptin, Vildagliptin)

Increase insulin release and decrease glucagon levels in a glucose-dependent manner.

B. Injectable Medications:

1. **Insulin** (Short-acting, Long-acting, Premixed)

Essential in patients with uncontrolled diabetes or in elderly patients with long-standing disease.

Requires regular blood sugar monitoring.

4. Factors Influencing Medication Choice:

1.Age of the patient (like 82 years in this case)
2.Kidney and liver function
3.Risk of hypoglycemia
4.Presence of heart disease or other complications
5.Cost and availability.

4. Survey of Medications Used in Diabetes Mellitus

The management of diabetes mellitus, particularly type 2, involves a wide range of pharmacological options, each with distinct mechanisms, benefits, and risks. The most commonly used first-line medication is Metformin, favored for its effectiveness, low risk of hypoglycemia, weight-neutral profile, cardiovascular benefits, and affordability. When Metformin alone is insufficient or contraindicated, other classes are considered. Sulfonylureas (e.g., glimepiride, gliclazide) are effective insulin secretagogues but can cause weight gain and hypoglycemia. SGLT2 inhibitors (e.g., empagliflozin, dapagliflozin) lower blood glucose by promoting urinary glucose excretion and also offer cardiovascular and renal protection. GLP-1 receptor agonists (e.g., liraglutide, semaglutide) enhance insulin secretion and suppress appetite, aiding in weight loss and heart health, though they can be costly and injectable. DPP-4 inhibitors (e.g., sitagliptin, linagliptin) are oral agents that moderately improve glycemic control with minimal side effects. Thiazolidinediones (e.g., pioglitazone) improve insulin sensitivity but are linked to weight gain and fluid retention. Insulin therapy is essential in type 1 diabetes and sometimes necessary in type 2, especially when blood glucose is significantly uncontrolled. Newer agents like dual GIP/GLP-1 agonists (e.g., tirzepatide) show promise for superior glucose and weight control. Medication choice depends on factors such as patient age, weight, comorbidities, cost, and risk of hypoglycemia, with combination therapies often used for optimal control.

4.1 Survey of Medications Used in Diabetes Mellitus: A Comparison with Metformin

In the treatment of type 2 diabetes mellitus, Metformin remains the cornerstone and first-line therapy due to its strong efficacy, safety profile, low cost, and additional cardiovascular benefits. However, as the disease progresses or if Metformin is contraindicated, other medications are introduced—each with unique characteristics and roles in management.

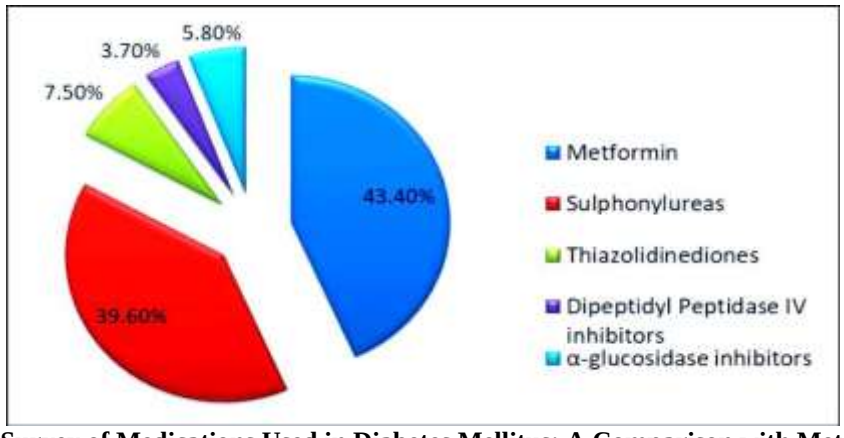


Fig. Survey of Medications Used in Diabetes Mellitus: A Comparison with Metformin

This pie chart represents the results of a survey on the usage of individual oral anti-diabetic drugs among patients. The chart highlights the proportion of patients using each class of medication.

According to the survey, Metformin is the most commonly used drug, with 43.4% of patients relying on it for diabetes management. This indicates its strong preference as a first-line therapy due to its effectiveness and safety profile. Sulphonylureas are the second most used class, taken by 39.6% of patients, suggesting their continued importance in controlling blood sugar levels, especially in patients who need an added effect beyond Metformin.

The usage of other drug classes Is considerably lower. Thiazolidinediones are used by 7.5% of the surveyed group,

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possibly due to their specific side effects and limited use cases. Dipeptidyl Peptidase IV (DPP-4) inhibitors account for 3.7%, which could reflect their higher cost or newer introduction to the market. Finally, α-glucosidase inhibitors are used by 5.8%, likely in patients needing post-meal blood sugar control.

Overall, the survey clearly shows a dominant reliance on Metformin and Sulphonylureas, while newer or alternative drugs are used by a smaller segment of the diabetic population

Sulfonylureas (e.g., glimepiride, gliclazide) are among the oldest oral antidiabetic drugs. They stimulate pancreatic insulin secretion and are effective in lowering blood glucose. However, compared to Metformin, they carry a higher risk of hypoglycemia and often lead to weight gain, which limits their use in overweight patients.

SGLT2 Inhibitors (e.g., empagliflozin, dapagliflozin) are newer agents that work by preventing glucose reabsorption in the kidneys, leading to glucose excretion in urine. Compared to Metformin, they are more expensive, but offer added benefits like weight loss, blood pressure reduction, and cardiovascular and kidney protection. They also have a low risk of hypoglycemia. However, they can increase the risk of genital infections and dehydration.

GLP-1 Receptor Agonists (e.g., liraglutide, semaglutide) mimic gut hormones to increase insulin secretion, suppress glucagon, and slow gastric emptying. They are more potent in weight reduction than Metformin and have proven heart benefits, but are usually injectable and expensive. Side effects like nausea or vomiting are also more common.

DPP-4 Inhibitors (e.g., sitagliptin, linagliptin) enhance endogenous incretin levels and have a modest glucose-lowering effect. They are well tolerated, with low risk of hypoglycemia or weight gain, but are generally less effective than Metformin and lack strong evidence for cardiovascular benefit.

Thiazolidinediones (e.g., pioglitazone) improve insulin sensitivity and can be combined with Metformin for better control. However, they are associated with weight gain, fluid retention, and risk of heart failure, making them less favorable in many cases.

Insulin Therapy remains essential for type 1 diabetes and is used in advanced type 2 diabetes when oral agents fail. While insulin is the most potent glucose-lowering agent, it requires injections, careful monitoring, and has the highest risk of hypoglycemia and weight gain.

Newer Therapies such as dual GIP/GLP-1 Receptor Agonists (e.g., tirzepatide) have shown superior effects on glucose control and weight reduction compared to both Metformin and older agents. However, their long-term safety, cost, and availability still limit widespread use.

In summary, while many alternatives exist, Metformin remains the preferred starting point due to its balance of efficacy, safety, tolerability, cost, and proven long-term benefits. Other medications are chosen based on individual patient needs, such as cardiovascular status, weight management goals, risk of hypoglycemia, kidney function, and cost considerations.

4.2. Survey on Common Drug Combinations Used for Diabetes Management:-

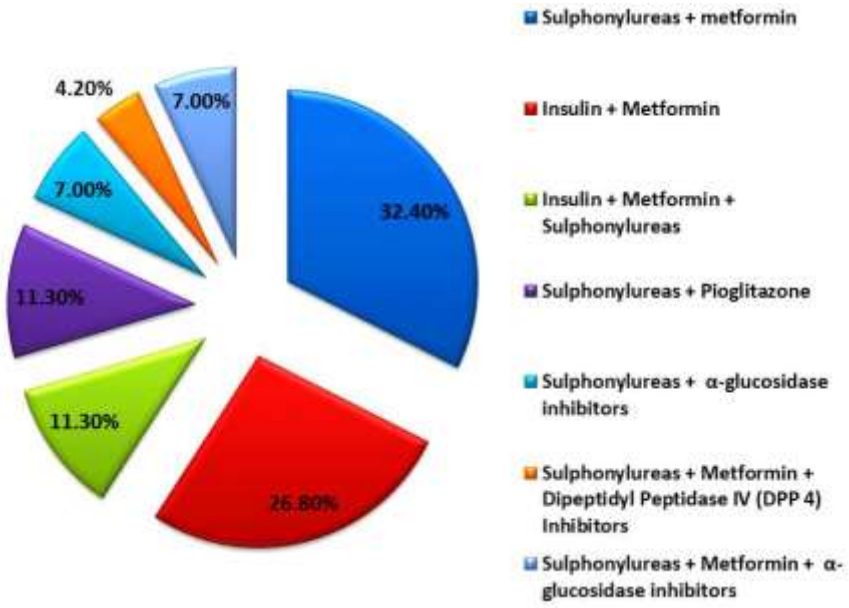


Fig.Survey on Common Drug Combinations Used for Diabetes Management:-

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This pie chart presents the distribution of various drug combinations used in the treatment of diabetes, based on a survey of patients or prescriptions. The data is categorized into different combinations of medications and their respective usage percentages.

Survey Results

1. **Sulphonylureas + Metformin**

32.4% of the participants use this combination, making it the most common treatment regimen.

2. **Insulin + Metformin**

Used by 26.8% of the participants, indicating a significant number requiring insulin support.

3. **Insulin + Metformin + Sulphonylureas**

Chosen by 11.3%, representing a triple-therapy approach.

4. **Sulphonylureas + Pioglitazone**

Also used by 11.3%, showing similar popularity as the above combination.

5. **Sulphonylureas + α-glucosidase inhibitors**

Preferred by 7.0% of the patients.

6. **Sulphonylureas + Metformin + α-glucosidase inhibitors**

Another 7.0% opt for this triple-therapy option.

7. **Sulphonylureas + Metformin + Dipeptidyl Peptidase IV (DPP-4) Inhibitors**

The least common, used by 4.2% of the survey participants.

This data highlights the variety of drug regimens employed in diabetes management, with a clear preference toward Sulphonylureas and Metformin as the base combination.

5. More detail survay of medications used in dibaties mellatus comparing to metformin tablet including advantage and disadvantage of other medications:-

1.Metformin

Mode of Action: Reduces glucose production in the liver and improves insulin sensitivity in muscles.

It effectively lowers blood sugar, helps in slight weight loss or maintaining weight, has a very low risk of causing hypoglycemia (low sugar), and is affordable. It also provides some heart protection.

However, it can cause stomach issues like nausea or diarrhea, especially in the beginning. It should be avoided in people wit**h severe kidney or liver problems due to the rare risk of lactic acidosis.**

2.Sulfonylureas (e.g., Glimepiride, Glipizide)

Mode of Action: Stimulates the pancreas to release more insulin.

These medicines work fast and are very effective in reducing blood sugar, especially in early-stage diabetes. They are also inexpensive and easy to take.

But they can lead to weight gain and a high risk of hypoglycemia. Long-term use may tire out the pancreas, and they should be used with caution in elderly people or those with kidney disease.

Simplified Comparison of Diabetes Mellitus Medications

Medication Class	Examples	Mechanism of Action	Effect on Weight	Hypoglycemia Risk	Route	Notable Side Effects / Risks
Biguanides	Metformin	↓ Liver glucose, ↑ insulin sensitivity	Neutral or slight loss	Low	Oral	GI upset, rare lactic acidosis
Sulfonylureas	Glimepiride, Gliclazide	↑ Insulin secretion	Weight gain	High	Oral	Hypoglycemia, weight gain
SGLT2 Inhibitors	Empagliflozin, Dapagliflozin	↓ Renal glucose reabsorption	Weight loss	Low	Oral	UTIs, dehydration, ketoacidosis
GLP-1 Receptor Agonists	Liraglutide, Semaglutide	↑ Insulin, ↓ glucagon, slow gastric emptying	Significant loss	Low	Injectable	Nausea, vomiting, pancreatitis
DPP-4 Inhibitors	Sitagliptin, Linagliptin	↑ Incretin levels, modest insulin increase	Neutral	Low	Oral	Headache, joint pain, pancreatitis (rare)
TZDs	Pioglitazone	↑ Insulin sensitivity	Weight gain	Low	Oral	Edema, heart failure risk, bone fractures
Insulin (Basal & Bolus)	Glargine, Aspart, Lispro	Replaces/supplements natural insulin	Weight gain	High	Injectable	Hypoglycemia, weight gain, injection burden
GIP/GLP-1 Dual Agonists	Tirzepatide	Dual incretin action, appetite control	Significant loss	Low	Injectable	GI upset, long-term safety under study

Fig. Comparison of Diabetes mellitus Medications

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3.DPP-4 Inhibitors (e.g., Sitagliptin, Linagliptin)
Mode of Action: Blocks DPP-4 enzyme, increasing incretin hormones that boost insulin and lower glucagon levels.

They are easy to tolerate, don't cause weight gain, have a low risk of hypoglycemia, and can be used even in people with kidney problems (some types).

However, they are more expensive and only moderately reduce blood sugar levels. Rare side effects include joint pain and pancreatitis.

4. SGLT2 Inhibitors (e.g., Empagliflozin, Dapagliflozin)
Mode of Action: Blocks glucose reabsorption in the kidneys, causing sugar to be removed through urine.

They help in weight loss, reduce blood pressure, and offer heart and kidney protection. They have a low risk of causing low sugar levels.

But they may cause urinary or genital infections, dehydration, and of diabetic ketoacidosis. These medicines are also expensive and less effective if kidney function is poor.

6. GLP-1 Receptor Agonists (e.g., Liraglutide, Semaglutide)
Mode of Action: Mimics the GLP-1 hormone, which increases insulin, decreases appetite, and slows stomach emptying.

They effectively lower blood sugar, aid weight loss, and offer cardiovascular benefits with low hypoglycemia risk. However, they are costly, mostly injectable (except oral semaglutide), and may cause nausea, vomiting, or rarely, pancreatitis.

7. Thiazolidinediones (e.g., Pioglitazone)
Mode of Action: Improves insulin sensitivity in fat, muscle, and liver cells.

They are helpful in insulin resistance, provide long-term control, and may preserve beta-cell function.

However, they can lead to weight gain, fluid retention, and a higher risk of heart failure. They may also increase the risk of bone fractures and possibly bladder cancer (debated).

8. Insulin:- Mode of Action: Directly replaces or supplements the body's insulin to lower blood sugar.
9.
It is the most effective option for lowering high blood sugar and is essential for people with type 1 diabetes or advanced type 2 diabetes. It offers flexible dosing based on needs.

The downsides include the need for injections, risk of low blood sugar, and weight gain. Managing insulin doses can be challenging for some

5. CONCLUSION

This comparative study highlights that metformin remains the cornerstone therapy for type 2 diabetes mellitus (T2DM) owing to its superior balance of efficacy, safety, tolerability, affordability, and cardiovascular protection. Unlike sulfonylureas and insulin, metformin achieves glycemic control with minimal risk of hypoglycemia and without promoting weight gain — both important factors for long-term disease management. Although newer classes like SGLT2 inhibitors and GLP-1 receptor agonists offer additional benefits such as weight loss and cardiovascular risk reduction, their higher cost, limited long-term data, and potential side effects restrict their universal use as first-line agents.

Pre-formulation studies of metformin further demonstrate its chemical stability, favorable pharmacokinetic profile, and adaptability into immediate and extended-release formulations, enhancing patient compliance and therapeutic outcomes. Moreover, its insulin-sensitizing mechanism addresses core pathophysiological defects in T2DM rather than merely controlling blood sugar levels.

Therefore, based on extensive clinical evidence, pharmacoeconomic advantage, and robust formulation possibilities, metformin continues to be preferred over other antidiabetic medications as initial monotherapy. However, therapy should be personalized, and adjunct or alternative agents considered in cases of contraindications, intolerance, or complex comorbidities. Future innovations should aim at maximizing metformin's benefits through novel combination regimens and improved delivery systems.

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