

FORMULATION AND EVALUATION OF METFORMIN HYDROCHLORIDE CAPSULES

Submitted in partial fulfillment of the requirements for the award of

BACHELOR OF PHARMACY

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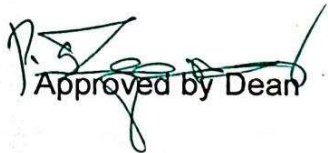
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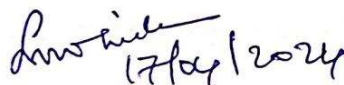
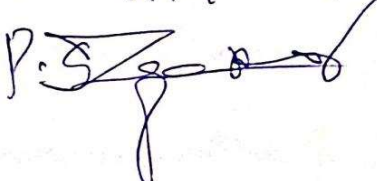
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DECLARATION

We hereby declare that the work presented in the thesis entitled "FORMULATION AND EVALUATION OF METFORMIN HYDROCHLORIDE CAPSULES" submitted by us to the Sathyabama Institute of Science and Technology (Deemed to be University), Chennai - 600119, for the award of Bachelor of Pharmacy (2020-2024) by research is an original record of research work carried out by us under the supervision of "Dr. Joan Vijetha R, Associate Professor, School of Pharmacy". The contents of this dissertation, in full or in parts, have not been submitted to any other institute or university for the award of any degree, diploma, membership, fellowship, associate-ship etc.. In keeping with the general practicing reporting scientific observation, due acknowledgement has been made whenever the work described is based on the findings of other investigators.

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ABSTRACT

Metformin Hydrochloride (MH) is a synthesis of N,N-dimethylguanidine, a type of medicament which is used to treat type II diabetes. Emil Worner and James Belin in the year 1922 were the first to synthesize dimethyl guanidine. MH has various other advantages such as; weight loss, improper fertility, slowing down the tumour growth and few more. The current work is focused on, to sustain the release of the drug in the body for a larger period of time. To perform this study various factors were taken into consideration such as drug, Excipients (HPMC, PVP K30, Magnesium stearate, MCC, NaCMC and Starch) compatibility study, Preformulation studies of raw material and granules. The granules were prepared using wet granulation method, and all the quality control parameter study for formulated 10 capsules were performed. Out of these 10 formulations, formulation 7 (F7) was subjected to have sustained release. Further, F7 was subjected to comparative study with other marketed available tablet and was found out that our formulation has sustained release up to the 13th hr and whereas marketed tablet up to 11th hr. Finally accelerated stability study was performed till 3 months and was found that there were no significant changes.

Key words: Metformin hydrochloride (MH); polyvinylpyrrolidone (PVP K30); Fourier Transform Infrared Spectroscopy (FTIR); Sustained release.

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LIST OF ABBREVIATIONS

DM	Diabetes Mellitus
BASs	Bile acid sequestrants
GD	Gestational Diabetes
FBST	Fasting Blood Sugar Test
GTT	Glucose Tolerance Test
RBST	Random Blood Sugar Test
GST	Glucose Screening Test
GTT	Glucose Tolerance test
CHF	Conjestic Heart Failure
MH	Metformin Hydrochloride
SR	Sustained release
cm	Centimeter
hrs	Hours
pH	Power of Hydrogen
qs	Quantity sufficient
HPMC	Hydroxypropyl Methylcellulose
PVP	Polyvinylpyrrolidone
MCC	Microcrystalline cellulose
NaCMC	Sodium carboxymethylcellulose
PB	Phosphate Buffer
IP	Indian Pharmacopoeia
UV	Ultraviolet
FTIR	Fourier Transform Infrared
RH	Relative Humidity
mg	milligram

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CHAPTER – 1

INTRODUCTION

CHAPTER-1

INTRODUCTION

"Life is not over because you have diabetes. Make the most of what you have, be grateful"

- Dale Evans.

Diabetes mellitus (DM) is Greek word *diabetes*, meaning siphon - to pass through and the Latin word *mellitus* meaning sweet [01]. It's a chronic heterogeneous metabolic disorder with complex pathogenesis. It is characterized by elevated blood glucose levels or hyperglycemia, which results from abnormalities in either insulin secretion or insulin action or both [02]. And there are different types or classes, of medications that work in different ways to lower blood glucose (also known as blood sugar) levels. Some drugs are taken orally and others by injected, the most commonly used classes of non-insulin medications include: Biguanide, Alpha-glucosidase inhibitors, bile acid sequestrants (BASs), Dopamine-2 agonists and DPP-4 inhibitors (gliptins) [03].

DIABETES MELLITUS (DM)

DM is a disorder in which the body does not produce enough or respond normally to insulin, causing blood sugar (glucose) levels to be abnormally high [04]. Diabetes are major cause of morbidity and mortality, though these outcomes are not due to the immediate effects of the disorder. They are instead related to the diseases that develop as a result of chronic diabetes mellitus [05]. These include diseases of large blood vessels (macrovascular disease, including coronary heart disease and peripheral arterial disease) and small blood vessels (microvascular disease, including retinal and renal vascular disease), as well as neurological disorder.

CAUSES

Insulin is a hormone secreted by beta cells, located within clusters of cells in the pancreas called the islets of Langerhans. Its role in the body is to trigger cells to take up glucose, so the cells can use this energy-yielding sugar. Patients with diabetes may have dysfunctional beta cells, resulting in decreased insulin secretion, or their muscle and adipose cells may be resistant to the effects of insulin, resulting in a

decreased ability of these cells to take up and metabolize glucose. In both cases the levels of glucose in the blood increase, causing hyperglycemia [06]. If glucose accumulates in the blood, excess levels of this sugar are excreted in the urine. Because of greater amounts of glucose in the urine, more water is excreted with it, causing an increase in urinary volume and frequency of urination as well as thirst [07].

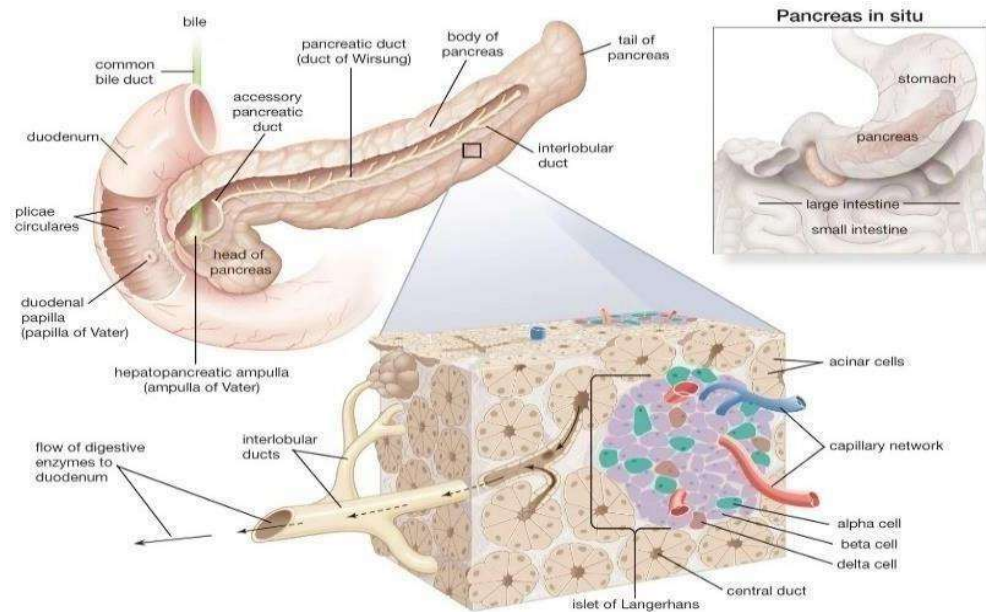


Figure 1.1: Islets of Langerhans
(<https://images.app.goo.gl/4P5fgEMSFvd9ru9K9>)

Islets of Langerhans [08]- It was responsible for the endocrine function of the pancreas. Each islet contains beta, alpha, and delta cells which are responsible for the secretion of pancreatic hormones. Beta cells secrete insulin, a well-characterized hormone that plays an important role in regulating glucose metabolism as shown in **Figure 1.1**.

THE ROLE OF GLUCOSE

Glucose, as a sugar, is a source of energy for the cells that make up muscles and other tissues.

- Glucose comes from two major sources: food and liver.
- Sugar is absorbed into the bloodstream, where it enters cells with the help of insulin.
- The liver stores and makes glucose [09].

TYPES OF DIABETES

There are three main types of diabetes: type 1, type 2, and gestational diabetes (diabetes while pregnant).

Type 1 Diabetes

Type 1 diabetes is a condition that arises from an autoimmune response, wherein the body mistakenly attacks itself, leading to the cessation of insulin production. The onset of symptoms associated with type 1 diabetes is typically rapid, and the condition is commonly diagnosed in children, adolescents, and young adults. To manage this condition, patients must administer insulin on a daily basis to ensure their survival [10].

Type 2 Diabetes

Type 2 diabetes is a metabolic disorder characterized by the body's inability to effectively utilize insulin, resulting in elevated blood sugar levels. This form of diabetes accounts for approximately 90-95% of all diabetes cases. Type 2 diabetes typically develops over an extended period and is commonly diagnosed in adults, although there is a growing incidence among children, teenagers, and young adults. [11]. Type 2 diabetes can be prevented or delayed with healthy lifestyle changes, such as:

- Losing weight.
- Eating healthy food.
- Being active.

Gestational Diabetes (GD)

GD is a condition that arises in pregnant women who do not have pre-existing diabetes. The presence of GD in a patient may increase the likelihood of health complications for their baby. However, it is important to note that GD typically resolves after childbirth [12].

DIAGNOSTIC TEST

a) A1C Test

The A1C or HbA1C test is utilized to determine an individual's average blood sugar level over a period of two to three months. A result of less than 5.7% is considered normal, while a result between 5.7% to 6.4% indicates the presence of prediabetes. A result of 6.5% or higher is indicative of diabetes [13].

b) Fasting Blood Sugar Test (FBST):

It is used to measure the blood sugar after an overnight fast (not eating). A fasting blood sugar level of 99 mg/dL or lower is normal, 100 to 125 mg/dL indicates the patient have prediabetes, and 126 mg/dL or higher indicates they have diabetes [14].

c) Glucose Tolerance Test (GTT):

This measure the blood sugar levels before and after they consume a glucose-containing liquid. Individual shouldn't eat overnight before the test and then the blood drawn to determine the fasting blood sugar level. Then they should drink the liquid and have to check blood sugar level checked 1 hour, 2 hours, and possibly 3 hours. At 2 hours, a blood sugar level of 140 mg/dL or lower is considered normal, 140 to 199 mg/dL indicates that the patient have prediabetes, and 200 mg/dL or higher indicates they have diabetes [15].

d) Random Blood Sugar Test (RBST):

This measures the blood sugar at the time the individual at the time of testing. Test can be taken at any time and don't need to fast (not eat). A blood sugar level of 200 mg/dL or higher indicates they have diabetes [16].

Table 1.1: Average Glucose level

Result	A1C Test	FBST	GTT	RBST	GST
Diabetes	6.5% or above	126 mg/dL or above	200 mg/dL or above	200 mg/dL or above	126 mg/dL or above
Prediabetes	5.7–6.4%	100–125 mg/dL	140–199 mg/dL	N/A	100–125 mg/dL
Normal	Below 5.7%	99 mg/dL or below	140 mg/dL or below	N/A	100 mg/dL

e) Tests for GD

Glucose Screening Test (GST):

This measures the blood sugar at the time of testing, they should drink liquid that contains glucose, and then 1 hour later their blood will be drawn to check the blood sugar level. A normal result is 140 mg/dL or lower. If their level is higher than 140 mg/dL, they need to take a glucose tolerance test [17].

Glucose Tolerance Test (GTT):

This measures the patient's blood sugar before and after they drink a liquid that contains glucose. They'll fast overnight before the test and have the blood drawn to determine their fasting blood sugar level. Then they'll drink the liquid that contains glucose and have the blood sugar level checked at an one hour interval for 3 hrs. Results can differ depending on the amount of glucose drink intake [18].

COMPLICATIONS FOR CHRONIC DIABETES

- a) **Heart and blood vessel (cardiovascular disease)** - Diabetes majorly increases the risk of many heart problems. These can include coronary artery disease with chest pain (angina), heart attack, stroke and narrowing of arteries (atherosclerosis). If a patient has diabetes, they're more likely to have heart disease or stroke.[19]
- b) **Nerve damage (diabetic neuropathy)**[19,20]-Too much sugar can injure the walls of the tiny blood vessels (capillaries) that nourish the nerves. This can cause tingling, numbness, burning or pain that usually begins at the tips of the toes or fingers and gradually spreads upward. Damage to the nerves related to digestion can cause problems with nausea, vomiting, diarrhea or constipation. For men, it may lead to erectile dysfunction.
- c) **Kidney damage (diabetic nephropathy)** - The kidneys hold millions of tiny blood vessel clusters (glomeruli) that filter waste from the blood. Diabetes can damage this delicate filtering system.[20]

- d) **Eyedamage(diabeticretinopathy)**-Diabetescandamagethebloodvessels of the eye. This could lead to blindness.[21]
- e) **Foot damage** - Nerve damage in the feet or poor blood flow to the feet increases the risk of many foot complications.
- f) **Skin and mouth conditions** - Diabetes may leadstoskinproblems,suchas bacterial and fungal infections.[21]
- g) **Hearing impairment** - Hearing problems are more common in people with diabetes. High and low blood sugar, referred to as hyper and hypoglycemia increase the risk of hearing loss by damaging nerves.
- h) **Alzheimer'sdisease**-Type2diabetesmayincreasetheriskofdementia, suchasAlzheimer'sdisease[21].

PREVENTION[22]

Type 1 diabetes can't be prevented. But an healthierlifestyle choices thatcan helpinhetreatmentofprediabetes,type2diabetesandgestationaldiabetessuch as;

- a) **Eating healthy foods:** Selecting meals that are high in fiber, low in calories, and low in fat. Emphasize on whole grains, fruits, and veggies.
- b) **Get more physical activity:** Try to get about 30 minutes of moderate aerobic activity on most days of the week or else set target up to 150 minutes of moderate aerobic activity a week. For example, take a brisk daily walk. If they can't fit in a long workout, breakit up into smaller sessions throughout the day.
- c) **Lose excess pounds:** During overweight condition, losing even 7% of your body weight can lower the risk of diabetes. For example, if you weigh 200 pounds(90.7kilograms), losing14pounds(6.4 kilograms) canlower theriskof diabetes and avoid try to lose weight during pregnancy.

Tokeeptheweightinahealthyrange,workonlongtermchangestorespective eating and exercise habits. Remember the benefits oflosing weight, such as a healthier heart, more energy and higher self-esteem.

TREATMENT

a) **Diet and exercise**

All diabetes patients are given diets chart designed to help them reach and maintain normal body weight, and they often are encouraged to exercise regularly, which enhances the movement of glucose into muscle cells and blunts the rise in blood glucose that follows carbohydrate ingestion [23].

b) **Insulin therapies**

If body can't produce enough insulin, then their bodies require insulin therapy. Beef or pork insulin, made from the pancreatic extracts of cattle or pigs, can be used to treat humans with diabetes. Human insulin treatments are based on recombinant DNA technology [24]. Research into other areas of insulin therapy include pancreas transplantation, beta cell transplantation, implantable mechanical insulin infusion systems, and the generation of beta cells from existing exocrine cells in the pancreas.

c) **Drugs used to control blood glucose levels**

There are various categories of oral medications utilized to regulate blood glucose levels, including Sulfonylureas, biguanides, and Thiazolidinediones.

Sulfonylureas, such as glipizide and glimepiride, are classified as hypoglycemic agents as they stimulate insulin release from beta cells in the pancreas, thereby reducing blood glucose levels. The most common adverse effect associated with sulfonylureas is hypoglycemia, which is more prevalent in elderly patients with impaired liver or kidney function.[25]

Biguanides, with metformin being the primary agent, are classified as antihyperglycemic agents as they decrease glucose production in the liver and increase insulin action on muscle and adipose tissues. A potentially fatal side effect of metformin is the accumulation of lactic acid in blood and tissues, which can cause vague symptoms such as nausea and weakness [26].

Thiazolidinediones, such as rosiglitazone and pioglitazone, function by reducing insulin resistance in muscle, adipose cells and increasing glucose transport into these tissues. These agents can cause edema, liver toxicity, and adverse cardiovascular events in certain patients. Additionally, oral hypoglycemic agents only lower mean blood glucose concentrations by

approximately 50-80 mg per 100 ml (2.8-4.4 mmol per litre), and sensitivity to these drugs tends to decrease over time. [27]

METFORMIN HYDROCHLORIDE: THE MOST PRESCRIBED TREATMENT FOR TYPE II DIABETES

Metformin Hydrochloride (MH) is a biguanide antihyperglycemic drug is a cornerstone of current therapy for the management of non-insulin dependent diabetic mellitus. It exhibits notable efficacy in reducing the risk of disease development MH (1,1-dimethylbiguanide hydrochloride) has been the most regularly used glucose-lowering drug for the past 60 years and has been the first-line medicine for those newly diagnosed with type 2 diabetes mellitus (T2DM) in several clinical guidelines. MH is used with doses ranging from 500 to 2,500 mg/day. It was formally purchased by the United States government in 1995, and by 2001, it had become the most often prescribed medication for type II diabetes [28]. MH has recently received a lot of attention thanks to studies linking it to conditions like type II diabetes. It is also referred as a miracle drug because it helps in preventing cancer, slows down the aging process, protects heart, brain and prevents cognitive decline, polycystic ovarian syndrome, and cell differentiation into oligodendrocytes, decreased oxidative stress in cells, weight loss, anti-inflammatory properties, and even the more recent COVID-19 disease. This medication was first identified through pioneering research using *Galega officinalis* herb extracts, which has properties of an active component known as *galegine* [29].

BOTANICAL BACKGROUND

Galega officinalis, commonly known as galega or goat's-rue, as it boosts breast milk production, which is why it's known as 'Goat's Rue,' because young goat moms eat it and flourish. It is an herbaceous plant in the subfamily Faboideae of the legume family Fabaceae. It is native to parts of northern Africa, western Asia and Europe, but is widely cultivated and naturalized elsewhere [30]. The plant has been extensively cultivated as a forage crop, an ornamental, a bee plant, and as green manure. Herbaceous perennials grew to 1.2 m by 0.8 m at a fast rate. It flowers from June to July, and the seeds ripen in August. The flowers are hermaphrodite (have both male and female organs) and are pollinated by Insects. It can fix nitrogen suitable for: light

(sandy), medium (loamy) and heavy (clay) soils and can grow in nutritionally poor soil suitable pH: acid, neutral and basic (alkaline) soils. It can grow in semi-shade (light woodland) or no shade. It prefers moist soil. The flowering aerial parts of *galega* (*Galega herba*) were used in the past to alleviate the polyuria associated with long-term hyperglycemia, but also to treat many other conditions from tuberculosis, bubonic plague, and malignant fevers to epilepsy, helminthiasis, and various infectious diseases [31].



Figure 1.2: *Galega officinalis*

(<https://owlcation.com/stem/Goats-Rue-and-Metformin-Plant-Facts-and-Medication-Action>)

CHARACTERISTICS

- Habitat-terrestrial
- Flower petal color-blue to purple and pink to red and white
- Leaf type-the leaves are compound (made up of two or more discrete leaflets)
- Leaf arrangement-alternate: there is one leaf per node along the stem
- Leaf blade edges-the edge of the leaf blade is entire
- Flower symmetry-there is only one way to evenly divide the flower (the flower is bilaterally symmetrical)
- Number of sepals, petals or tepals-there are five petals, sepals, or tepals in the flower and there are four petals, sepals, or tepals in the flower
- Fusion of sepals and petals-the petals or these sepals are fused into a cup or tube

- Stamennumber-10
- Fruitttype(general)-thefruitisdryand splitsopenwhen ripe
- Fruitlength-30-50mm[32].

Table1.2:Taxonomicalclassificationof*Galegaofficinalis*

Biological name	<i>Galegaofficinalis</i>
Kingdom	Plantae
Class	Dicotyledons
Family	Fabaceae
Subfamily	Faboideae
Order	Fabales
Genus	Galega
Commonname	English-Galega,goat's-rue,Milkpea,FrenchLilac
Distribution	SouthAmerica,NorthAfrica,Pakistan,Turkey,andNew Zealand

Around 13th compound were isolated from *Galegaofficinalis* Linn. Among which the most common identified compounds are flavonoids (0.0972%), alkaloids (0.1 - 0.2%), such as derivatives of guanidine—galegine and hydroxyl-4-galegine; derivatives of quinazoline—peganine and 2-3-oxy-quinazolone-4. Besides of alkaloids, the aboveground portion contains glycoside galuteolin, flavonoids (kaempferol, quercetin, rutin), tannins, hydroxycinnamic acids, saponins, bitters, pectins, essential amino acids, vitamins (carotene, ascorbic acid) chromium salts, hydroxycinnamic acids, caffeic acid, ferulic acid, chicoric acid, rutin, quercetin, hyperoside, and apigenin [33].

HISTORY OF MH [34]

Table 1.3: History of MH

S.NO	YEAR	INVENTIONS
1	1653	Culpeper's Complete Herbal listed <i>g.officinalis</i> as a remedy for worms, falling sickness (epilepsy), fever and pestilence, while it also has proven weight loss and anticoagulant properties
2	1840-1860	The chemical origins of MH run in parallel with the herbal origins and date from the preparation of guanidine by Strecker
3	1870	Guanidine was found to reduce blood glucose
4	1879	The fusion of two guanidines into biguanide by Rathke
5	1922	MH was first described by Emil Werner and James Bell. They synthesized dimethyl biguanide
6	1940	MH is the independent development of a guanidine-based antimalarial agent proguanil (paludrine)
7	1949	Searching for other guanidine-based antimalarials, proguanil was modified to metformin, and during tests for antimalarial activity by Garcia in the Philippines. This gave rise to MH as an anti-influenza agent called flumamine
8	1956	Translated the anti-hyperglycemic potential of MH into a therapeutic reality was Jean Sterne
9	1957	MH was used to treat diabetes and came into surveillance.
10	1958	Dr Gerry Daniel brought MH to the USA, Aron Laboratories was acquired by Lipha Pharmaceuticals.

DRUGPROFILE[35]
Table1.4:DrugProfile

GENERICNAME	MetforminHydrochloride
BRANDNAME	<i>ActoplusMet,Avandamet,Fortamet</i>
USES	Antihyperglycemicdrug
CHEMICALFORMULA	$C_4H_{11}N_5$
STRUCTURE	
TYPE	Smallmolecule
MOLECULARWEIGHT	129.16g/mol
SYNONYMS	• 1,1-Dimethylbiguanide • N,N-dimethylimidodicarbonimidicdiamide • Metiguanide
CLASS	Guanides(Biguanides)
IUPACNAME	3-(diaminomethylidene)-1,1dimethylguanidine
MELTINGPOINT	223-226°C
BOILINGPOINT	224.1°Cat760 mmhg
SOLUBILITY	Freelysoluble
CLEARANCE	Renalclearanceisabout3.5timesgreaterthancreatinine clearance,whichindicatesthattubularsecretionisthemajor route of MH elimination.

FOOD INTERACTION	Avoid alcohol Take with food Food reduces irritation
-------------------------	--

PHARMACOKINETICS

Absorption

- MH is orally administered in the dose range of 500 mg/b.i.d. or t.i.d. and up to a total of 2,550 mg/day or approximately 35 mg/kg/day.
- It has an onset of action of about 1.5 hours, half-life in the circulation of about 1.5–4.9 hours
- Rapidly absorbed from the gastrointestinal tract.
- Mainly absorbed in the upper part of the small intestine (jejunum), and absorption begins soon after ingestion and peaks within 2 to 3 hours.

Bioavailability:

- Bioavailability is approximately 50–60%.
- Studies using different amounts of MH tablets (ranging from 500 mg to 1500 mg and 850 mg to 2550 mg) show that when the dose increases, the drug isn't absorbed as efficiently, which affects its effects more than how the body gets rid of it [36].

There are also various factors that affect absorption and bioavailability of MH such as: Dose, Formulation, Age, Bodyweight, Kidney function and Food intake

Distribution

The drug is widely distributed into body tissues including the intestine, liver, and kidney by organic cation transporters. MH doesn't attach much to blood proteins like sulfonylureas do. It tends to gather in red blood cells over time. When people take regular MH doses, the amount of MH in their blood becomes steady within a day or

two and is usually quite low, around less than 1 mg/ml. Even with higher doses, like in clinical trials, the most MH in the blood doesn't go above 5 micrograms per ml. The apparent volume of distribution (V/F) of MH after one oral dose of MH 850 mg averaged at 654 ± 358 L [37].

- MH spreads well throughout the body due to its watery nature.
- It doesn't stick much to blood proteins, so it moves around freely.
- It gathers in organs like the liver and kidneys, where it works.
- MH doesn't get distributed to the brain very much because of its properties.
- MH can cross the placenta during pregnancy, but it does not accumulate significantly in the fetal tissues. But still a little amount is distributed into breast milk, but not too much.
- The places it goes affect how it leaves the body, mainly through the kidneys.

Metabolism

MH undergoes minimal metabolism in the body, which means it is not extensively broken down into different substances. Instead, it is primarily eliminated from the body through the kidneys.

Elimination

Active tubular secretion in the kidney is the principal route of MH elimination. MH is removed from the body mainly through the kidneys, and certain proteins called transporters help move it around. These transporters, like OCT1 and OCT3, are found in liver cells and are crucial for MH uptake into the liver. Another transporter, MATE1, is important for moving MH out of the liver and kidneys [38]. In the kidneys, transporters like OCT2, MATE1, and MATE2-K help get MH from the blood into the kidney cells and then into the urine. While MH isn't changed in the liver, its movement can be affected by other drugs that interfere with these transporters.

A recent study suggests the potential for a transporter-mediated drug-drug interaction between MH and specific tyrosine kinase inhibitors (e.g. imatinib, nilotinib, gefitinib, and erlotinib), which may have clinical implications in the disposition, efficacy, and toxicity of MH.

MECHANISMOFACTION

MH was absorbed into the hepatocyte by the organic cation transporter-1 (OCT1). MH's ionization and positive charge in the cells is due to the difference in hepatocyte pH and pK_a , which causes it to accumulate in the cells. Furthermore, there are concentrations up to 1000 times higher in the mitochondria than in the extracellular medium. The membrane potential difference between the plasma membrane and the inner mitochondrial membrane, which has a positive charge on the outside, affects metformin's capacity to enter the mitochondria. Once inside, metformin interferes with complex 1, causing ATP synthesis to decrease and AMP and ADP levels to rise. An effect of inhibiting the respiratory chain is an increase in the ratio of ADP to ATP, which as seen in experimental cells involved in this process, slightly impairs the process of gluconeogenesis. Due to its high energy requirement, it also prevents hepatocytes from effectively synthesizing gluconeogenesis. Changes in the ratios of NAD^+ to $NADH$ are another effect that have a detrimental impact on gluconeogenesis [39].

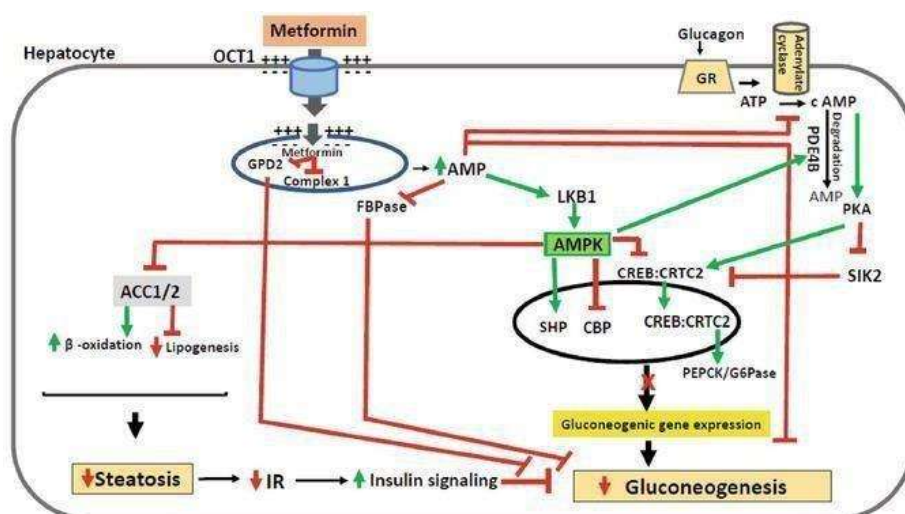


Figure 1.3: MH-Mechanism of Action

(<https://images.app.goo.gl/sbU4sy7fE3MQi7Kk8>)

CLINICAL SYMPTOMS OF METFORMIN [40]

- Gastrointestinal upset can cause severe discomfort
- It is most common when MH is first administered, or when the dose is increased.
- The discomfort can often be avoided by beginning at a low dose (1.0 to 1.7 g/day) and increasing the dose gradually, but even with low doses, 5% of people may be unable to tolerate metformin.
- Use of slow or extended-release preparations may improve tolerability.
- Long-term use of MH has been associated with increased homocysteine levels and malabsorption of vitamin B12.
- Higher doses and prolonged use are associated with increased incidence of vitamin B12 deficiency.

OVERDOSE LEADS TO:

- Most common symptoms following an overdose include vomiting, diarrhea, abdominal pain, tachycardia, drowsiness, and rarely, hypoglycemia or hyperglycemia.
- Treatment of MH overdose is generally supportive, as no specific antidote is known. Extracorporeal treatments are recommended in severe overdoses.
- Due to MH low molecular weight and lack of plasma protein binding, these techniques have the benefit of removing MH from the blood plasma, preventing further lactate overproduction.
- Metformin may be quantified in blood, plasma, or serum to monitor therapy, confirm a diagnosis of poisoning, or to assist in a forensic death investigation.
- Blood or plasma MH concentrations are usually in a range of 1-4 mg/L in persons receiving therapeutic doses, 40-120 mg/L in victims of acute overdose, and 80-200 mg/L in fatalities.
- The risk of metformin-associated lactic acidosis is also increased by a massive overdose of metformin, although even quite large doses are often not fatal [41].

DRUG INTERACTION:

- The H₂-receptor antagonist cimetidine causes an increase in the plasma concentration of MH by reducing clearance of MH by the kidneys. MH also interacts with anticholinergic medications, due to their effect on gastric motility.
- Anticholinergic drugs reduce gastric motility, prolonging the time drugs spend in the gastrointestinal tract.
- This impairment may lead to more MH being absorbed than without the presence of an anticholinergic drug, thereby increasing the concentration of MH in the plasma and increasing the risk for adverse effects [42].

ADVANTAGES OF MH:

- MH can help with weight loss and reduce the size of your waist.
- MH can also improve fertility.
- It even helps people with certain medical conditions live longer.
- There's evidence that MH can help treat obesity and obesity-related conditions, like metabolic syndrome.
- MH can slow some tumor growth and stop certain tumors from forming.
- MH exerts its anti-hyperglycemic effects mostly by suppressing hepatic glucose production through AMPK-dependent or independent pathways [43].

DISADVANTAGES OF MH:

- Feeling sick (nausea) Take MH with food to reduce the chances of feeling sick.
- Being sick (vomiting).
- Take small, frequent sips of water or squash to avoid dehydration.
- Diarrhoea.
- Stomachache.
- Loss of appetite.
- A metallic taste in the mouth. [43]

Some side effects of MH may occur that usually do not need medical attention. These side effects may go away during treatment as the individual body adjusts to the medicine. Also, the health care professional may be able to tell about ways to prevent or reduce some of these side effects. GI side effects on irritation Impaired renal function Impaired hepatic function Pharmacologically treated CHF Alcoholism [44].

EXCIPIENT PROFILE

SODIUM CARBOXYMETHYLCELLULOSE

Generic name: Sodium Carboxymethylcellulose

Brand name: Leader Lubricant Eye Drops, Refresh Drops, Refresh Liquigel, Refresh Optive Advanced, Refresh Optive Extended Therapy, Retaine, Thera Tears, Theratears

Uses: Thickening agent, stabilizer, suspending agent, ophthalmic lubricant

Chemical formula: $C_8H_{15}NaO_8$

Type: Small Molecule

Molecular weight: 262.19 g/mol

Synonymous: Sodium cellulose glycolate, NaCMC, CMC, cellulose gum, sodium CMC

IUPAC name: sodium; 2,3,4,5,6-pentahydroxyhexanal; acetate

Melting point: 270 °C

Boiling point: 525.00 to 528.00 °C.

Solubility: Yields viscous colloidal solution with water; insoluble in ethanol [45]

MAGNESIUM STEARATE

Generic name: Magnesium stearate Brand

name: HI-MAST

Uses: Anticaking agent, emulsifier, binder, lubricant, stabilizer.

Chemical formula: $C_{36}H_{70}MgO_4$

Type: Small Molecule

Molecularweight:591.2g/mol

IUPACname:magnesium;octadecenoate

Synonymous: Dibasic magnesium stearate, Magnesium Di stearate, Magnesium octadecenoate, Octadecanoic acid, magnesium salt, Stearic acid, magnesium salt

Meltingpoint:88°C

Boiling point:359.4°C at 760mmHg

Solubility:Practicallyinsolubleinwater[46]

MICROCRYSTALLINECELLULOSE

Genericname:Microcrystallinecellulose

Brand name: Alprazolam

Uses:Emulsifier, stabilizer, anticaking, filler, binders, excipients and dispersing agent

Chemical formula:C₁₂H₂₂O₁₁

Type:SmallMolecule

Molecular weight:370.35 g/mol

Synonymous: Cellulose gel, Cellulose, Cellulose crystalline, Cellulose powder, Cellulose regenerated, microcrystalline, Hydroxycellulose, Powdered cellulose, Pyrocellulose, Rayon.

Class:polysaccharidewithglucoseunitslinkedasincellobiose

IUPACname:2-[4,5-dihydroxy-2-(hydroxymethyl)-6-methoxyoxan-3-yl]oxy-6-(hydroxymethyl)-5-methoxyoxane-3,4-diol

Meltingpoint:260-270°C

Boilingpoint:237.6±35.0°C at 760mmHg

Solubility:Insolubleinwater, ethanol, ether and dilute mineral acids. Slightly soluble in sodium hydroxide solution [47]

HYDROXYPROPYLMETHYLCELLULOSE

Genericname:Hydroxypropylmethylcellulose

Class: ophthalmic lubricants and irrigations

Brand name: Gonak Hypromellose

Chemical formula:C₅₆H₁₀₈O₃₀

Molecular weight: 1,261.45 g/mol

Uses: emulsification, adhesion, bonding, thickening, suspension, film forming

Melting point: 225 to 254 degrees C

Boiling point: 1,102 °C

Solubility: practically dissolved in water

Food interaction: Nutritionally it counts as 100% soluble fibre and is considered completely non-toxic and food safe to levels much higher than those used in Lo-Dough. [48]

POLYVINYLPIRROLIDONE

Generic name: Polyvinylpyrrolidone

Synonym: Povidone

Solubility: water- soluble

Chemical formula: $(C_6H_9NO)_n$

Molar mass: 2,500-2,500,000 g·mol⁻¹

Appearance: white to light yellow, hygroscopic, amorphous powder Density:

1.2 g/cm³

Melting point: 150 to 180 °C (302 to 356 °F; 423 to 453 K) (glass temperature) IUPAC

name: 1-Ethenylpyrrolidin-2-one

Brand name: Clear Eyes Natural Tears, Colirio Ocusan, Minidrops, Refresh Lubricant Uses:

It is used as a binder in many pharmaceutical tablets

Boiling point: 90-93 °C [49]

STARCH

Generic name: Starch, amyllum

Synonyms: Starch 1500, Starch LM

Chemical formula: $(C_6H_{10}O_5)_n$

Molecular weight: Depends on extent of gelatinization

Solubility: Insoluble in cold water or alcohol, becomes soluble on heating. Molar

mass: Variable

Appearance: White powder

Melting point: Decomposes

Uses: Odorless, tasteless functional categories, Thickening agent, stiffening agent, gluing agent. [49]

CHAPTER – 2

LITERATUREREVIEW

CHAPTER-2

REVIEW OF LITERATURE

Natalia Tobar *et al.*, (2023) performed and investigated the effects of MH on basolateral intestinal glucose uptake (BIGU), and its consequences on hepatic glucose production (HGP). They observed that in diabetic patients and mice, the primary site of MH action was the gut, increasing BIGU, evaluated through PET-CT. And in mice and CaCo₂ cells, this increase in BIGU resulted from an increase in GLUT1 and GLUT2, secondary to ATF4 and AMPK. Hyperglycemic condition, MH increased the lactate (reducing pH and bicarbonate in portal vein) and acetate production in the gut, modulating liver pyruvate carboxylase, MPC1/2, and FBP1, establishing a gut-liver crosstalk that reduces HGP. In normoglycemia, MH-induced increases in BIGU are accompanied by hypoglycemia in the portal vein, generating a counter-regulatory mechanism that avoids reductions or even increases HGP. MH increases BIGU and through gut-liver crosstalk influences HGP [50].

Reihaneh Fatehi *et al.*, (2023) have designed and investigate the effect of MH in combination with resveratrol and cisplatin in MCF-7 cells. Study groups are untreated control group, single treatment groups (metformin, resveratrol, and cisplatin), double treatment groups (metformin + resveratrol, metformin + cisplatin, and cisplatin + resveratrol) and triple treatment groups (metformin + resveratrol + cisplatin). Finally proved that MH inhibits proliferation of MCF-7 cells, an effect that was associated with ROS production and G0/G1 cell cycle arrest, but not apoptosis. In conclusion, our results advocate the anti-cancer properties of metformin and resveratrol on MCF-7 cell via induction of cell cycle arrest. Additionally, synergistic anti-cancer effects of metformin in a triple combination with cisplatin and resveratrol was attributed to induction of autophagy-mediated cell death and apoptosis along cell cycle arrest [51].

Kaitlin M Love *et al.*, (2022) have studied that MH improves insulin's action on whole body glucose metabolism in various insulin-resistant populations. Beyond metabolic actions, MH also impacts microvascular function. However, the effects of MH on microvascular function and microvascular insulin actions specifically are poorly defined. And they summarize what is currently known about metformin's beneficial impact on both microvascular function and the microvascular response to insulin while

highlighting methodologic issues in the literature that limit straightforward mechanistic understanding of these effects. They examine potential mechanisms for these effects based on pharmacologically dosed studies and propose that MH may improve human microvascular insulin resistance by attenuating oxidative stress, inflammation, and endothelial dysfunction [52].

Shankar Dhobale et al., (2022) have worked on the development pharmaceutical combination dosage form for simultaneous treatment of patients with type 2 diabetes with a high-risk of coronary disease associated co-morbidities. MH was used to treat the diabetic patient and combined with Simvastatin which is HMG-CoA reductase inhibitor drug to treat the high-risk coronary diseases simultaneously. In this formulation, three batches were prepared by the direct compression method. Preformulation parameters such as identification, solubility, melting point, Precompression parameters such as bulk density, tapped density, angle of repose, Hausner ratio and post-compression parameters like weight uniformity, hardness, drug content. *In vitro* drug release of all formulations, B1, B2, and B3 was carried out in 0.1N HCl for 2hrs and 10hrs in phosphate buffer (pH 6.8) dissolution media. Among all the formulations, B3 was an optimized batch. B3 formulation showed drug release of 85% for Metformin Hydrochloride and 93% for Simvastatin over a period of 12hrs [53].

Shailesh Kulkarni et al., (2021) they focused on developing an oral jelly formulation of MH. The therapeutic dose range is 250mg to 1000mg. And the research introduces a unit packaged oral jelly, providing a safe and palatable option for geriatric patients. Formulations were optimized for up to 1000mg per 5g strength and they found stable in laminated sachets for six months. This oral jelly offers a viable solution to swallowing issues, enhancing patient compliance and convenience [54].

Faraz Chogan et al., (2020) were investigated how to alleviate fibrosis and accelerate wound healing by using three layer nanofiber scaffold which was designed with two polycaprolactone chitosan layers on the sides and a Polyvinyl alcohol MH in the middle. The Physico-chemical and biological properties along with scaffold biocompatibility, cell attachment, and antibacterial activity were conducted. Histopathological and immunohistochemical evaluation revealed the group having significantly lower inflammation, higher angiogenesis, the smallest scar width and

depth, maximum epitheliogenesis score and the most optimal modulation of collagen density for Local administration of MH substantially down regulated the expression of fibrosis-involved genes TGF- β 1, Col-I, Col-III and α -SMA. Inhibiting these genes alleviates scar formation but delays wound healing; thus, an engineered scaffold was used to prevent delay in wound healing [55].

Djebbar Mohamed *et al.*, (2019) have worked on developing effervescent floating tablet of MH by melt granulation method with stearic acid. HPMC has produced floating matrices with good buoyancy properties and extended release of metformin hydrochloride. Also, the drug release kinetic was found to be dependent on HPMC viscosity at the concentration 17.5%. At this concentration, when the viscosity grade of HPMC increases, the dissolution kinetic of MH was more slowed and extended. The floating tablets HPMC K15M and HPMC K100M have exhibited extended release kinetics (>8 hours). These formulations have constituted promote systems for the development of extended-release metformin HCl floating tablets [56].

Gaware Ravi *et al.*, (2019) have formulated sustained released matrix tablet of MH by direct compression method using HPMCK100 and ethyl cellulose as matrix forming polymer. This attempt has been made, to formulate the sustained release matrix tablets of MH and tested for controlled delivery of drug using hydrophilic matrix polymer HPMC in combination with hydrophobic ethyl cellulose, resulting in reduction in the dosing frequency of Metformin and thereby its dose related side effects. They have combined the hydrophilic and hydrophobic polymer and optimized formulation containing HPMC and EC had successfully sustained the release of MH up to 12 hrs [57].

Sara Baldassari *et al.*, (2018) have developed an injectable slow-release metformin and carried out the formulation and evaluation of its potential anti-tumour effects. Metformin is an antidiabetic drug which possesses antiproliferative activity in cancer cells. The aim of this work was to develop a pharmacological tool for the release of metformin in proximity of the tumour, allowing high local concentrations, and to demonstrate the *in vivo* antitumor efficacy after a prolonged metformin exposition. A 1.2% w/w metformin thermo responsive parenteral formulation based on poloxamers P407 and P124, injectable at room temperature and undergoing a sol-gel transition at body temperature, has been developed and optimized for rheological, thermal and

release control properties; the formulation is easily scalable, and proved to be stable during a 1 month storage at 5°C. Using NOD/SCID mice pseudo-orthotopically grafted with MDA-MB-231/luc+ human breast cancer cells, we report that multiple administrations of 100mg of the optimized metformin formulation close to the tumor site cause tissue accumulation of the drug at levels significantly higher than those observed in plasma, and enough to exert antiproliferative and pro-apoptotic activities. The results demonstrate that this formulation is endowed with good stability, tolerability, thermal and rheological properties, representing a novel tool to be pursued in further investigations for adjuvant cancer treatment [58].

Padma Bookya *et al.*, (2018) have developed and optimized the MH matrix tablets for sustained release application. The sustained release matrix tablet of MH was prepared by wet granulation technique using chitosan, xanthan gum, and HPMC at varying concentrations. Formulation with chitosan MS1 drug release was 86%, xanthan gum MS 489%, and finally MS7 with HPMC which exhibited the highest drug release retardation also had the lowest matrix concentration. Hence, lower concentration of polymers was suitable to prepare MH was compared to high concentrations [59].

Mhase SR *et al.*, (2018) has developed and characterized the dual release tablet formulation containing Metformin in extended release matrix form and Pioglitazone in immediate release form for the treatment of Diabetes mellitus using hot melt granulation method with the combination of PEO and SA for extended-release layer. Their optimization results indicated that release rate of Metformin is directly proportional to the levels of stearic acid (SA) and poly-ethylene-oxide (PEO). As a result, a dual release tablet containing an extended-release MH and immediate release Pioglitazone was successfully developed for the treatment of Diabetes mellitus [60].

Nizar Al-Zoubi *et al.*, (2017) have worked on co-spray drying of MH to improve compression behavior by using hydrophilic polymers. They were evaluated by laser diffraction, light microscopy with image analysis, SEM, PXRD, DSC, instrumented press and diametrical loading of compacts. Obtained powders consist of agglomerated spherical particles with median diameters between 6.7 and 11.0 µm. Co-spray drying with polymers resulted in increase of amorphous content of MH. Compactability and

tablet ability was improved by co-spray drying with the anionic polymers (Na alginate and Na CMC) [61].

Fabián Martínez-Gómez *et al.*, (2017) have worked on hydrogels of full characterized sodium alginate (M_n 87,400 g/mol) and commercial (PVA) sensitive to pH and temperature stimuli were obtained using a simple, controlled, green, low-cost method based on freeze-thaw cycles. Stable hydrogels of Na alginate/PVA with 0.5:1.5 and 1.0:1.0 w/v concentrations showed good swelling ratio values in distilled water (14 and 20 g/g, respectively). Encapsulation and release of MH in hydrogels of 1.0:1.0 w/v sodium alginate/PVA was followed by UV spectroscopy. And that hydrogel released a very low amount of MH at pH 1.2; the highest release value (55%) was obtained after 6 hr at pH 8.0 [62].

Ibtissem Benmessaoud *et al.*, (2016) have screened the influence of solvent on solubility, nucleation and crystallization of an (API)-MH. They started with 13 solvents covering a wide variety of polarity and proticity. In that they found 63 crystallization mediums for MH solid generation: good solvents, good co-solvents & anti-solvent system crystal habit of MH was studied by a cooling temperature method. Variety of crystal habits were observed by optical and scanning electron microscope then solid phase were characterized by X-ray powder diffraction, indicating that all the crystals correspond to the thermodynamic stable polymorphic form of MH. At last the enthalpy of fusion and the melting temperature of MH were determined by DSC [63].

Ashim Kumar Sen *et al.*, (2016) were developed and validated for simultaneous estimation of teneligliptin hydrobromide hydrate and metformin hydrochloride in tablet formulation which were simple, sensitive, precise and accurate. In simultaneous equation method, absorbance was measured at 237 and 246 nm for both the drugs. Teneligliptin hydrobromide hydrate and MH was estimated using 237 and 247.5 nm in absorbance ratio method. Developed methods were validated according to ICH guidelines including parameters viz., specificity, linearity and range, precision, accuracy, limit of detection and quantification. Based on the assay results obtained, methods were compared using one-way ANOVA followed by Bonferroni multiple comparison tests (95% confidence level) using computer based fitting program (Prism, Graphpad version 5, Graphpad Software Inc). Furthermore, the outcome of this

statistical analysis proved that there was no considerable dissimilarity between all the developed methods [64].

Carolyn Chiswick *et.al.*, (2015) have worked and made research on randomized, double-blind, placebo-controlled trial in antenatal clinics at 15 National Health Services hospitals in the UK. Pregnant women (aged ≥ 16 years) between 12- and 16-weeks' gestation who had a BMI of 30 kg/m² or more and normal glucose tolerance were randomly assigned (1:1), via a web-based computer-generated block randomization procedure (block size of two to four), to receive oral metformin 500 mg (increasing to a maximum of 2500 mg) or matched placebo daily from between 12- and 16-weeks' gestation until delivery of the baby. Randomization was stratified by study site and BMI band (30-39 vs ≥ 40 kg/m²). Participants, caregivers, and study personnel were masked to treatment assignment. The primary outcome was Z score corresponding to the gestational age, parity, and sex-standardized birthweight percentile of liveborn babies delivered at 24 weeks or more of gestation [65].

Venkatesh Teja Banala *et.al.*, (2014) have worked on symmetric membrane capsules and found it was one of the novel osmotic delivery devices which offer the delivery of a wide range of drugs in a controlled manner. The capsule walls were made by dip coating phase inversion process using cellulose acetate butyrate as polymer and propylene glycol as plasticizer/pore forming agent. The resulting asymmetric membrane wall was evaluated by scanning electron microscopy studies revealed the thin dense region supported on a thicker, porous region. Fourier transform infrared studies showed phase inversion of the asymmetric membrane as compared to plain membrane. Osmotic release study and *in vitro* behaviour was studied for controlled delivery of MH as a model drug [66].

M. Nafady *et al.*, (2014) have worked on Hydro dynamically Balanced System (HBS) for MH as a single unit floating capsule. The formulation blends were prepared by physical blending of drug and polymer in varying concentration. Drug compatibility with polymer was confirmed by FTIR, DSC and XRD studies. The bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose were determined to study the micromeritic properties of physical mixtures of different blends. Prepared HBS capsules were also evaluated for drug content and weight uniformity, *in vitro* drug release in HCl pH 1.2. The drug release pattern varied significantly with increased

polymer concentration in the formulations. The release rate can be effectively modified by using hydrophobic and hydrophilic polymers. All the HBS capsules of MH extended drug release compared to capsule contains only pure MH [67].

Vinay Pandit *et al.*, (2013) have worked on the formulation of floating microsphere in order to increase its residence time at a site of absorption and does improve its bioavailability and extend duration of action with possibilities of dose reduction. The microsphere was prepared by emulsion solvent evaporation method evaluated for particle size and further characterized by powder X-ray diffraction. Conclusion an effective oral anti diabetic treatment can be achieved by formulating MH into floating Microsphere which result in increased bioavailability and along with extended duration of action result in possible reduction in dose [68].

Momoh M.A *et al.*, (2013) have worked on the formulation and evaluation of PEGylated-mucin matrices-based solid microparticles for oral administration of MH. PEGylated-mucin matrices were formulated with PEG-2000 and Mucin were used to prepare metformin-loaded PEGylated-mucin using solvent interaction method. Characterizations based on size and morphology, zeta potential and polydispersity index, loading and encapsulation efficiency (EE%) were carried out on the PEGylated matrices. In vitro release of metformin from the preparation was performed in phosphate buffer while in vivo release as a function of the antidiabetic effects were conducted in alloxan induced diabetes rats. The release of MTH in phosphate buffer varied widely with the PEG and Mucin contents. Moreover, a significant amount of MTH was released *in vivo* from the matrices as demonstrated in the basal glucose reduction than the positive control. These results demonstrated that PEGylated matrices would likely to offer a reliable means of delivering metformin orally [69].

CHAPTER–3

AIM AND OBJECTIVE OF WORK

CHAPTER-3

AIM AND OBJECTIVE

Aim:

The aim of current research is to prepare and to perform *in vitro* evaluation of Sustained release capsule of Metformin Hydrochloride Capsules.

Objective:

The objective of the current research was focused on the design, develop and evaluate metformin hydrochloride sustained release capsules.

Following are the objective of the study:

- Selection of drugs and polymers for sustained release capsule of metformin hydrochloride.
- To perform the preformulation studies of raw material.
- To perform the preformulation studies of granules.
- To fill the granules in zero size capsule.
- To perform evaluation parameters for the formulated sustained release metformin hydrochloride capsule.
- To perform *in vitro* comparative study with already available marketed metformin hydrochloride sustained release tablets.
- To conduct stability studies of the optimized formulation as per ICH guidelines.

CHAPTER – 4
MATERIALS AND
EXPERIMENTAL METHODS

CHAPTER-4

MATERIALS AND EXPERIMENTAL METHODS

MATERIALS:

INSTRUMENTS:

Table 4.1: Instruments

S.No	Name	Manufacturer
1.	Electronic weighing balance	Scale Tec, Gujarat, India
2.	Sieve	Gloson Test Sieve, Gujarat, India
3.	Bulk density apparatus	DBK Instruments Mumbai, India
4.	Disintegration apparatus	Lab India Analytical Pvt Ltd, Mumbai, India
5.	Dissolution apparatus	DURALAB, Parlin, New Jersey
6.	Ultraviolet spectrophotometer	SHIMADZU, Japan
7.	FTIR Spectrophotometer	BRUKER, USA
8.	Manual Capsule filling machine	Adinath Machines, Gujarat, India
9.	pH meter	King Lab Instrument Pvt Ltd, Tamilnadu, India
10.	Mortar and pestle	Jain Scientific Suppliers, Ambala, India
11.	Screw gauge	Zoom, Scientific World, Ambala, India
12.	Melting point apparatus	VS Electronic Pvt Ltd Mohali, Punjab

CHEMICALS:

Table 4.2: Chemicals

S.No	Materials	Supplier
1.	Metformin Hydrochloride	Cadila Pharmaceuticals, Gujarat, India
2.	Polyvinylpyrrolidone	Fine Chemicals Bangaluru, Karnataka, India
3.	Magnesium stearate	Nice Chemicals Pvt Ltd, Kerala, India

4.	Hydroxypropylmethylcellulose	HIMEDIA Laboratories Pvt. Ltd. Maharashtra, India
5.	Sodium Carboxymethylcellulose	Nice Chemicals Pvt. Ltd. Kerala, India
6.	Microcrystalline cellulose	HIMEDIA Laboratories Pvt. Ltd. Maharashtra, India
7.	Starch	ISCO Research Laboratories Pvt. Ltd. Maharashtra, India

Freshly prepared distilled water was used in the research work.

GLASSWARE:

Glassware is an essential equipment for the formulation of MH capsules. Some of the glassware used in the formulation of MH capsules are:

- Beakers
- Graduated cylinders
- Volumetric flasks
- Pipettes
- Burette
- Conical flasks

All the above glassware are of class A (Borosil Ltd., Mumbai, India)

SOFTWARE:

Table 4.3: Software

S.No	Software Used
1.	Statistical tool using Microsoft Excel 2018 Software (Microsoft, USA)

EXPERIMENTAL METHODS:

FORMULATION AND IN VITRO EVALUATION OF MH SUSTAIN RELEASE CAPSULE:

Preformulation studies

For the Preformulation studies, the physicochemical characterization of drug substance, selection of excipients, compatibility studies, estimation of drug content in MH by UV-Visible Spectroscopy were carried out.

Physicochemical characterization:

MH was characterized and identified by its physical appearance, melting point, ultraviolet (UV) spectroscopy, solubility profile and infrared (IR) spectroscopy.

a) Physical appearance [70]

Description of the drug is the first line indication for purity for its identification.

1.0 g of MH was weighed and transferred into a clean, dry petridish and physical appearance, colour was observed visually, the results were shown in **5.1 a**.

b) Melting point

Checking the melting point is the fundamental physical property very often used to identify compounds. Melting point of MH was carried out by capillary method using melting point apparatus. [71]

A little amount of MH was added into a glass capillary tube, sealed one end and open at other end; slowly the temperature was increased and observed. The temperature at which melting starts was observed in the attached laboratory thermometer. Average of three readings were taken and compared with the standard melting point of MH, the results were shown in the **Table 5.1**.

c) Solubility studies

The solubility of MH in various solvents like distilled water, methanol, ethanol, and phosphate buffer PB (pH 6.8) were carried out individually. [72]

MH 100 mg was added in 100 mL of the various solvents in a volumetric flask and sonicated for 30 min. It was considered as stock solution; from it 1 mL was taken and diluted to 10 mL with same solvent and filtered through, 0.2 μ m Whatman's filter

paper. The absorbance was measured at 233 nm by UV-Visible spectrophotometer; the results were shown in the **Table 5.2**.

d) Ultraviolet (UV) absorption maxima (λ_{max})

The absorption maxima of MH were determined by light absorption method in the UV-Visible spectrophotometer [73].

A standard stock solution I was prepared by dissolving 100 mg of MH in 100 mL of PB. Subsequently, 1 mL was extracted from stock solution and diluted with PB (pH 6.8) to a final volume of 100 mL, resulting in a concentration of 10 $\mu\text{g/mL}$. The resulting solution was then filtered using a 0.2 μm Whatman filter paper.

The solution of MH was scanned at 233 nm, using PB (pH 6.8), as blank. The R^2 value was calculated; and the λ_{max} was found. The result is shown in **Table 5.3**.

e) Fourier Transform Infrared (FTIR) spectroscopy

Spectra were taken after preparing the pellet with 2-3 mg of sample using potassium bromide in the ratio of 1:100 and were scanned from 4000–400 cm^{-1} . The FTIR spectra were scanned for pure MH was detected and the characteristic peaks are shown in **Table 5.4**. [74]

Selection of Excipients for Preformulation Studies of MH

Table 4.4: Selection of excipients for Preformulation Studies of MH

List of polymers available [75][76]	List of selected polymers used in the formulation	Reason for selection
1. Natural a) Cellulose b) Starch c) Gelatin d) Shellac e) Agar f) Acacia	a) Starch	Abundance and Low Cost: Starch is abundant in nature, primarily found in plants. It serves as a major form of stored energy in carbohydrates. It is a desirable raw material for many applications due to its accessibility and affordable price.

g)GuarGum h)Chitosan		• Biodegradability: Unlike many synthetic polymers, starch is biodegradable. When disposed of, it breaks down naturally over time, reducing environmental impact. • Non-toxicity: Starch is non-toxic, making it safe for various uses. • Customized Properties: Starch can be modified into diverse biomaterials with varying functionalities such as flavour, texture, thickness, taste, stability and shelf life.[78]
2.Semi-synthetic a)Cellulose derivatives b)Cellulose nitrates c)Cellulose Acetates	a)Sodium Carboxymethyl cellulose(CMC)	NaCMC: Its water-solubility makes it easy to incorporate into various formulations. CMC is a good thickening agent, stabilizer, and has film-forming properties. Additionally, its biocompatibility and non-toxic nature contribute to its widespread use. The specific interactions could involve binding metformin particles, providing controlled release, or facilitating better dispersion.[80]
	b)Hydroxypropyl Methylcellulose (HPMC)	Hydroxypropyl Methylcellulose (HPMC) is a versatile polymer widely used in pharmaceuticals and other applications. The reason why HPMC K100M was selected is due to its; • Sustained Release Properties: HPMC K100 is an excellent release retardant polymer. It is extensively studied for

		developing controlled-release dosage forms. • Biocompatibility and Safety: HPMC is derived from cellulose and is considered non-toxic. It is well-tolerated in the body, making it suitable for oral drug delivery systems. • Water Solubility: HPMCK100 is water-soluble, which facilitates its use in various formulations. It can form gels and thick solutions, aiding in drug release control. • Film Formation: HPMC K100 can form thin, flexible films. This property is valuable for coating tablets, improving swallowability, and protecting the drug from environmental factors. • Stabilization and Thickening: HPMC K100 acts as a stabilizer. It also provides thickening properties, enhancing the texture of formulations [81].
	c) Microcrystalline Cellulose (MCC)	Microcrystalline Cellulose (MCC) is a fascinating polymer with several advantageous properties that make it an excellent choice for various applications. The reasons why MCC was selected as a polymer are: • Biocompatible: MCC being biocompatible, it is widely used in pharmaceuticals, food, and other sensitive applications.

		• Binder and Disintegrant: In pharmaceutical formulations, MCC acts as a binder, holding tablet ingredients together, and as a disintegrant, aiding in tablet disintegration upon ingestion. • Stabilizer: MCC stabilizes emulsions, suspensions and foams due to its ability to absorb water and form a gel-like network. • Inert and Non-Toxic: MCC is inert, non-toxic, and does not interfere with the chemical stability of other ingredients. This makes it suitable for oral dosage forms. [77]
3.Synthetic a) Polyvinyl pyrrolidone b) PolyEthyl Methacrylate c) Polyurethane d) Polyethylene Imine	a) Polyvinylpyrrolidone (PVP)	Polyvinylpyrrolidone (PVP) is often chosen as a binder in pharmaceutical formulations due to its excellent binding properties. It forms a strong film around the active pharmaceutical ingredient (API) particles, promoting cohesion. PVP is also water-soluble, facilitating disintegration upon ingestion, which is crucial for drug absorption. • Its binding properties make PVP valuable in other areas as well, such as in the production of solid dispersions, where it aids in improving the solubility of poorly soluble drugs. • Polyvinylpyrrolidone (PVP) is used in pharmaceutical formulations to enhance the solubility and

		dissolution rate of poorly soluble drugs, including metformin. This interaction can lead to increased surface area and improved wetting of the drug particles, resulting in better dissolution and bioavailability of metformin. [79]
4. Lubricant	Magnesium Stearate	MgSt: It exhibits good lubricating properties, reducing friction between particles and facilitating the manufacturing process of tablets or capsules. Anti-Adhesive Properties: Magnesium stearate helps prevent sticking during the tablet compression process, ensuring smooth and efficient production. [82]

Study of Analytical Method for Estimation of MH by UV

Preparation of standard curve for MH by UV method

The calibration curve for MH was established as follows: Initially, 100 mg of MH was dissolved in 100 mL of PB (pH 6.8), constituting the working standard stock I. Subsequently, 1 mL was withdrawn from Stock-I and diluted to 100 mL with PB (pH 6.8), forming the working standard stock II. From Stock-II, aliquots of 2, 4, 6, 8, and 10 mL were measured and adjusted to a total volume of 10 mL with PB (pH 6.8), resulting in concentrations of 2, 4, 6, 8, and 10 µg/mL. [83]

The absorbance of these solutions was measured at 233 nm using a spectrophotometer, with PB (pH 6.8) serving as the blank. Data processing was carried out using Microsoft Excel, and a calibration curve for MH was generated by plotting absorbance values against concentrations (µg/mL). The results are shown in **Figure 5.3** and **Table 5.5**.

Drug-excipients compatibility studies by FTIR

The drug-excipients compatibility studies are carried out in order to ensure, the interaction between the drug and polymer, when they are physically mixed together. MH was subjected for IR spectroscopic study.

Spectra were taken after preparing the pellet with 2-3 mg of sample using potassium bromide in the ratio of 1:100 and were scanned from 4000-400 cm^{-1} .

The FTIR spectra were scanned for pure MH, polymer, and MH-physical mixture individually to detect any appearance or disappearance of characteristic peaks.[84] The results of the FTIR spectra are shown in the **Figure 5.4** and **5.5**.

Formulation Development of MH sustain release capsule:

- a) **Purification procedure for MH:** MH was purified by recrystallization by centrifugation method to reduce the contain of N- nitrosodimethylamine.
- b) **Procedure:** 500mg MH was taken and the excipients PVP K30, Sodium CMC, HPMC K100 and MCC were taken in the mortar and pestle and was triturated slowly. Prepared starch solution was added until a mass formed. This prepared mass was kept for drying for 10 minutes. Further it was sieved using sieve size 10 to get an uniform sized granules. To this Mg Stearate was added as a lubricating agent further these granules were filled in empty zero size hard gelatin capsules using manual capsule filling machine.

Table 4.5: Formulation development of MH sustain release capsule

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Metformin HCl	500	500	500	500	500	500	500	500	500	500
PVP K30	16.5	10	23	5	28	14	10	18	5	23
Mg Stearate	2	2	2	2	2	2	2	2	2	2
Sodium CMC	5	5	5	5	5	10	10	10	10	10
HPMC K100	16.5	23	10	28	5	14	18	10	23	5
MCC	10	10	10	10	10	10	10	10	10	10
Starch	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
TOTAL WEIGHT	550	550	550	550	550	550	550	550	550	550

METHODS FOR OPTIMIZATION:

In vitro evaluation of MHs sustain release blend

The flow properties of formulated MHs sustain release blend were characterized by measuring **(General chapter, powder flow <1174>, USP 42)**.

a) Angle of repose

To determine the angle of repose, the following were followed

Setup: Choose a clean, flat surface. Place a funnel or a similar device at a fixed height above the surface.

Material Placement: Pour the granular or powdered material through the funnel onto the surface. Allow the material to form a cone-shaped pile naturally.

Measurement: Measure the height (h) of the cone from the base to the tip. Measure the radius (r) of the base of the cone and the results are shown in **Table 5.7**.

Calculation:

Use the tangent of the angle of repose formula:

$$\tan(\theta) = r/h$$

Where, θ = Angle of repose, h = height of blend and r = radius of blend heap.

Table 4.6: Angle of Repose

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

b) Bulk Density:

Procedure: Allow an excess of powder to flow through the apparatus into the sample receiving cup until it overflows, using a minimum of 25 cm³ of powder with the square cup and 35 cm³ of powder with the cylindrical cup. Carefully scrape excess

powder from the top of the cup by Cylinder smoothly moving the edge of the blade of a spatula perpendicular to and in contact with the top surface of the cup, taking care to keep the spatula perpendicular to prevent packing or removal of powder from the cup. Remove any material from the sides of the cup, and determine the weight, M, of the powder to the nearest 0.1%. Calculate the bulk density, in g/mL, by the formula:

Calculation:

$$\text{Bulk Density (g/mL)} = M/V_0$$

in which V_0 is the volume, in mL, of the cup. Record the average of three determinations using three different powder samples. The results were shown in **Table 5.7**.

c) Tapped Bulk Density:

Procedure: Tapped density of a powder is the ratio of the mass of the powder to the volume occupied by the powder after it has been tapped for a defined period of time. The tapped density of a powder represents its random dense packing. Tapped density can be calculated using the formula;

Calculation:

$$\text{Tapped Bulk Density (g/mL)} = M/V_f$$

where M = mass in grams, and V_f = the tapped volume in milliliters. The results are shown in **Table 5.7**.

d) Carr's compressibility index:

Procedure: Carr's Compressibility Index, also known as the Carr Index or Carr's index, is a parameter used to quantify the compressibility and flowability of a powdered or granular material. It is calculated from bulk density and tapped bulk density measurements and is expressed as a percentage. The results were shown in the **Table 5.7**.

Calculation:

$$\text{Carr's Index (\%)} = \left(\frac{\text{Tapped Bulk Density} - \text{Bulk Density}}{\text{Tapped Bulk Density}} \right) \times 100$$

Table 4.7: Carr's compressibility index

Carr's index(%)	Properties
5–15	Excellent
12–16	Good
18–25	Fair to passable
26–32	Poor
33–38	Very poor
>40	Very very poor

e) Hausner's ratio:

Procedure: Hausner's Ratio is a parameter used to assess the flowability of powdered or granular materials. It is calculated from bulk density and tapped bulk density measurements and is expressed as a ratio. The results are shown in **Table 5.7**.

Calculation:

$$\text{Hausner's Ratio} = \text{Bulk Density} / \text{Tapped Bulk Density}$$

Table 4.8: Hausner's ratio

Hausner's Ratio	Properties
1.00-1.11	Excellent
1.12-1.18	Good
1.19-1.34	Fair to passable
1.35-1.45	Poor
1.46-1.59	Very poor
>1.60	Very very poor

Evaluation of MH sustain release capsule:

The filled capsules are subjected to various quality control tests such as visual inspection, weight variation, content uniformity, friability, disintegration and dissolution. The following parameters were investigated and the results are shown in **Table 5.10**.

a) Visual Inspection:

- Inspect for various defects, including dirt, scratches, foreign particles, cracks, chips, deformation, different colors or discoloration, blurred or scratched print, coating and embossing defects.
- Ensure the consistency of capsule size. Check the fill level inside the capsules whether they are adequately filled with the medication.
- Shape inspection: collapsed, dent, length, double capping, bent, etc. [85]

b) Weight Variation:

- Ten hard gelatin capsules are usually weighed individually and the contents are removed.
- The emptied shells are individually weighed and the net weight of the contents is calculated by subtracting the weight of the shell from the respective gross weight.
- The content of active ingredient in each capsule may be determined by calculation based on the percent drug content in the formulation. [86]

c) Content Uniformity:

- This test is performed only when the content is specified in the individual monographs and when capsules fail weight variation test. If the weight of capsules is completely filled, no need of this test.
- Unless otherwise stated in the monograph for an individual capsule, the amount of drug substance, determined by assay, is within the range of 85.0% to 115.0 % of the label claim for nine (9) of ten (10) dosage units assayed, with no unit outside the range of 75.0 % to 125.0 % of the labelled drug content.

- Additional tests are prescribed when two or three dosage units are outside of the desired range but within the stated extremes. [87]

d) Disintegration Test:

- The capsules are placed in the basket-rack assembly, which is repeatedly lowered 30 times per minute into a thermostatically controlled bath of fluid at $37 \pm 2^\circ\text{C}$ and observed over the time described in the individual monograph.
- To fully satisfy the test, the capsules disintegrate completely into a soft mass with no firm core and only some fragments of the capsule shell. [88]

e) Dissolution Test:

- The dissolution test for capsules evaluates how well they release the drug substance in a specified medium, contributing to their therapeutic efficacy.
- A cylindrical vessel made of borosilicate glass or other transparent material and a motor with a speed regulator that rotates the basket within the vessel.
- The basket ensures smooth rotation without significant wobble.
- The dissolution medium is typically PB (pH 6.8) and the temperature of the medium should be maintained at 36.5 to 37.5°C . [89]

Release kinetics studies of the optimized formulation

The *invitro* release data of the MHF7 was fitted to various kinetic models (Zero-order, First-order, Higuchi, and Korsmeyer-Peppas models). The best fit was found out to describe the kinetics of drug release. Release kinetics study of various equations was incorporated in the release data of MH F7. Cumulative percent drug released vs. time (zero order rate kinetics)

$$Q = K_0 t$$

Where Q is the fraction of drug release at time t & K_0 is the Zero order release rate constant. A plot of fraction of drug release against time will be linear, if the release obeys Zero order release kinetics. (Unit-concentration/time) Log cumulative percent drug retained vs. time (First order rate kinetics)

$$\text{Log } C = \text{Log } C_0 - Kt$$

$$2.303$$

C_0 is the initial concentration of drug, K is the first order constant and t are time Log cumulative percent drug released vs. square root of time (Higuchi's classical diffusion equation)

$$Q = KHt^{1/2}$$

KH is the Higuchi's square root of time kinetic drug release constant Log of cumulative % release vs log time (Korsmeyer Peppas exponential equation)

$$M_t/M_\infty = Kx^n$$

M_t is the amount of drug released at time t and M_∞ is the amount released at time. The results are shown in 5.5.3.

Table 4.9: Release kinetics study of the optimized formulation

Sl. No.	Model	Graph	Diffusion exponent(n)	Overall solute diffusion mechanism
1.	Zero order	Cumulative release V vs time	0.45	Fickian diffusion
2.	First order	Log Cumulative release V vs time	$0.45 < n < 0.89$	Non Fickian (Anomalous) diffusion
3.	Higuchi model	% Cumulative release V vs $t^{1/2}$	0.89	Case-I transport
4.	Korsmeyer-Peppas model	% CR_t/CR_∞ vs $t^{1/2}$	$n > 0.89$	Super case-II transport

Stability Studies

The MHF7 was subjected for the stability study by placing the sample at $25^\circ\text{C} \pm 2^\circ\text{C}/60\%\text{RH} \pm 5\%$ for three months in the humidity chamber and was examined on 0, 1, 2 and 3 months and checked for changes in physical appearance, disintegration test, dissolution test, weight variation (mg) and % drug content (mg) as per ICH guidelines for the stability testing of new substance and products. The results are shown in 5.5.4.

CHAPTER – 5

RESULTANDDISCUSSION

CHAPTER-5

RESULTANDDISCUSSION

RESULTS OF FORMULATION, INVITRO EVALUATION OF MH SUSTAIN RELEASE CAPSULE:

RESULTS OF PREFORMULATION STUDIES:

Results of physicochemical characterization

a) Results of physical appearance:

The physical appearance of MH was found to be white crystalline powder which meets the criteria as per **IP monograph, 2007** specification.

b) Results of melting point:

The melting point of MH by capillary method was found in the range of 219-223°C and the average of three readings was found to be 220.9°C as shown in **Table** ; which meets the criteria as per **IP monograph, 2007** specification.

Table 5.1 Results of melting point of MH

S.No	Melting point of MH (°C)
1	220.4
2	221.3
3	221.0
Average	220.9

c) Results of solubility studies:

The results of the solubility studies were performed in the selected solvents/media such as distilled water, methanol, ethanol and PB (pH 6.8) are provided in **Table 5.2** based on the solubility data it can be inferred that the solubility in distilled water < methanol < PH (pH 6.8) < ethanol. Procedure followed as per **4.2.1.1.1 c**.

Table 5.2 Results of solubility studies of MH

Solvents/media	Solubility
Distilled water	Freely soluble
Methanol	Freely soluble
Phosphate buffer pH 6.8	soluble
Ethanol	Insoluble

d) Results of Ultraviolet (UV) absorption maximum (λ_{max}):

The spectral scanning was carried out by using PB (pH 6.8) as solvent by using UV-Visible spectrophotometer. The UV-visible spectrum of MH was shown in **Table 5.3** and **Figure 5.1**. The spectra showed a sharp peak at 233 nm. The wavelength provided sensitivity and high repeatability in absorbance values as mentioned by the earlier authors λ_{max} of 233 nm was selected for all further studies.[90]

Table 5.3 Results of determination of λ_{max}

S.no	Solvent	λ_{max}
1	PB (pH 6.8)	233

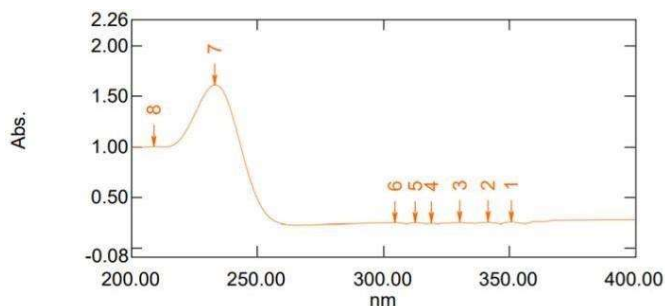


Figure 5.1 Results of UV Spectrum scanning for MH

e) Fourier Transform Infra-Red (FTIR) spectroscopy:

MH was characterized by FTIR; the MH working standard was compared with reference standard of MH with their spectral data from the scanned sample at 4000-400 cm^{-1} . It was observed that the presence of N-H stretching amide, C=O carboxylic acid stretching, C=O amide stretching, C=O ester stretching, and COOH stretching were characteristic peaks of MH which were similar to that of the working sample. MH indicating that both the working standard and reference standard of MH were similar. The FTIR values of MH results were coinciding with the works of earlier authors[91]. The results are shown in the **Figure 5.2(a)(b)** interpretation data of FTIR Spectrum of pure drug was mentioned in the **Table 5.4**

Table 5.4 Interpretation data of FTIR Spectrum of pure drug

Characteristic peak	Standard range (cm^{-1})	MH peaks (cm^{-1})
N-H stretching amide	3500-3310	3367.01
C=O carboxylic acid stretching	1760-1720	1729.83
C=O amide stretching	1681-1613	1621.84
C=O stretching ester	1200-1100	1166.72
COOH	3300-2500	3147.57

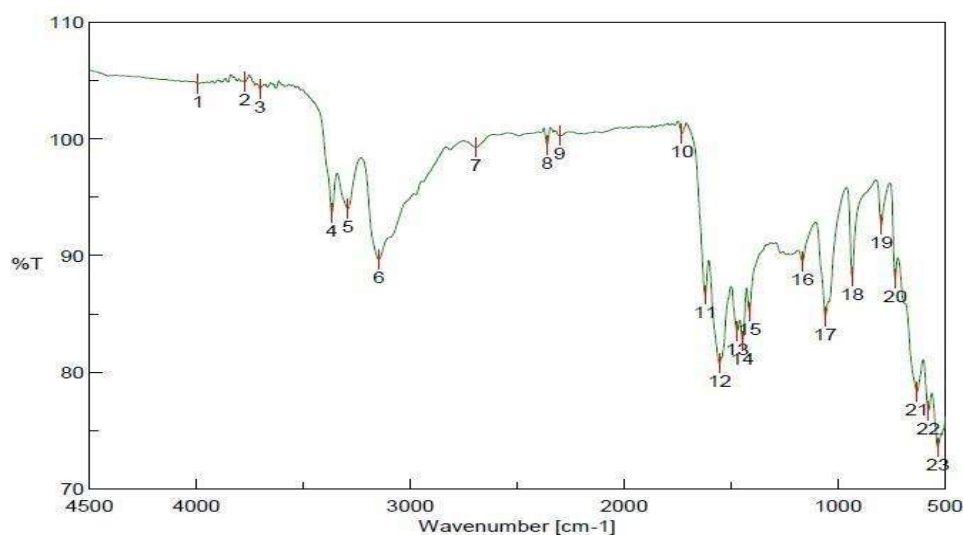


Figure 5.2(a) Results of FTIR of working standard

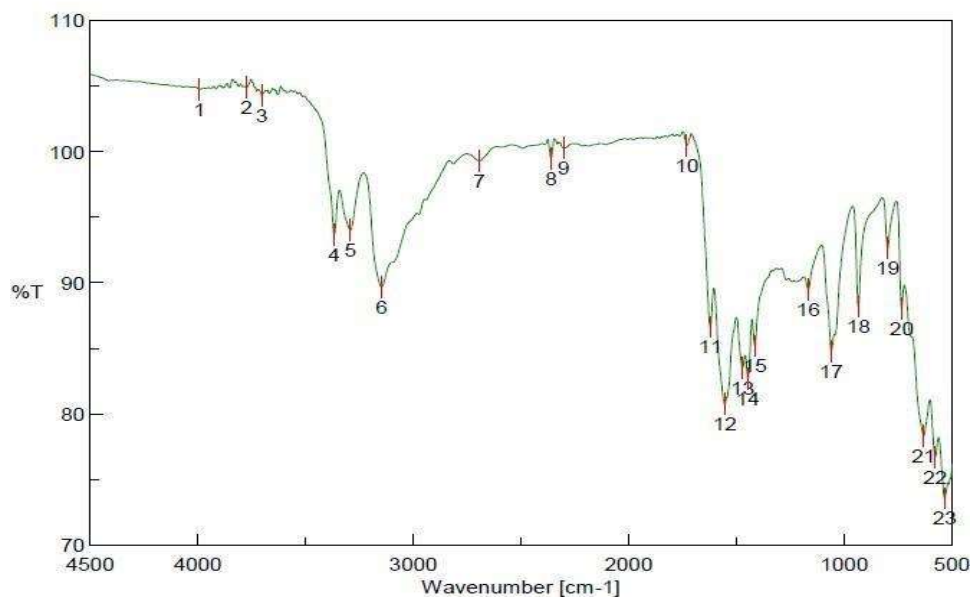


Figure 5.2(b) Results of FTIR of Reference standard

RESULTS OF SELECTION OF EXCIPIENTS IN THE PREFORMULATION STUDIES OF MH:

The selection of the polymers for the preparation of the MH was based on the literature and following the criteria of the earlier authors **YLuo et al., 2021** summarised that Polyvinylpyrrolidone has a notable enhancement in its bioavailability, stability, and modified release rate [92]. **S Lakio et al., 2013** explained that the Magnesium stearate prevents sticking and clumping, acts as a lubricant, and can reduce friction between particles [93]. **Ibrahim SM et al., 2014** explained that Sodium carboxymethylcellulose is very hydrophilic in nature and has a significant affinity for water, making it an effective stabilizer and emulsifier [94]. **Saigal N et al., 2009** were summarised that the Microcrystalline cellulose functions as a flexible binder, binding the constituents precisely and acting as disintegrants [95]. **Ghadermazi R et al., 2019** had explained that the HPMC as a film coating agent, acting as a binder and disintegrant [96].

STUDY OF ANALYTICAL METHOD FOR ESTIMATION OF MH BY UV:

The calibration curve of MH was prepared using PB (pH 6.8), the absorbance values were found in the range of 2-10 µg/ml are provided in **Table 5.5**. The standard calibration curve of MH was shown in **Figure 5.3**. From the least square regression analysis, a linear response was obtained over a range of 2 to 10 µg/ml with a regression coefficient (R^2) value of 0.996. The best-fit linear equation obtained was $y = 0.205x - 0.011$, y is the absorbance (AU) and x is the concentration of MH in µg/ml as reported by *Dange et al.*, [97].

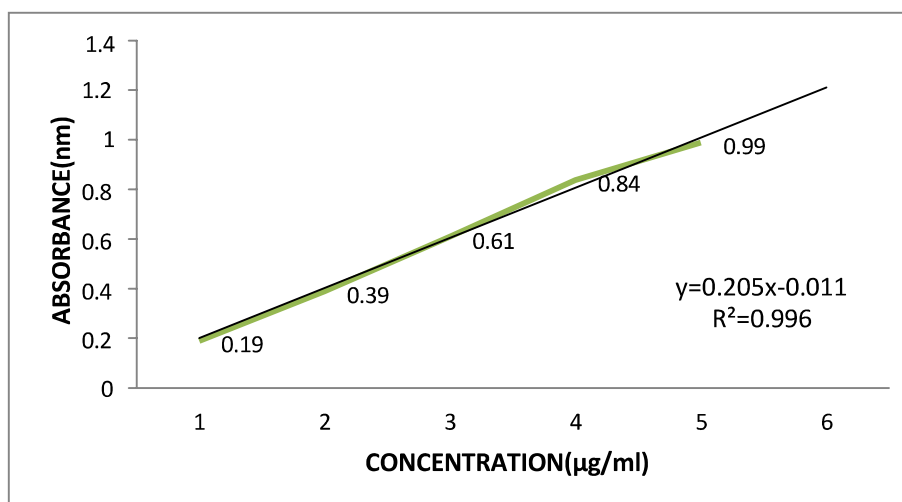


Figure 5.3 Results of standard graph of MH in PB (pH 6.8)

Table 5.5 Results of calibration data of MH in UV spectrophotometer

S.no	Concentration (µg/mL)	Absorbance(nm)
1.	0	0
2.	2	0.19
3.	4	0.39
4.	6	0.61
5.	8	0.84
6.	10	0.99

DRUG-EXCIPIENTS COMPATIBILITY STUDIES BY FTIR:

The compatibility between the MH and excipient was evaluated using FTIR peak matching method. The IR spectra of physical mixture of MH, MCC, HPMCK100, PVP, Na CMC and Magnesium Stearate were superimposable with that of MH, which confirmed the absence of any chemical interaction between the drug with excipients. Further, it can be found that it involves only weak physical bonding interaction of and studied excipients which was confirmed by the shifting of FTIR spectrum of pure drug was recorded and interpretation was done. The original characteristics IR absorption peaks of pure drug (MH) at 3367.1cm^{-1} (N-H stretching amide), 1729.83cm^{-1} (C=O carboxylic acid stretching), 1621.84cm^{-1} (C=O amide stretching), 1166.72cm^{-1} (C=O Stretching ester), 3147.26cm^{-1} (COOH), these peaks are observed in physical mixture spectra, with less intensity. The compatibility studies were coinciding the previous author work of **Panda BP et al., 2018**. [98] The result was shown in the **Table 5.6** and **Figure 5.4 to 5.10**.

Table 5.6 Drug-excipients compatibility studies by FTIR

Characteristic peaks	Frequency cm^{-1}	
	MH	MH+Physical mixture
N-H stretching amide	3367.01	3291.89
C=O carboxylic acid stretching	1729.83	1627.63
C=O amide stretching	1621.84	1561.09
C=O Stretching ester	1166.72	1203.36
COOH	3147.26	2917.77

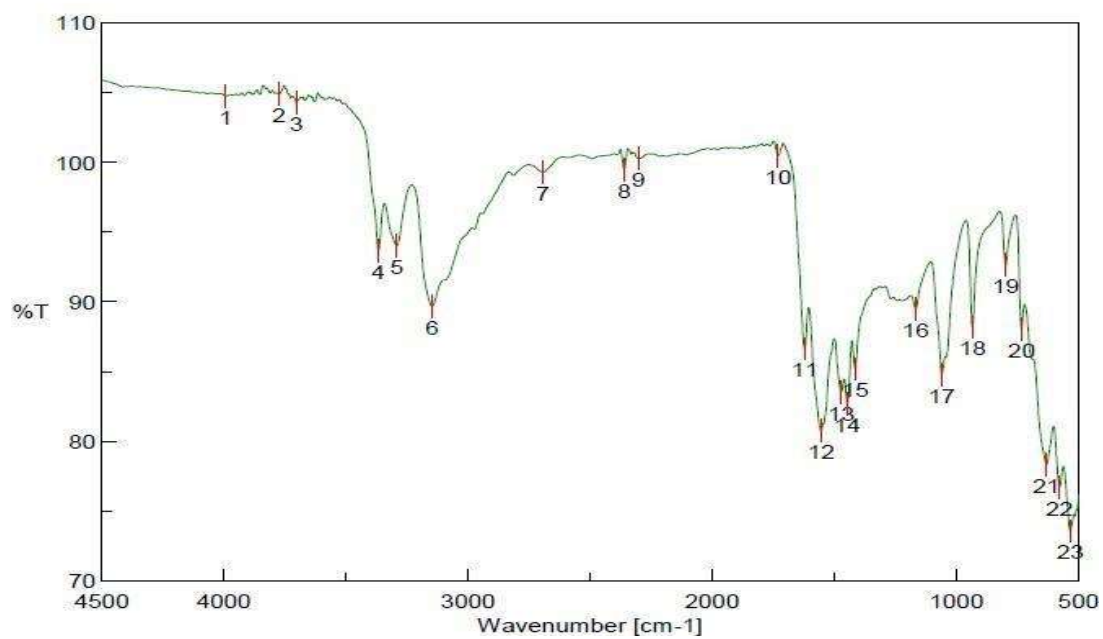


Figure 5.4 Result of FTIR spectra of pure drug MH

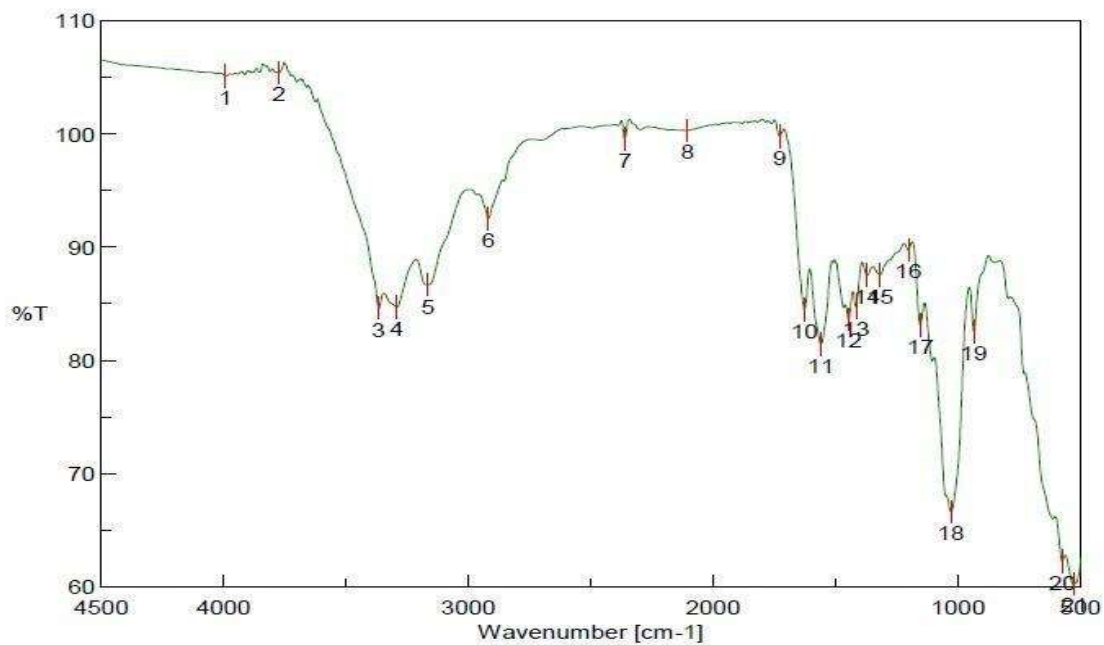


Figure 5.5 Result of FTIR spectra of pure drug MH & physical mixture

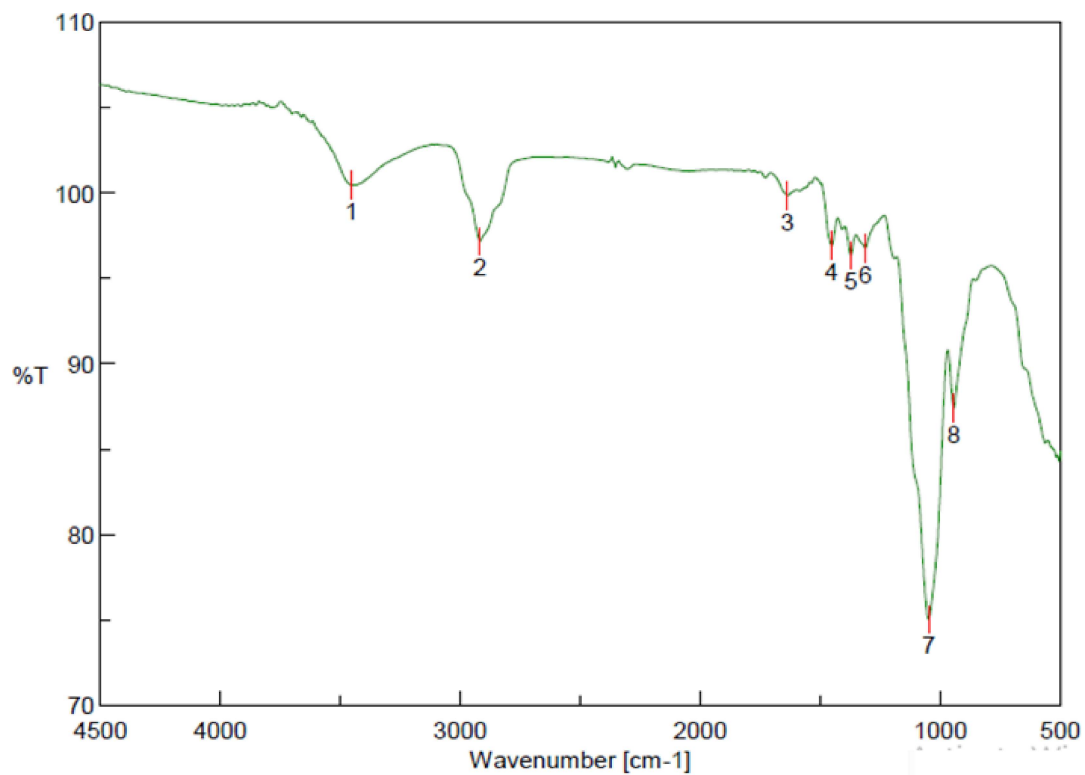


Figure 5.6 Result of FTIR spectra of HPMCK100

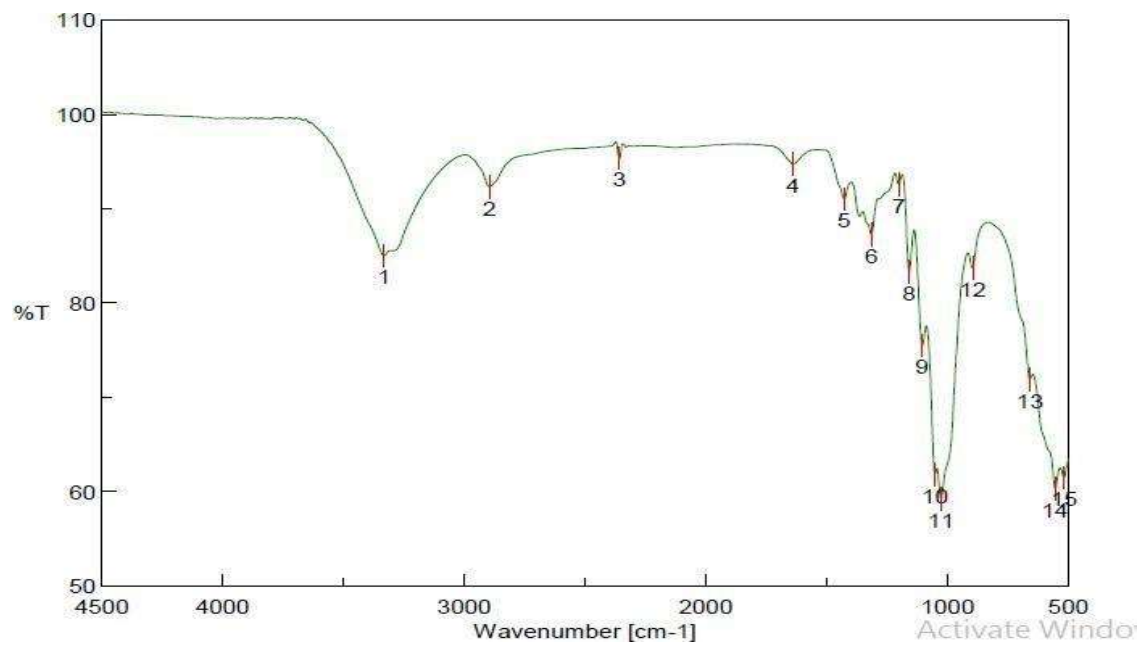


Figure 5.7 Result of FTIR spectra of MCC

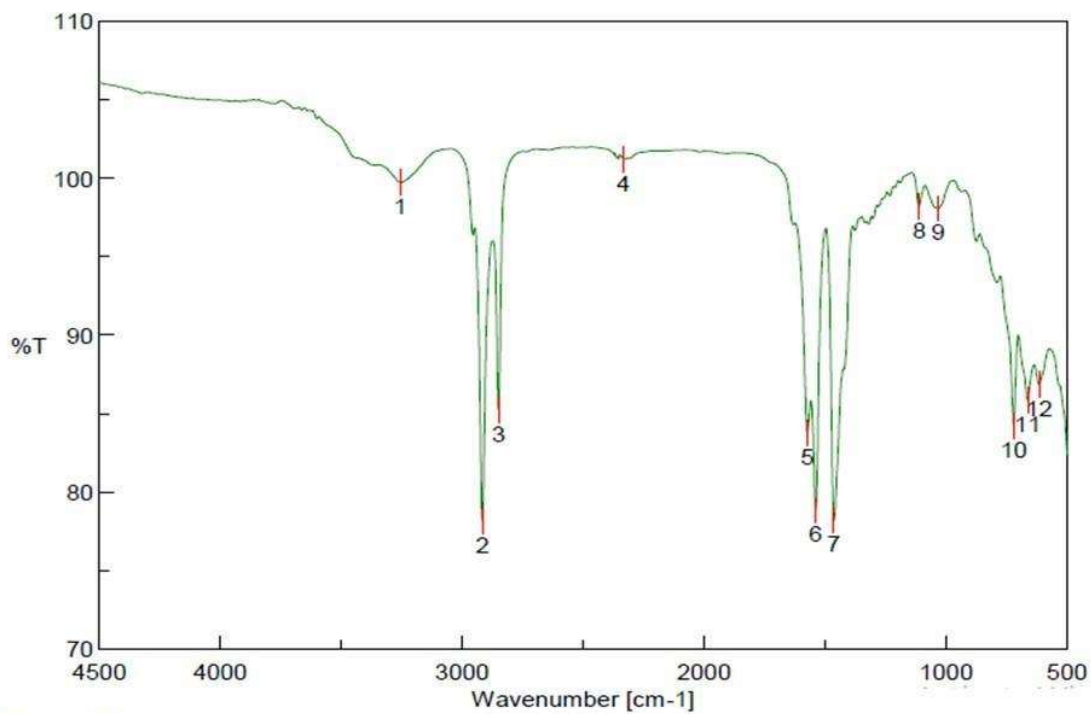


Figure 5.8 Result of FTIR spectra of Magnesium stearate

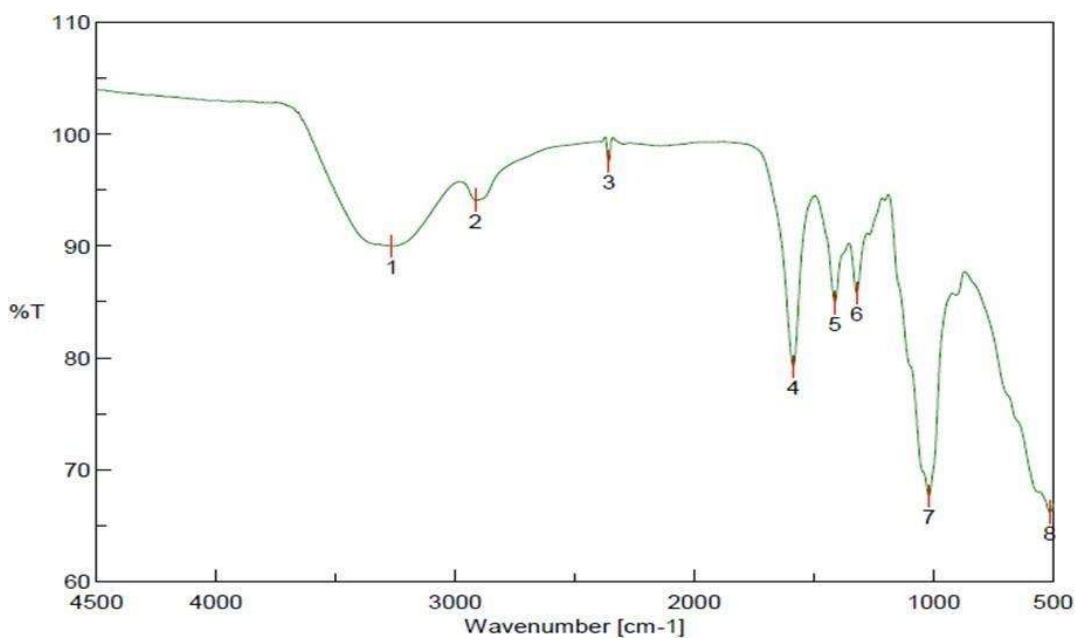


Figure 5.9 Result of FTIR spectra of Sodium CMC

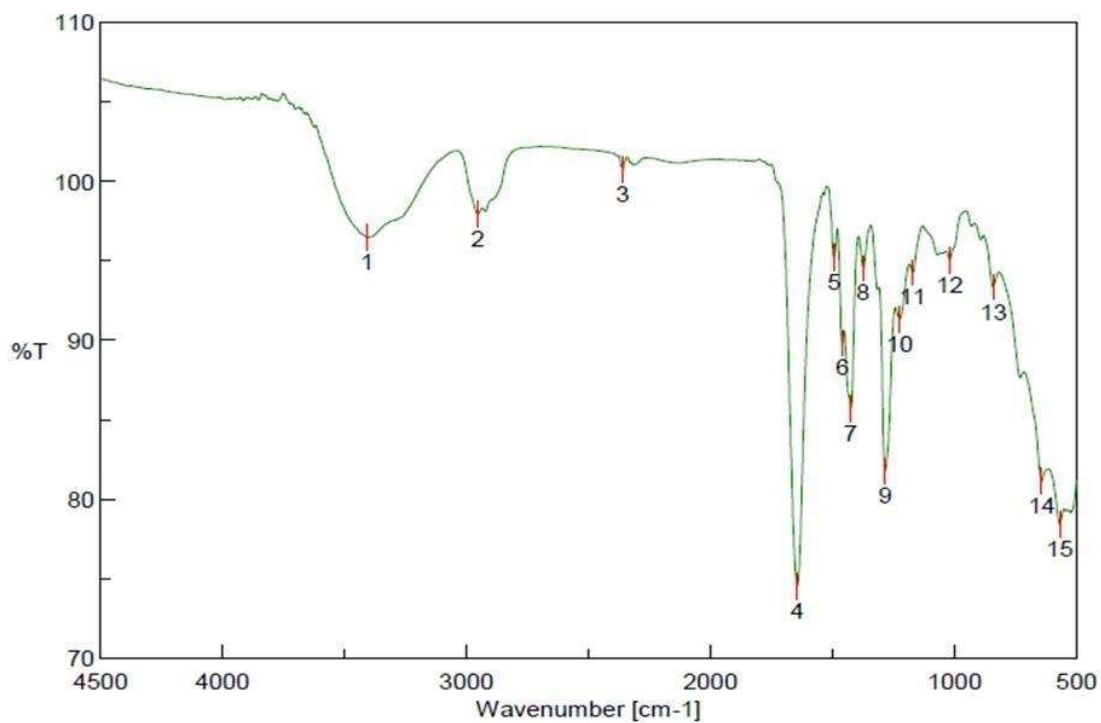


Figure 5.10 Result of FTIR spectra of Polyvinylpyrrolidone

Result of MH sustain release:

In vitro evaluation of MH sustain release blend

The flow properties of formulated MH sustain release blend were characterized by measuring (General chapter, powder flow <1174>, USP 42). The procedure is shown in session 4.2.1.6.1- 4.2.1.6.5



Figure 5.11 Metformin Hydrochloride granules (F7)

- Angle of repose
- Bulk density and tapped density
- Carr's compressibility index
- Hausner's ratio and the results are tabulated in **Table 5.7**,

Table 5.7 Result of Preformulation studies of MH powder blend

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Bulk Density	0.27	0.26	0.25	0.27	0.25	0.25	0.26	0.27	0.26	0.28
Tapped Density	0.33	0.32	0.31	0.33	0.31	0.31	0.32	0.33	0.32	0.35
Carr's compressibility index	18.18	18.75	19.35	18.18	19.35	19.35	18.75	18.18	21.21	20
Hausner's ratio	1.22	1.23	1.29	1.22	1.32	1.24	1.23	1.22	1.23	1.25
Angle of repose	31.20	31.95	32.54	33.07	32.54	33.58	32.24	33.26	32.66	34.19

***In vitro* evaluation of MH sustain release capsule:**

The *in vitro* evaluation study for MH sustain release capsule results are shown in Table 5.8



Figure 5.12 Metformin hydrochloride capsule (F7)

Table 5.8 Evaluation for the formulated capsule:

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Uniformity of content (%)	98.24	102.98	99.21	97.92	101.5	99.71	103.41	97.33	99.01	101.8
Disintegration time (min)	36.2	37.4	37.7	35.1	37.4	34.8	37.9	35.4	36.8	38.2
Dissolution test (%) at 13th hr	99.74	99.12	98.45	98.57	97.09	99.54	96.23	99.27	98.54	97.22
Uniformity of weight	512.45	498.55	547.71	531	487.92	497.20	514.68	487	541.71	480.54

Out of the 10 formulation it was found out that F7 had better sustain release when compared with other formulation. Hence, F7 was subjected to comparative study.

Comparative study:

F7 was taken and the comparative study with two different brand of Metformin hydrochloride 500 mg SR was performed. The results are shown in **Table 5.9** and **Figure 5.12**.

Table 5.9 Comparative study with two different brand of Metformin hydrochloride 500 mg SR

Time(min)	F7(%)	Brand1(%)	Brand2(%)
5	0.45	1.87	0.97
10	3.46	5.89	1.54
15	5.51	6.74	4.75
30	11.76	19.75	18.54
60	12.61	28.48	19.89
90	16.64	32.07	20.61
120	22.13	33.72	34.75
180	37.42	46.30	42.46
240	40.87	50.18	47.94
300	47.64	57.31	58.42
360	54.78	60.77	65.48
420	67.56	77.05	80.33
480	71.97	83.68	88.04
540	77.50	89.	96.08

600	85.46	99.75	98.94
660	96.23		
720	99.10		
780	99.21		

Table 5.9 Comparative study with two different brands of Metformin hydrochloride 500 mg SR

Result of release kinetic studies of the optimized formulation:

The *in vitro* release data for F7 was fitted to various models, the best fit was found to be first order rate kinetics.

Result of stability studies:

The descriptions of the F7 at 0, 1, 2, and 3 months were checked and results are shown in **Table 5.10**. During the stability studies, there was no significant change.

Table 5.10 Result of the Stability studies for F7 on storage at (25°C ± 2°C and 60% ± 5% RH)

Description	Storage conditions (25°C ± 2°C / 60% RH ± 5%)			
	Initial	After 1 month	After 2 months	After 3 months
Physical appearance	Violet and pink color capsule	Violet and pink color capsule	Violet and pink color capsule	Violet and pink color capsule
Weight variation (mg)	497.20	489.20	497	498.12
Disintegration time (min)	37.9	37.9	36.45	36.87
Dissolution test (%) Abs. at 13th hr	99.21	98.90	98.85	99.13
Uniformity of content (%)	103.41	103.17	101.56	101.32

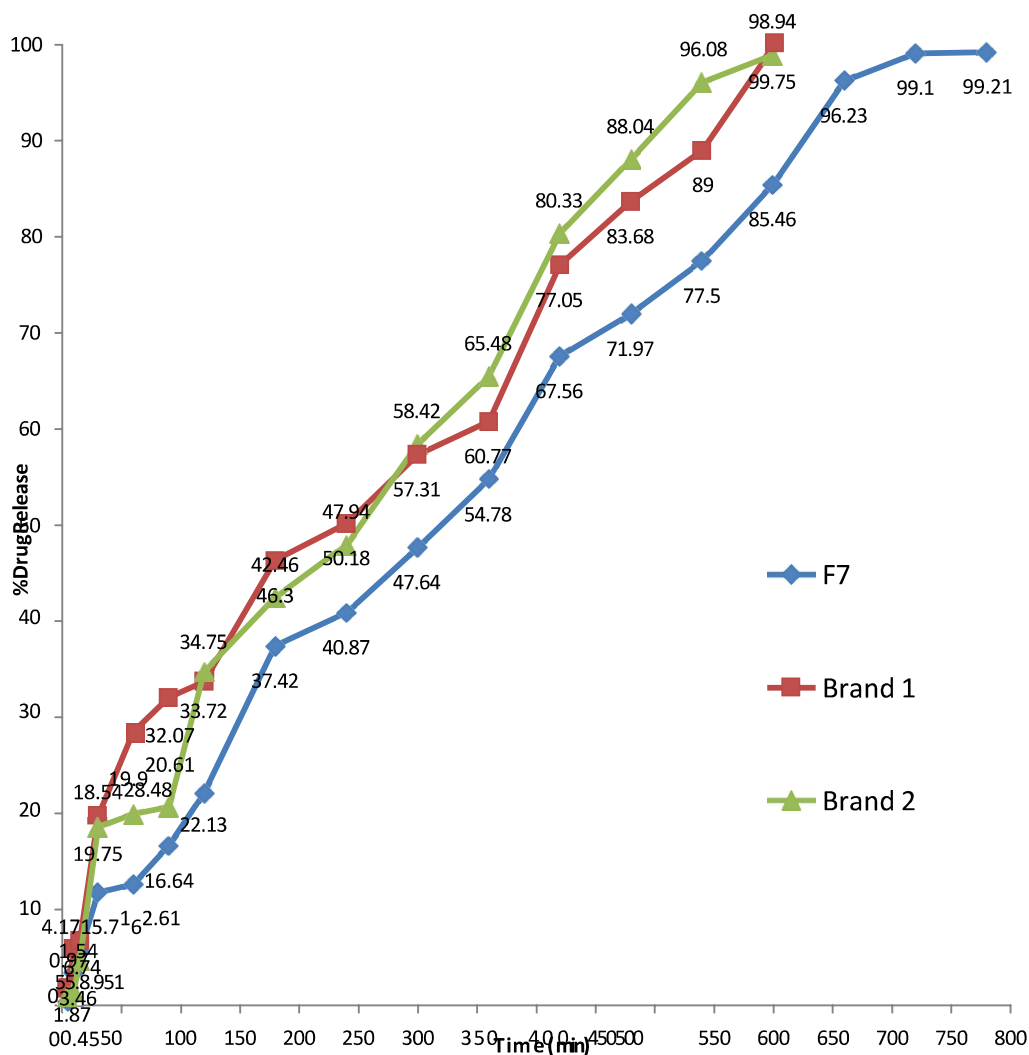


Figure 5.13 Comparative study with two different brands of Metformin hydrochloride 500 mg SR

This dissolution study demonstrates F7, exhibit a sustained release pattern, from the initial to the end of 13th hr at a constant rate. Drug release may be attributed to presence the combination of Starch, PVPK30, HPMC, MCC, Magnesium stearate and NaCMC polymers which may tend to sustained and extended the drug release up to 13th hr. When compared with marketed MH tablet it showed that brand 1 had release upto 10th hr, brand 2 upto 11th hr and our formulation F7 had a release upto 13th hr.

CHAPTER-6

**SUMMARY, CONCLUSION AND
FUTURESCOPEOFRESEARCH**

CHAPTER-6

SUMMARY, CONCLUSION AND FUTURE SCOPE OF RESEARCH

SUMMARY:

The human quest for illness prevention and treatment has given rise to innovations in new formulations for pharmaceutical research. To be effective in clinical therapy, the medicine must comply with stringent regulatory standards. In addition to a medication's inherent physiochemical properties, the design and quality parameters of the drug product would be sold in would also determine the drug's capacity to fulfill this requirement. Effective and successful therapy is dependent not only on drug safety and efficacy, but also on a variety of other aspects, including the best drug delivery mechanism.

Conventional dosage form of MH is released immediately after ingestion, providing a rapid onset of action. In contrast, sustained release capsules release the medication gradually over an extended period, allowing for a more prolonged and controlled release of the drug by using suitable polymers and lubricants, which can lead to a smoother blood glucose-lowering effect and potentially fewer side effects.

The title of the current the thesis is "Formulation and Evaluation of Metformin hydrochloride capsule" is divided into six chapter. Chapter 1- Introduction, Chapter 2- Literature review, Chapter 3 - Aim and Objectives, Chapter 4 - Materials and Experimental methods, Chapter 5 - Result and discussion, Chapter 6 - Summary, Conclusion and Future scope of research.

CHAPTER 1 – MH stands as a widely prescribed and effective medication for managing type 2 diabetes. Its ability to improve insulin sensitivity, reduce glucose production in the liver, and enhance peripheral glucose uptake contributes to its positive impact on glycemic control. Despite potential side effects, the overall safety profile and established efficacy make metformin a cornerstone in the treatment of type 2 diabetes.

CHAPTER 2 - The literature review underscores the consistent and robust evidence supporting MH as a primary pharmacological intervention for type 2 diabetes. The

literature review had been taken for ten years. Numerous studies highlight its effectiveness in lowering blood glucose levels, improving insulin sensitivity, and reducing cardiovascular risk factors. While acknowledging variations in individual responses and some reported side effects, the overall body of research reinforces MH's pivotal role in the management of type 2 diabetes.

CHAPTER 3 – Brief about the aim and objective of the formulation and evaluation of MH sustained release capsule target have been accomplished. *In vitro* comparative studies and the objectives like preformulation studies of raw material, granules, formulation, its evaluation and comparative study with market product and stability studies are performed.

CHAPTER 4 - The experimental study on MH sustained release capsules yields valuable insights into the drug's formulation and its impact on the treatment of type 2 diabetes. This dissolution study demonstrates that formulation 7 exhibits a sustained release pattern, from the initial to the end of 13 hours at a constant rate. Drug release may be attributed to the presence of Starch, PVP K30, HPMC K100, MCC, Magnesium stearate, and NaCMC polymers which may tend to sustain and extend the drug release. The findings contribute to our understanding of the capsule's efficacy, bioavailability, and potential benefits in terms of glycemic control. While acknowledging the limitations of any experimental study, the results provide a foundation for further exploration and refinement of metformin formulations, potentially leading to enhanced therapeutic outcomes and improved patient experiences in the management of type 2 diabetes.

CHAPTER 5 - The *in vitro* study of MH sustained release capsules provides valuable insights into the formulation's dissolution characteristics and release profile. And the overall formulation resulted that F7 had better sustained release. The observed sustained release of metformin suggests potential benefits in achieving prolonged therapeutic effects. However, it's essential to acknowledge that *in vitro* studies have limitations and may not fully replicate the complexities of *in vivo* conditions.

Further research, including *in vivo* studies and clinical trials, is imperative to validate these findings and ascertain the practical implications of MH sustained release capsules in real world therapeutic settings.

CHAPTER 6—Describe the summary, conclusion and future scope of research work of Formulation and Evaluation of MH capsules.

CONCLUSION:

India is home to 7.7 million diabetes, making its second highest in the world. The formulation and evaluation of MH sustained release capsules have shown positive outcomes. The meticulous formulation process has resulted in a controlled release product, as evidenced by thorough evaluation criteria such as stability, dissolution characteristics. These findings suggest the potential of the sustained release capsule to enhance therapeutic outcomes and patient adherence in the context of diabetes treatment. Further research and clinical studies may be warranted to validate the long-term effectiveness and real-world application of this formulation.

FUTURE SCOPE OF RESEARCH:

1. Optimization of Formulation to enhance its efficiency, ensuring sustained release over extended periods with minimal fluctuations in drug levels.
2. To perform *in vivo* study for the formulated capsule.
3. In-depth investigations into the biocompatibility and long-term safety profile of the sustained release capsule to address concerns related to potential side effects and patient tolerance.
4. Developing the scale-up of prepared capsule formulation.
5. Exploring personalized medicine approaches by tailoring dosage regimens based on individual patient characteristics, aiming for optimized therapeutic responses.

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Metformin hydrochloride: The most prescribed treatment for type II diabetes - gets banned

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Abstract

Metformin hydrochloride (MH) is synthesis of N, N-dimethylguanidine medicament which is used for the treat of type-II diabetes which was discovered by Emil Werner and James Bell, which belongs to BCS class III. MH is chosen first-line oral blood glucose-lowering medication for the treatment of type-II diabetes, almost around 120 million patients are using worldwide. It works by decreasing the hepatic glucose production through a mild inhibition of mitochondrial respiration chain complex. MH which has been further tested and also proven that it can be used for various treatments such as, weight loss, improving fertility, slow the growth of tumour, anti-malaria, and few others. MH is synthesis from Galega officinalis which is a perennial plant that blooms in the summer and is native to most temperate areas. In this study, complete information about the drug history, drug profile, pharmacokinetic, drug interaction, clinical symptoms, advantages & disadvantages of MH and reason why its getting banned has been explained in detail.

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INTRODUCTION

The term diabetes mellitus is derived from the Greek word 'diabetes', which means 'to pass through', and the Latin word 'mellitus', which means 'sweetened with honey'. Diabetes mellitus is a long-term and diverse metabolic disorder with a complicated cause. It is marked by high blood

sugar levels or hypoglycaemia, which comes from problems in either insulin production or insulin action or both [1]. Furthermore, there were other kinds, or classes, of drugs that reduced blood glucose, or blood sugar, in various ways. Non-insulin treatments include metformin, alpha-glucosidase inhibitors, bile acid sequestrants (BASs), dopamine-2 agonists, and DPP-4 inhibitors (gliptins), which are taken orally and others are injected.

Diabetes mellitus (DM)

Diabetes mellitus (DM) is a metabolic disorder in which the body does not create enough insulin or does not respond adequately to insulin, resulting in abnormally high blood sugar (glucose) levels.

Diabetes is a major source of mortality as well as morbidity, albeit these results are not directly related to the condition. On the contrary, they are

associated with conditions that arise from long-term diabetes mellitus. These include disorders of the nerves as well as disorders of the large and small blood vessels, such as microvascular illnesses, which include renal and retinal vascular diseases, coronary heart disease, and peripheral arterial disease [2].

Causes

The pancreatic islets of Langerhans are cell clusters that house beta cells, which secrete the hormone insulin. Its function in the body is to cause cells to absorb glucose so they may use this sugar, which provides energy. Diabetes patients may have malfunctioning beta cells, resulting in decreased insulin secretion, or their muscle and adipose cells may be insulin resistant, resulting in a reduced ability of these cells to take up and utilize glucose [3]. In both circumstances, blood glucose levels rise, resulting in hyperglycemia. Excess glucose is eliminated in the urine if it accumulates in the blood. Because more glucose is excreted in the urine, more water is expelled with it, resulting in an increase in urinary volume, frequency of urination, and thirst.

The role of glucose

Glucose, a type of sugar, is the primary source of energy for cells in muscles and other tissues.

- Food and the liver are the main sources of glucose.
- Insulin helps sugar to enter the cells through the bloodstream.
- The liver can store or produce glucose depending on the body's needs [4].

Botanical background

Galega officinalis, commonly known as galega or goat's-rue, as it boosts breast milk production, which is why it's known as 'Goat's Rue,' because young goat moms eat it and flourish. Is an herbaceous plant in the subfamily Faboideae of the legume family Fabaceae. It is native to parts of northern Africa, western Asia and Europe, but is widely cultivated and naturalised elsewhere [5]. The plant has been extensively cultivated as a forage crop, an ornamental, a bee plant, and as green manure. Herbaceous perennial growing to 1.2 m by 0.8 m at a fast rate. It is in flower from June to July, and the seeds ripen in August. The flowers are hermaphrodite (have both male and

female organs) and are pollinated by insects. It can fix Nitrogen. Suitable for: light (sandy), medium (loamy) and heavy (clay) soils and can grow in nutritionally poor soil. Suitable pH: acid, neutral and basic (alkaline) soils. It can grow in semi-shade (light woodland) or no shade. It prefers moist soil. The flowering aerial parts of galega (*Galega herba*) were used in the past to alleviate the polyuria associated with long-term hyperglycemia, but also to treat many other conditions from tuberculosis, bubonic plague, and malignant fevers to epilepsy, helminthiasis, and various infectious diseases [6].



Figure 1: *Galega officinalis*

Characteristic [7]

- Ground-based environment.
- The flower petals range in color from blue and purple to shades of pink, red, and white.
- The leaves exhibit a compound structure, composed of two or more distinct leaflets.
- The leaves are arranged alternately, with a single leaf per node along the stem.
- The leaf blade has an entire edge, devoid of teeth or lobes.
- The flower displays bilateral symmetry, with only one way to evenly divide it.
- The flower possesses a total of five petals, sepals, or tepals, or alternatively, it has a count of four.
- Either the petals or sepals are fused, forming a cup or tube structure.
- There are a total of 10 stamens.
- The fruit is of a dry nature and undergoes splitting upon reaching maturity.
- The length of the fruit ranges from 30 to 50 mm.

Taxonomical classification

Around 13th compound were isolated from *Galega officinalis* Linn. Among which the most common identified compounds are flavonoids (0.0972%) and their broad classification are listed in Table 1.

Table 1 Taxonomical classification [8]

Biological name	<i>Galega officinalis</i>
kingdom	plantae
class	Dicotyledons
family	fabaceae
subfamily	faboideae
order	fabales
genus	Galega
Common name	Galega, goat's-rue, Milkpea, French Lilac
Distribution	North Africa, Pakistan, South America, Turkey and New Zealand

Pharmacokinetics**Absorption**

- MH is given orally at a dosage of 500 mg, either twice daily or three times daily, with a total daily dose not exceeding 2,550 mg or around 35 mg per kilogram of body weight.
- The onset of action is approximately 1.5 hours, and the half-life in circulation ranges from 1.5 to 4.9 hours.
- Primarily absorbed in the upper segment of the small intestine, specifically in the jejunum [11].

Bioavailability

Approximately 50-60% of the substance is bioavailable.

Research involving varying MH tablet doses (ranging from 500 mg to 1500 mg and 850 mg to 2550 mg) indicates that as the dose increases, the drug's absorption efficiency diminishes. This phenomenon has a more pronounced impact on the drug's effects compared to its elimination from the body.

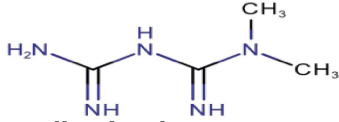
There are also various factors that affect absorption and bioavailability of MH such as

Dose, Formulation, Age, Bodyweight, Kidney function and Food intake.

Table 2 History of MH

Year	Inventions
1653	Culpeper's Herbal touted <i>G. officinalis</i> for worms, epilepsy, fever, pestilence, highlighting weight loss and anticoagulant benefits in treating various ailments.
1840-1860	MH's chemical roots align with its herbal origins, tracing back to the synthesis of guanidine by Strecker
1870	It was discovered that guanidine had the ability to lower blood glucose levels.
1879	Rathke's process involves combining two guanidines to form a biguanide.
1922	MH was first described by Emil Werner and James Bell. They synthesised dimethyl guanids.
1940	The creation of an antimalarial agent, proguanil (paludrine), involves the independent development of guanidine.
1949	Proguanil underwent modification to metformin in the search for guanidine-based antimalarials. Garcia's tests in the Philippines revealed its antimalarial activity, leading to the development of MH, repurposed as the anti-influenza agent named flumamine.
1956	Jean Sterne played a crucial role in turning the potential antihyperglycemic effects of MH into a therapeutic reality.
1957	MH was employed for diabetes treatment and subsequently underwent surveillance.
1958	Dr. Gerry Daniel introduced MH to the United States, and Aron Laboratories was later acquired by Lipha Pharmaceuticals, now known as Merck [9].

Table3DrugProfile[10]

GENERICNAME	Metforminhydrochloride
BRANDNAME	ActoplusMet, Avandamet,Fortamet
USES	Antihyperglycemicdrug
CHEMICAL FORMULA	C ₄ H ₁₁ N ₅
STRUCTURE	
TYPE	Smallmolecule
MOLECULAR WEIGHT	129.16g/mol
SYNONYMS	N, N- dimethylimidodicarbonimidic diamide 1,1-Dimethylbiguanide Metiguanide
CLASS	Guanides (Biguanides)
IUPAC NAME	3-(diaminomethylidene)- 1,1dimethylguanidine
BOILING POINT	224.1°C at 760 mmHg
MELTING POINT	223-226 °C
SOLUBILITY	Freelysoluble
SIDE EFFECTS	Physicalweakness,myalgia, nausea,vomiting,diarrhoea, flatulence, hypoglycemia, upper respiratory tract infection, abdominal pain, lactic acidosis, chest discomfort, chills and dizziness, constipation, heartburn, bloating.
CLEARANCE	Therenalclearanceexceeds creatinine clearance by approximately 3.5 times, signifying that the primary pathwayforMHelimination isthroughtubularsecretion.
FOOD INTERACTIONS	Avoid alcohol. Takewithfood.Foodreduces irritation.

Distribution

Organic cation transporters facilitate the widespread distribution of the drug into various body tissues, including the intestine, liver, and kidney. MH doesn't attach much to blood proteins like sulfonylureas do. It tends to gather in red

blood cells over time. When people take regular MH doses, the amount of MH in their blood becomes steady within a day or two and is usually quite low, around less than 1 microgram per millilitres. Even with higher doses, like in clinical trials, the most MH in the blood doesn't go above 5 micrograms per millilitres. Following a single oral dose of 850 mg MH, the apparent volume of distribution (V/F) averaged 654 ± 358 L [11].

- It doesn't stick much to blood proteins, so it moves around freely.
- It gathers in organs like the liver and kidneys, where it works.
- MH doesn't get distributed to the brain very much because of its properties.
- MH can cross the placenta during pregnancy, but it does not accumulate significantly in the fetal tissues. But still a little amount is distributed into breast milk, but not too much.
- The places it goes affect how it leaves the body, mainly through the kidneys.

Metabolism

MH undergoes minimal metabolism in the body, which means it is not extensively broken down into different substances. Instead, the main route of excretion is through the kidneys.

Elimination

The primary way MH is eliminated from the body is through active tubular secretion in the kidneys. MH is removed from the body mainly through the kidneys, and certain proteins called transporters help move it around. These transporters, like OCT1 and OCT3, are found in liver cells and are crucial for MH uptake into the liver. Another transporter, MATE1, is important for moving MH out of the liver and kidneys. In the kidneys, transporters like OCT2, MATE1, and MATE2-K help get MH from the blood into the kidney cells and then into the urine. While MH isn't changed in the liver, its movement can be affected by other drugs that interfere with these transporters. A recent study indicates a potential drug interaction between MH and certain tyrosine kinase inhibitors (e.g., imatinib, nilotinib, gefitinib, erlotinib). This could impact MH's effectiveness, toxicity, and overall clinical outcomes [12].

Mechanism of action [14]

The organic cation transporter-1 (OCT1) took up MH and transported it into the hepatocyte. MH's ionization and positive charge in the cell is due to the difference in hepatocyte pH and pKa, which causes it to accumulate in the cells. Furthermore, there are concentrations up to 1000 times higher in the mitochondria than in the extracellular medium. The membrane potential difference between the plasma membrane and the inner mitochondrial membrane, which has a positive charge on the outside, affects metformin's capacity to enter the mitochondria. Once inside, metformin interferes with complex I, causing ATP synthesis to decrease and AMP and ADP levels to rise. Inhibiting the respiratory chain has the consequence of increasing the ratio of ADP to ATP, which as seen in experimental cells involved in this process, slightly impairs the process of gluconeogenesis. Due to its high energy requirement, it also prevents hepatocytes from effectively synthesizing gluconeogenesis. Changes in the ratios of NAD⁺ to NADH are another effect that have a detrimental impact on gluconeogenesis.

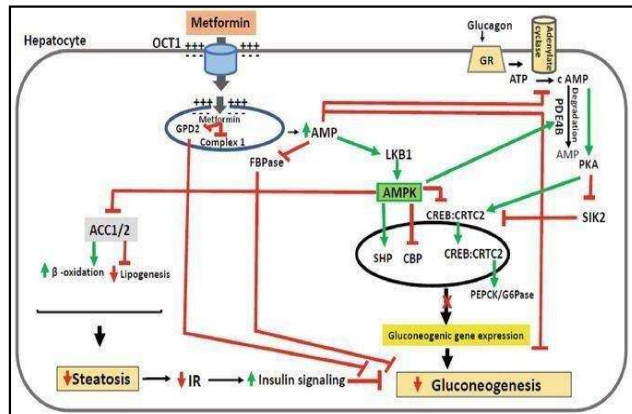


Figure 2: MH mechanism of action

Clinical symptoms of MH

Gastrointestinal distress can lead to significant discomfort. This discomfort is most frequently experienced during the initial administration of MH or when the dosage is raised.

Starting at a lower dosage (1.0 to 1.7 g/day) and gradually increasing it can often prevent discomfort, although approximately 5% of individuals may still find metformin intolerable even at lower doses.

Utilizing slow or extended-release formulations may enhance tolerability.

Prolonged use of MH has been linked to elevated homocysteine levels and vitamin B12 malabsorption.

Increased doses and prolonged usage are correlated with a higher likelihood of vitamin B12 deficiency [1].5

Overdose leads to

An overdose of MH typically manifests with symptoms such as vomiting, diarrhea, abdominal pain, tachycardia, drowsiness, and, in rare cases, hypoglycemia or hyperglycemia. Managing metformin overdose is primarily supportive, as there is no specific antidote identified. Severe overdoses may require extracorporeal treatments.

Extracorporeal treatments are recommended in severe cases due to metformin's low molecular weight and absence of plasma protein binding. These methods effectively eliminate metformin from the blood plasma, preventing excessive lactate production.

Monitoring metformin levels in blood, plasma, or serum is useful for therapy management, confirming poisoning diagnoses, or aiding forensic death investigations.

Normal blood or plasma metformin concentrations range from 1 to 4 mg/L in individuals receiving therapeutic doses, 40 to 120 mg/L in cases of acute overdose, and 80 to 200 mg/L in fatalities.

Although a massive metformin overdose heightens the risk of metformin-associated lactic acidosis, even substantial doses often do not result in fatality [16].

Drug interaction

The H₂-receptor antagonist cimetidine elevates MH plasma concentration by diminishing MH clearance through renal processes. Additionally, MH interacts with anticholinergic medications, influencing gastric motility.

Anticholinergic drugs, by decreasing gastric motility, extend the duration that drugs remain in the gastrointestinal tract.

This delay may result in a greater absorption of MH when an anticholinergic drug is present, consequently raising the plasma concentration of MH and amplifying the potential for adverse effects [17].

Medicinal uses of MH

MH was the first-choice oral treatment for type 2 diabetes and its various medicinal uses are shown in figure 3.

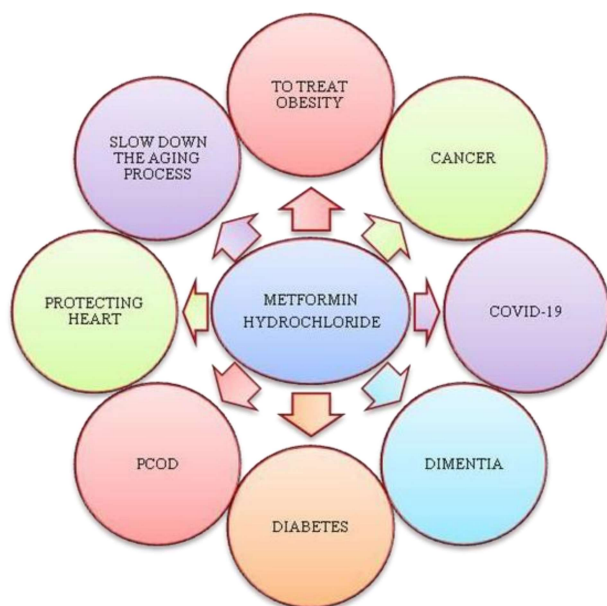


Figure 3: Medicinal uses of MH Advantages of MH [18]

- MH can do much more than treat diabetes.
- MH can help with weight loss and reduce the size of your waist.
- MH can also improve fertility.
- It even helps people with certain medical conditions live longer.
- There's evidence that MH can help treat obesity and obesity-related conditions, like metabolic syndrome
- MH can slow some tumor growth and stop certain tumors from forming.

Disadvantage of MH [19]

- Feeling queasy
- Sickness (vomiting)
- Takes small, frequent sips of water or squash to avoid dehydration.
- Diarrhea.
- Stomach discomfort

- Appetite loss.
- A sensation of metallic taste in the tongue.

It's important to note that some side effects of MH may arise, typically not requiring immediate medical attention. These effects often diminish as the body adjusts to the medication. Healthcare professionals can offer guidance on preventive measures or ways to alleviate these side effects, such as addressing gastrointestinal irritation, impaired renal function, impaired hepatic function, pharmacologically treated congestive heart failure (CHF) and alcoholism.

Why MH is being recalled

According to the average rating out of 100%, 55% have given positive feedback and 45% have given negative feedback. And few documents show that MH contains N-nitrosodimethylamine which may promote cancer. Hence FDA has announced that to recall MH from market (July 2020). The maximum limit of N-nitrosodimethylamine can be consumed is 96 ng/day. But study shows that MH has excess amount, so it was banned [20].

CONCLUSION

Sixty years after its introduction in diabetes treatment, MH has become the most prescribed glucose-lowering medicine worldwide with the potential for further therapeutic applications. MH as the first-choice treatment for obese patients with type 2 diabetes. The drug's anti-atherosclerotic and cardioprotective effects have been confirmed in prospective and retrospective studies, but it took another decade for these findings to be translated into official recommendations. In 2012, diabetes experts in the USA and Europe declared that MH is the drug of the first choice for all patients with type 2 diabetes. Furthermore, MH was banned by FDA, but still it is being continued to use for anti-diabetic medication which is recommended by American Diabetes Association.

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