FORMULATION AND EVALUATION OF BILAYER MATRIX TABLET OF GLIBENCLAMIDE AND METFORMIN

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ABSTRACT

The primary goal of our work is to produce a sustained release preparation with more uniform maintenance of blood plasma active concentration. Thus, potentially avoiding undesirable peaks and troughs associated with multiple immediate release preparations, and to reduce frequent dosing interval of the drug. Therefore, it is an object to produce a bilayer tablet with two different release profiles with glibenclamide as immediate release layer and metformin hydrochloride as a sustain release layer to provide a desired pharmacokinetic and therapeutic action. Rationale for combination of glibenclamide with metformin hydrochloride, suggests the use of combined formulations of medicaments capable of finding a remedy for both the deficiency in insulin secretion and the insulin resistance condition. Reduces the incidence of secondary failure of mono therapy and also increases the patient compliance by administering the drug in a single dosage form 5mg of glibenclamide and 500mg of metformin hydrochloride is suitable for the treatment of type II diabetes mellitus at any time of the progression of the disease, from its onset to most severe cases. In sudden occurrence of hyperglycemia, a dose of 5mg of glibenclamide is required to reduce the hyperglycemic effect and 500mg of metformin hydrochloride is required to sustain the normal glycemic level for the type II diabetic patient.

KEYWORDS: Bilayer Matrix Tablet, Glibenclamide, Metformin, Diabetes mellitus.

1. INTRODUCTION

In recent years, a growing interest has been developed in designing drug delivery systems that include an immediate release (IR) component to controlled release (CR) dosages. The
addition of an IR component allows one to design delivery system shaving optimal pharmacokinetic profiles and enables the combination of different drugs thereby improving patient compliance. Multi-layer tablet dosage forms were designed for variety of reasons; to control the delivery rate of either single or two different active pharmaceutical ingredient(s) (API), to separate incompatible APIs from each other, to control the release of API from one layer by utilizing the functional property of the other layer to modify the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release, to administer fixed dose combinations of different APIs, prolong the drug product life cycle, fabricate novel drug delivery systems. A relatively constant plasma level of a drug is often preferred to maintain the drug concentration within the therapeutic window. However, it is difficult to achieve, especially for once-daily dosage forms, partly because the environment for drug diffusion and/or absorption varies along the gastrointestinal (GI) tract. On the basis of these considerations, we have proposed a bilayer tablet, in which the one layer is formulated to obtain immediate release of the drug, with the aim of reaching a high serum concentration in a short period of time. The second layer is a controlled release hydrophilic matrix, which is designed to maintain an effective plasma level for a prolonged period of time. The pharmacokinetic advantage relies on the fact that drug release from fast releasing layer leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining layer. They are preferred for the following reasons: to co-administer two different drugs in the same dosage form, to minimize physical and chemical incompatibilities, for staged drug release, IR and CR in the same tablet for chronic condition requiring repeated dosing.

In the present study a combination drug therapy is recommended for treatment of diabetes to allow medications of different mechanism of action to complement each other and together effectively lower blood glucose at lower than maximum doses of each. The rational for combination therapy is to encourage the use of lower doses of drug to reduce the patient’s blood glucose, minimize dose dependent side effects and adverse reactions.

**Diabetes Mellitus**

Diabetes mellitus (DM)\(^2\) or simply diabetes is a group of metabolic diseases in which a person has high blood sugar, either because the pancreas does not produce enough insulin, or because cells do not respond to the insulin that is produced. This high blood sugar produces
symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger).

**Diabetes mellitus is classified into four broad categories**

- Type 1
- Type 2
- Gestational Diabetes
- Other Specific Types

The "other specific types" are a collection of a few dozen individual causes. The term "diabetes", without qualification, usually refers to diabetes mellitus. The rare disease diabetes insipidus has similar symptoms as diabetes mellitus, but without disturbances in the sugar metabolism (insipidus means "without taste" in Latin) and does not involve the same disease mechanisms.

**Type 1 DM**

It results from the body's failure to produce insulin, and currently requires the person to inject insulin or wear an insulin pump. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes".

Type 1 diabetes mellitus[^2] is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas, leading to insulin deficiency. This type can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated nature, in which beta cell loss is a T-cell-mediated autoimmune attack. There is no known preventive measure against type 1 diabetes, which causes approximately 10% of diabetes mellitus cases in North America and Europe. Most affected people are otherwise healthy and of a healthy weight when onset occurs. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Type 1 diabetes can affect children or adults, but was traditionally termed "juvenile diabetes" because a majority of these diabetes cases were in children.

"Brittle" diabetes, also known as unstable diabetes or labile diabetes, is a term that was traditionally used to describe to dramatic and recurrent swings in glucose levels, often occurring for no apparent reason in insulin-dependent diabetes. This term, however, has no biologic basis and should not be used. There are many reasons for type 1 diabetes to be
accompanied by irregular and unpredictable hyperglycemias, frequently with ketosis, and sometimes serious hypoglycemias, including an impaired counter regulatory response to hypoglycemia, occult infection, gastroparesis (which leads to erratic absorption of dietary carbohydrates), and endocrinopathies (e.g., Addison's disease). These phenomena are believed to occur no more frequently than in 1% to 2% of persons with type 1 diabetes.

**Type 2 DM**

It results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. This form was previously referred to as non-insulin dependent diabetes mellitus (NIDDM)[2] or "adult-onset diabetes". The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. However, the specific defects are not known. Diabetes mellitus cases due to a known defect are classified separately. Type 2 diabetes is the most common type. In the early stage of type 2, the predominant abnormality is reduced insulin sensitivity. At this stage, hyperglycemia can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce glucose production by the liver.

**Gestational diabetes**

The third main form, gestational diabetes occurs when pregnant women without a previous diagnosis of diabetes develop a high blood glucose level. It may precede development of type 2 DM.

Other forms of diabetes mellitus include congenital diabetes, which is due to genetic defects of insulin secretion, cystic fibrosis-related diabetes, steroid diabetes induced by high doses of glucocorticoids, and several forms of monogenic diabetes.

Untreated, diabetes can cause many complications. Acute complications include diabetic ketoacidosis and non ketotic hyperosmolar coma. Serious long-term complications include cardiovascular disease, chronic renal failure, and diabetic retinopathy (retinal damage). Adequate treatment of diabetes is thus important, as well as blood pressure control and lifestyle factors such as stopping smoking and maintaining a healthy body weight.

All forms of diabetes have been treatable since insulin became available in 1921, and type 2 diabetes may be controlled with medications. Insulin and some oral medications can cause hypoglycemia (low blood sugars), which can be dangerous if severe. Both types 1 and
2 are chronic conditions that cannot be cured. Pancreas transplants have been tried with limited success in type 1 DM; gastric bypass surgery has been successful in many with morbid obesity and type 2 DM. Gestational diabetes usually resolves after delivery.

Other types
Prediabetes indicates a condition that occurs when a person's blood glucose levels are higher than normal but not high enough for a diagnosis of type 2 DM. Many people destined to develop type 2 DM spend many years in a state of prediabetes which has been termed "America's largest healthcare epidemic."

Latent autoimmune diabetes of adults (LADA) is a condition in which type 1 DM develops in adults. Adults with LADA are frequently initially misdiagnosed as having type 2 DM, based on age rather than etiology.

Some cases of diabetes are caused by the body's tissue receptors not responding to insulin (even when insulin levels are normal, which is what separates it from type 2 diabetes); this form is very uncommon. Genetic mutations (autosomal or mitochondrial) can lead to defects in beta cell function. Abnormal insulin action may also have been genetically determined in some cases. Any disease that causes extensive damage to the pancreas may lead to diabetes (for example, chronic pancreatitis and cystic fibrosis). Diseases associated with excessive secretion of insulin-antagonistic hormones can cause diabetes (which is typically resolved once the hormone excess is removed). Many drugs impair insulin secretion and some toxins damage pancreatic beta cells. The ICD-10 (1992) diagnostic entity, malnutrition-related diabetes mellitus (MRDM or MMDM, ICD-10 code E12), was deprecated by the World Health Organization when the current taxonomy was introduced in 1999.

Signs and Symptoms
The classic symptoms of untreated diabetes are loss of weight, polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger).

Symptoms may develop rapidly (weeks or months) in type 1 diabetes, while they usually develop much more slowly and may be subtle or absent in type 2 diabetes.

Prolonged high blood glucose can cause glucose absorption in the lens of the eye, which leads to changes in its shape, resulting in vision changes. Blurred vision is a common
complaint leading to a diabetes diagnosis. A number of skin rashes that can occur in diabetes are collectively known as diabetic dermavromes.

Causes
The cause of diabetes depends on the type.
Type 1 diabetes is partly inherited, and then triggered by certain infections, with some evidence pointing at Coxsackie B4 virus. A genetic element in individual susceptibility to some of these triggers has been traced to particular HLA genotypes (i.e., the genetic "self" identifiers relied upon by the immune system). However, even in those who have inherited the susceptibility, type 1 DM seems to require an environmental trigger. The onset of type 1 diabetes is unrelated to lifestyle.

Type 2 diabetes is due primarily to lifestyle factors and genetics. The following is a comprehensive list of other causes of diabetes:

a. Genetic defects of β-cell function
   - Maturity onset diabetes of the young
   - Mitochondrial DNA mutations

b. Genetic defects in insulin processing or insulin action
   - Defects in proinsulin conversion
   - Insulin gene mutations
   - Insulin receptor mutations

c. Exocrine pancreatic defects
   - Chronic pancreatitis
   - Pancreatectomy
   - Pancreatic neoplasia
   - Cystic fibrosis

   • Hemochromatosis
   • Fibrocalculouspancreatopathyd. Endocrinopathies
     • Growth hormone excess (acromegaly)
     • Cushing syndrome
     • Hyperthyroidism
     • Pheochromocytoma
     • Glucagonomae. Infections
     • Cytomegalovirus infection
     • Coxsackievirus Bf. Drugs
     • Glucocorticoids
     • Thyroid hormone
     • β-adrenergic agonists
     • Statins

2. MATERIALS
2.1 Metformin hydrochloride
It is a highly water soluble anti-hyperglycemic agent used in the treatment of type II (non-insulin dependent) diabetes mellitus. It is the only agent specifically affecting elevated plasminogen activator (PAI) - levels both in hypertriglyceridemia and in noninsulin
dependent diabetes. In spite of its favorable clinical response metformin hydrochloride suffers from certain drawbacks of which, the most prominent being the high dose (1.5-2.0 g/day), low bioavailability (40-60%), short biological half-life (0.9-2.6 h) which requires repeated administrations of high doses to maintain effective plasma concentrations, and high incidence of gastrointestinal side effects (30% cases) such as abdominal discomfort, nausea, and diarrhea, may occur during the treatment. Gastrointestinal absorption of metformin is incomplete under fasting conditions in combination with rapid elimination and 20–30% of an oral dose is recovered in feces. Bioavailability decreases as the dose increases, suggesting some form of saturable absorption process and need for twice to three times a day administration which can also reduce patient compliance and hinder more successful therapy.

<table>
<thead>
<tr>
<th>Therapeutic category</th>
<th>Oral Hypoglycemic Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Name</td>
<td>Imidodicarbonimidicdiamide, N,N-dimethylmono hydrochloride.</td>
</tr>
<tr>
<td>Molecular Formula</td>
<td>C₄H₁₁N₅HCl</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>165.62gm/mole</td>
</tr>
<tr>
<td>Description</td>
<td>White to off white crystalline compound.</td>
</tr>
<tr>
<td>Appearance</td>
<td>White Crystals.</td>
</tr>
<tr>
<td>Solubility</td>
<td>Freely soluble in water, Slightly soluble in alcohol, Practically insoluble in ether, chloroform</td>
</tr>
<tr>
<td>Melting point</td>
<td>232 °C</td>
</tr>
<tr>
<td>Water</td>
<td>Not more than 0.5 %</td>
</tr>
<tr>
<td>Loss on Drying</td>
<td>It loses not more than 0.5% of its weight.</td>
</tr>
<tr>
<td>Residue on ignition</td>
<td>Not more than 0.1%</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>0.001%.</td>
</tr>
<tr>
<td>Dose</td>
<td>0.5 to 2g daily, in divided doses.</td>
</tr>
<tr>
<td>L.D in rats (g/kg)</td>
<td>1000 orally, 300 subcutaneously.</td>
</tr>
<tr>
<td>Storage</td>
<td>Oral solution, store at 15°C-30°C (59°F-86°F), Tablets, store at 20°C to 25°C (68°F to 77°F), protect from light and moisture.</td>
</tr>
</tbody>
</table>
Mechanism of action
Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves intestinal sensitivity by increasing peripheral glucose uptake and utilization.

Pharmacokinetic profile
Absorption : Absorbed throughout GIT.
Distribution : 654± 358L, partition into erythrocytes.
Half life : 4-9 hours.
Excretion : Urine (90% as unchanged drug; active secretion)
Oral Bioavailability : 50-60%

Therapeutic Uses
Management of Type II diabetes mellitus, as monotherapy when hyperglycemia cannot be controlled with diet and exercise alone, in adults may be used concomitantly with a sulfonyl urea or insulin to improve glycemic control.

Contraindications
Hypersensitivity to Metformin,
Acute Myocardial Infarction, or Septicemia,
Acute or Chronic metabolic acidosis with or without coma.

Adverse Drug Reaction
Diarrhoea, Nausea/vomiting, Flatulence, Chest discomfort, Flushing, Palpitation, Headache, Rash, Hypoglycemia, Indigestion, Abdominal discomfort, Dyspepsia, heart burn, Myalgia and Dyspnea

Drug Interaction
Cephalexin : May increase the serum concentration of Metformin.
Cimetidine : May decrease the excretion of Metformin.
Corticosteroids : May diminish the hypoglycemic effect of anti-diabetic agents.

Leutinizing Hormone Releasing
Hormone Analogs : May diminish the therapeutic effect of ant diabetic agents.
Thiazide Diuretics : May diminish the therapeutic effect of ant diabetic agents.

Dosage Forms
Tablet, as hydrochloride; 500mg, 850mg, 1000mg.

Marketed Preparations
Avimet, Baymet, Diabeta-Sr, Gluconorm-Sr, gluformin-XI.

2.2 Glibenclamide
It is a second generation sulphonyl urea capable of stimulating insulin release, but are not capable of acting on insulin resistance, and metformin hydrochloride able to act on insulin resistance, whereas they are not able to stimulate insulin secretion.

Glibenclamide[^4] is 1-[4-[2-(chloro-2-methoxy benzamido) ethyl]-benzenesulphonyl]-3cyclohexylurea,5-chloro-N-[2-[4[[[cyclohexyl( amino)carbonyl]- amino]sulphonyl]phenyl] ethyl]-2-methoxy benzamide or 1-[[p-[-2-(5-chloro-oanisamido)ethyl]phenyl]-sulphonyl-3-cyclohexylurea,a sulphonyl urea derivative is a second generation oral hypoglycemic agent which is more potent than those of first group and is used to assist in the control of mild to moderately severe type II. Diabetes mellitus (adult, maturity-onset) that does not require insulin, but that can be adequately controlled by diet alone. It is drug of choice for initiating treatment in noninsulin-dependent diabetes when diet and weight control fails. It stimulates the secretion and enhances the utilization of insulin by appropriate tissues.

Therapeutic category : Anti Diabetic Agents
Molecular Formula : C_{23}H_{28}ClN_{3}O_{5}S.
Molecular Weight : 494.004g/ mole.
Description : White to yellowish powder.
Appearance : White powder.
Solubility : Sparingly soluble in water and soluble in organic solvents.
Melting point : 169-170 °C
Chloride : Not more than 2%w/w.
Loss on drying : Not more than 1.0%w/w.
Dose : 1.25-20mg in single or divided doses.
L.D in rats and mice 1g/kg) : >20 orally, >12.5 intraperitoneally, >20 subcutaneously.
Storage : Store in air tight container.

Fig. 2: Chemical structure of Glibenclamide

Mechanism of action
Glibenclamide binds to ATP-sensitive potassium channel receptors on the pancreatic cell surface, reducing potassium conductance and causing depolarization of the membrane. Depolarization stimulates calcium ion influx through voltage sensitive calcium channels, raising intracellular concentration of calcium ions, which induces the secretion, or exocytosis, of insulin.

Pharmacokinetic Profile
Absorption : Significant within one hour.
Distribution : 9-10L
Half life : 10 hour may be prolonged with renal or hepatic impairment.
Excretion : Faeces 50% and urine 50% as metabolites.
Oral Bioavailability : Variable among oral dosage forms.

Therapeutic Use
Adjunct to diet and exercise for the management of Type II Diabetes Mellitus (non –insulin dependent, NIIDDM).
Contraindications
Diabetic ketoacidosis, Hypersensitivity to Glibenclamide.

Adverse Drug Reactions
Hypoglycemia, hyponatremia, anorexia, heart burn, nausea, nocturia, agranulocytosis, aplastic anaemia, hemolytic anaemia, leucopenia, pancytopenia, allergic reaction, arthralgia, angioedema, erythema, pruritis, purpura, dizziness, headache and vasculitis blurred vision

Drug Interaction
*Ethyl alcohol:* sulfonyl ureas may enhance the adverse/toxic effect of ethyl alcohol a flushing reaction may occur.

*Beta-Blockers:* may enhance the hypoglycemic effect of sulfonylureas. All Beta-Blockers appear to mask tachycardia as an initial symptom of hypoglycemia.

*Salicylates:* May enhance the hypoglycemic effect of sulfonylureas of concern with regular, higher doses of salicylates, not sporadic, low doses.

*Thiazide Diuretics:* May diminish the therapeutic effect of Antidiabetic agents.

Dosage Forms: Tablet
1.25mg, 2.5mg, 5mg, 10mg.

Marketed preparations
Aviglen, Betanase, Codica, Daonil, Glucosafe, Glunil.

2.3 Lactose
Lactose[^5] is a disaccharide sugar derived from galactose and glucose that is found in milk. Lactose makes up around 2~8% of milk (by weight), although the amount varies among species and individuals. It is extracted from sweet or sour whey. The name comes from lac or lactis, the Latin word for milk, plus the -ose ending used to name sugars. It has a formula of C\textsubscript{12}H\textsubscript{22}O\textsubscript{11}. 

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Lactose is a disaccharide derived from the condensation of galactose and glucose, which form a β-1→4 glycosidic linkage. Its systematic name is β-D-galactopyranosyl-(1→4)-D-glucose. The glucose can be in either the α-pyranose form or the β-pyranose form, whereas the galactose can only have the β-pyranose form; hence α-lactose and β-lactose refer to anomer form of the glucopyranose ring alone.

Lactose is hydrolysed to glucose and galactose, isomerised in alkaline solution to lactulose, and catalytically hydrogenated to the corresponding polyhydric alcohol, lactitol.

Lactose crystals have a characteristic tomahawk shape that can be observed with a light microscope.

- Molecular formula: \(\text{C}_{12}\text{H}_{22}\text{O}_{11}\)
- Molar mass: 342.30 g/mol
- Appearance: white solid
- Density: 1.525 g/cm\(^3\)
- Melting point: 202.8 °C
- Boiling point: 668.9 °C
- Solubility in water: 21.6 g/100 ml

### 2.4 Microcrystalline cellulose (MCC)

Microcrystalline cellulose\(^6\) is a term for refined wood pulp and is used as a texturizer, an anti-caking agent, a fat substitute, an emulsifier, an extender, and a bulking agent in food production. The most common form is used in vitamin supplements or tablets. It is also used in plaque assays for counting viruses, as an alternative to carboxy methyl cellulose. In many ways, cellulose makes the ideal excipient. A naturally occurring polymer, it is composed of glucose units connected by a 1-4 beta glycosidic bond. These linear cellulose chains are bundled together as micro fibril spiralled together in the walls of plant cell. Each micro fibril exhibits a high degree of three-dimensional internal bonding resulting in a crystalline structure that is insoluble in water and resistant to reagents. There are, however, relatively
weak segments of the micro fibril with weaker internal bonding. These are called amorphous regions but are more accurately called dislocations since micro fibril containing single-phase structure. The crystalline region is isolated to produce microcrystalline cellulose.

2.5 Magnesium stearate
Magnesium stearate\cite{7}, also called octadecanoic acid, magnesium salt, is a white substance, powder which becomes solid at room temperature. It has the chemical formula Mg(C\textsubscript{18}H\textsubscript{35}O\textsubscript{2})\textsubscript{2}. It is a salt containing two equivalents of stearate (the anion of stearic acid) and one magnesium cation (Mg\textsuperscript{2+}). Magnesium stearate melts at about 120 °C, is not soluble in water, and is generally considered safe for human consumption at levels below 2500 mg/kg per day. In 1979, the FDA's Subcommittee on GRAS (generally recognized as safe) Substances (SCOGS) reported, "There is no evidence in the available information on ... magnesium stearate ... that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current and in the manner now practiced, or which might reasonably be expected in the future."

Magnesium stearate is created by the reaction of sodium stearate with magnesium sulfate.

![Chemical structure of Magnesium Stearate](image)

**Fig. 4: Chemical structure of Magnesium Stearate**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular formula</td>
<td>Mg(C\textsubscript{18}H\textsubscript{35}O\textsubscript{2})\textsubscript{2}</td>
</tr>
<tr>
<td>Molar mass</td>
<td>591.27 g/mol</td>
</tr>
<tr>
<td>Appearance</td>
<td>light white powder</td>
</tr>
<tr>
<td>Odor</td>
<td>slight</td>
</tr>
<tr>
<td>Density</td>
<td>1.026 g/cm\textsuperscript{3}</td>
</tr>
<tr>
<td>Melting point</td>
<td>88.5 °C, 362 K, 191 °F</td>
</tr>
<tr>
<td>Solubility</td>
<td>In water;</td>
</tr>
<tr>
<td></td>
<td>0.003 g/100 ml (15 °C)</td>
</tr>
<tr>
<td></td>
<td>0.004 g/100 ml (25 °C)</td>
</tr>
<tr>
<td></td>
<td>0.008 g/100 ml (50 °C)</td>
</tr>
</tbody>
</table>
Negligible in ether and alcohol
Slightly soluble in benzene

Uses
Magnesium stearate is often used as an anti-adherent in the manufacture of medical tablets, capsules and powders. In this regard, the substance is also useful, because it has lubricating properties, preventing ingredients from sticking to manufacturing equipment during the compression of chemical powders into solid tablets; magnesium stearate is the most commonly used lubricant for tablets. Studies have shown that magnesium stearate may affect the release time of the active ingredients in tablets, etc., but not that it reduces the overall bioavailability of those ingredients. As a food additive or pharmaceutical excipient, its E number is E470b.

Magnesium stearate is also used to bind sugar in hard candies like mints, and is a common ingredient in baby formulas. In pure powder form, the substance can be a dust explosion hazard, although this issue is effectively insignificant beyond the manufacturing plants using it.

Magnesium stearate is manufactured from both animal and vegetable oils. Some nutritional supplements specify that the magnesium stearate used is sourced from vegetables.

Magnesium stearate is a major component of "bathtub rings." When produced by soap and hard water, magnesium stearate and calcium stearate both form a white solid insoluble in water, and are collectively known as "soap scum."

2.6 Aerosil
Aerosil[8] or Fumed silica, also known as pyrogenic silica because it is produced in a flame, consists of microscopic droplets of amorphous silica fused into branched, chainlike, three-dimensional secondary particles which then agglomerate into tertiary particles. The resulting powder has an extremely low bulk density and high surface area. Its three-dimensional structure results in viscosity-increasing, thixotropic behavior when used as a thickener or reinforcing filler.

Fumed silica has a very strong thickening effect. Primary particle size is 5–50 nm. The particles are non-porous and have a surface area of 50–600 m²/g. Density 160–190 kg/m³.
Fumed silica serves as a universal thickening agent and an anticaking agent (free-flow agent) in powders. Like silica gel, it serves as a desiccant. It is used in cosmetics for its light-diffusing properties. It is used as a light abrasive, in products like toothpaste. Other uses include filler in silicone elastomer and viscosity adjustment in paints, coatings, printing inks, adhesives and unsaturated polyester resins. It is also used in the production of cat box filler.

Fumed silica is not listed as a carcinogen by OSHA, IARC, or NTP. Due to its fineness and thinness, fumed silica can easily become airborne, making it an inhalation risk, capable of causing irritation.

2.7 HPMC K100M

1. Technical specifications

- Methoxy content (WT%) : 19.0-24.0
- Hydroxy propoxy content (WT%) : 4.0-12.0
- Gelation temperature : 70.0-90.0
- Drying loss (WT%) : ≤5.0
- Residue on ignition (WT%) : ≤1.0
- pH (1% solution, 25) : 4.0-8.0

2. Properties

White or similar to white granular powder; odorless. Almost insoluble in ethanol, ether and acetone; quickly dispersed in 80-90 water; aqueous solution is very stable in room temperature; has good wetting/dispersing/adhesive/thickening/emulsifying/water preserving/film forming properties; can prevent the infiltration of grease; filmformed has excellent flexibility and transparency; has good compatibility with other emulsifier; easy salting-out. Its solution is stable with pH 2-12. Apparent density: 0.300-0.70g/cm³, density: 1.3g/cm³.

3. Dissolving process

HPMC⁹¹ will agglomerate when directly added to water and then dissolve. In this way it dissolves very slow and hard. Suggested methods as followers:
(1.) **In hot water**
HPMC does not dissolve in hot water. The primary HPMC can be uniformly disperse in hot water. Then cool down in two ways:

a) Add hot water in container and heated to over 70. Add HPMC gradually while slowly, sti.
   At the beginning, HPMC float on the top of water, then turns into slurry state stir and cool down.

b) Add water in container to 1/3 or 2/3 of its content. Heated to over 70 add HPMC by sequence of a). Make it disperse to form slurry state. Add cool water or ice to the residual content, stir and cool down the mixture.

(4.) **Application**
It is widely used as thickener, adhesive, water preserving agent, film forming agent in construction, building materials, dispersion coating, wallpaper paste, polymerization aids, leathers, printing ink and paper making etc. Also used in petroleum drilling and daily-use chemicals.

2.8 **Talc**
Talc[^10] is a mineral composed of hydrated magnesium silicate with the chemical formula $\text{H}_2\text{Mg}_3(\text{SiO}_3)_4$ or $\text{Mg}_3\text{Si}_4\text{O}_{10}(\text{OH})_2$. In loose form, it is the widely used substance known as talcum powder. It occurs as foliated to fibrous masses, and in an exceptionally rare crystal form. It has a perfect basal cleavage, and the folia are non-elastic, although slightly flexible. It is the softest known mineral and listed as 1 on the Mohs hardness scale. It can be easily scratched by a fingernail. It is also sectile (can be cut with a knife). It has a specific gravity of 2.5–2.8, a clear or dusty luster, and is translucent to opaque. Talc is not soluble in water, but it is slightly soluble in dilute mineral acids. Its colour ranges from white to grey or green and it has a distinctly greasy feel. Its streak is white.

Talc is used in many industries such as paper making, plastic, paint and coatings, rubber, food, electric cable, pharmaceuticals, cosmetics, ceramics, etc. A coarse grayish-green high-talc rock is soapstone or steatite and has been used for stoves, sinks, electrical switchboards, crayons, soap, etc. It is often used for surfaces of lab counter tops and electrical switchboards because of its resistance to heat, electricity and acids. Talc finds use as a cosmetic (talcum powder), as a lubricant, and as a filler in paper manufacture. Talc is used in baby powder, an astringent powder used for preventing rashes on the area covered by a diaper. It is also
often used in basketball to keep a player's hands dry. Most tailor's chalk, or French chalk, is
talc, as is the chalk often used for welding or metalworking.

Talc is also used as food additive or in pharmaceutical products as a glidant. In medicine talc
is used as a pleurodesis agent to prevent recurrent pleural effusion or pneumothorax. In
the European Union the additive number is E553b.

Talc is widely used in the ceramics industry in both bodies and glazes. In low-fire artware
bodies it imparts whiteness and increases thermal expansion to resist crazing. In stonewares,
small percentages of talc are used to flux the body and therefore improve strength
and vitrification. It is a source of MgO flux in high temperature glazes (to control melting
temperature). It is also employed as a matting agent in earthenware glazes and can be used to
produce magnesia mattes at high temperatures.

2.9 HPMC 4KM

HPMC 4KM\(^\text{[11]}\) is a white to light yellow powder or granular product. HPMC 4KM is nearly
insoluble in anhydrous ethanol, ethyl ether and acetone. It is swelled in cold water to form a
transparent or a slight cloudy solution. HPMC can be dissolved into some organic solvents
and also in water-organic solvent mixed solvents.

The oversize product above 100 mesh should not exceed 5.0%. With reduction of methoxyl g
groups content, HPMC is increased in gelling temperature and decreased in water solubility an
and surface activity. Resistance to salting out: HPMC is a nonionic cellulose ether and it is not a
polyelectrolyte. The aqueous solution of HPMC is comparatively stable even in the presence
of metal salts or organic electrolytes. However, when the concentration of electrolytes exceed
a certain limit, gelation and precipitation may result. An aqueous solution of HPMC has a hi
gh surface activity and functions as a protective colloid agent, emulsion stabilizer and dispers
ant. An aqueous solution of HPMC will gel or precipitate when heated to a certain temperatur
e, but it reverts to the original solution state on subsequent cooling. The temperature at which
gelation or precipitation occur depends on the type of HPMC, its concentration and the rate of
heating. The viscosity of an aqueous solution of HPMC is hardly affected by acid or alkali, an
d the product can develop an original viscosity in the range of 3.0~11.0. Therefore, the solut
on viscosity tends to keep stable during prolonged storage. HPMC is a high effective water ret
ention agent. Its pharmaceutical grade product can be widely used in food, cosmetics and ma
ny other fields. HPMC provides a strong, flexible and transparent film having a good barrier p
property against oil and grease. In food application, this property is often utilized for water retention and oil adsorption. HPMC, as a high performance binder, can also be used for molding food and medicine.

4. METHODS

3.1 Simultaneous Estimation of Glibenclamide and Metformin by UV Spectroscopy\[^3\]
12.5 mg of glibenclamide was dissolved in 30 ml of phosphate buffer (pH 6.8) in a 50 ml volumetric flask and the volume was made up with the buffer. 25 mg of Metformin was dissolved in 30 ml of phosphate buffer (pH 6.8) in another 50 ml volumetric flask and the volume was made up with the buffer. 1 ml of each of the solutions were pipette out in a 100 ml volumetric flask and the volume was made up with the buffer solution.

Absorbance of the resulting solution was measured at the maximum at 229.5 nm and 237 nm and the percentage purity of both the drugs were calculated.

\[
\begin{align*}
C_{\text{GLB}} &= \frac{A_2(55.33) - A_1(119.55)}{-3541.08} \\
C_{\text{MET}} &= \frac{A_1(91.85) - A_2(72.13)}{-3600.1}
\end{align*}
\]

where;

- \(C_{\text{GLB}}\) = Concentration of Glibenclamide
- \(C_{\text{MET}}\) = Concentration of Metformin
- \(A_1\) = Absorbance at 229.5 nm
- \(A_2\) = Absorbance at 237 nm

3.2 Preparation of Granules\[^{12}\]

In formulation F1 Metformin: Polymers (HPMC K100M + HPMC 4KM) ratio was taken as 1: 1. In formulation F2 Metformin: Polymer ratio was taken as 1: 0.7 and in formulation F3 Metformin: Polymer ratio was taken as 1: 0.5. The ratio between the two polymers i.e. HPMC K100M: HPMC 4KM is 2: 1 which was kept constant.

Preparation of Immediate Release Granules

Table No. 1: Compositions of immediate release layer containing glibenclamide

<table>
<thead>
<tr>
<th>S.NO.</th>
<th>INGREDIENTS</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Glibenclamide</td>
<td>2.5 mg</td>
<td>2.5 mg</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>2</td>
<td>Lactose</td>
<td>45 mg</td>
<td>45 mg</td>
<td>45 mg</td>
</tr>
<tr>
<td>3</td>
<td>MCC</td>
<td>47.5 mg</td>
<td>47.5 mg</td>
<td>47.5 mg</td>
</tr>
<tr>
<td>4</td>
<td>Magnesium Stearate</td>
<td>2 mg</td>
<td>2 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td>5</td>
<td>Aerosil</td>
<td>1 mg</td>
<td>1 mg</td>
<td>1 mg</td>
</tr>
<tr>
<td>6</td>
<td>Starch</td>
<td>2 mg</td>
<td>2 mg</td>
<td>2 mg</td>
</tr>
</tbody>
</table>
The ingredients for the immediate release layer are shown in the Table No.1. Glibenclamide, lactose and microcrystalline cellulose were sifted through 40#. Sifted materials were mixed thoroughly in a porcelain mortar for 15 minutes and granulated using starch binder solution to form a wet coherent mass. Passed through 20#. Granules were dried in hot air oven at 50°C for 30 minutes and passed through 20#. Prepared granules were lubricated with magnesium stearate and aerosil previously passes through 60#. Prepared granules were compressed with round shaped concave punches with average weight of 100 mg per tablet.

**Preparation of Sustained Release Granules**

Table No. 2: Compositions of sustained release layer containing metformin hydrochloride

<table>
<thead>
<tr>
<th>S.NO.</th>
<th>INGREDIENTS</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Metformin hydrochloride</td>
<td>125 mg</td>
<td>125 mg</td>
<td>125 mg</td>
</tr>
<tr>
<td>2</td>
<td>Lactose</td>
<td>139 mg</td>
<td>175 mg</td>
<td>199 mg</td>
</tr>
<tr>
<td>3</td>
<td>HPMC K100M</td>
<td>84 mg</td>
<td>60 mg</td>
<td>44 mg</td>
</tr>
<tr>
<td>4</td>
<td>HPMC 4KM</td>
<td>42 mg</td>
<td>30 mg</td>
<td>22 mg</td>
</tr>
<tr>
<td>5</td>
<td>Magnesium Stearate</td>
<td>4 mg</td>
<td>4 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>6</td>
<td>Talc</td>
<td>4 mg</td>
<td>4 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>7</td>
<td>Aerosil</td>
<td>2 mg</td>
<td>2 mg</td>
<td>2 mg</td>
</tr>
</tbody>
</table>

The ingredients for the sustained release layer of metformin hydrochloride are shown in the Table No.2. Metformin hydrochloride, lactose, HPMC K100M and HPMC 4KM were sifted through 40#. Sifted materials were mixed thoroughly for 15 minutes in a porcelain mortar. It is then wetted with isopropyl alcohol. When HPMC was wetted with Isopropyl alcohol it formed a coherent mass. It was passed through 20#. Granules were dried in hot air oven at 50°C for 30 minutes and passed through 20#. Prepared granules were lubricated with magnesium stearate, Talc and aerosil previously passed through 60# were added. Prepared granules were compressed with round shaped concave punches for initial assessments with average weight of 400 mg per tablet.

**3.3 Preparation of Bilayer Tablet**

Immediate release granules were weighed accurately and filled in the die. The immediate release granules were punched to form tablet. The punched tablet was filled in the die and the sustained release granules were weighed accurately and filled in the die above the previously punched tablet. The sustained release layer was punched over the immediate release layer thus forming bilayer tablet. The same procedure was followed for rest of the formulations.
Optimal formulation from both the layers was compressed with plain punches in with average weight of 500 mg.

### 3.4 Pre-Formulation Study \[13\]

The prepared granules were subjected to the following pre-formulation studies.

#### Angle of repose

Angle of repose was measured according to the fixed funnel and free standing cone method. A funnel was clamped with its tip 2 cm above a graph paper placed on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the cone thus formed just reached the tip of the funnel. The mean diameters of the base of the powder cones were determined and the tangent of the angle of repose calculated using the following equation.

Results are found in Table No. 3 and 4.

\[
\tan \theta = \frac{h}{r}
\]

Where,

- h = Height of the cone;
- r = Radius of surface area of the pile.

#### Bulk density and tapped density

2.0 g quantity each of the powder sample was placed in a 10 ml measuring cylinder and the volume, \(V_0\), occupied by each of the samples without tapping was noted. After 100 taps on the table, the occupied volume \(V_f\) was read. The bulk and tap densities were calculated as the ratio of weight to volume (\(V_b\) and \(V_f\) respectively) by the following equations.

Results are found in Table No. 3 and 4.

- Bulk density = \(w/v_0\)
- Tapped density = \(w/v_f\)

Where,

- \(W\) = weight of the powder;
- \(V_0\) = initial volume;
- \(V_f\) = final volume
**Compressibility index**

The compressibility index was calculated with the following equation,

\[
\text{compressibility index} = \frac{v_0 - v_f}{v_0}
\]

Results are found in Table No. 3 and 4.

**Hausner’s ratio**

Hausner’s ratio was calculated with the following formula

\[
\text{Hausner’s ratio} = \frac{v_o}{v_f}
\]

Results are found in Table No. 3 and 4.

**Table No 3: Preformulation studies on immediate release layer granules**

<table>
<thead>
<tr>
<th>S.NO.</th>
<th>TESTS</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bulk density (g/ml)</td>
<td>0.36</td>
<td>0.34</td>
<td>0.33</td>
</tr>
<tr>
<td>2</td>
<td>Tapped density (g/ml)</td>
<td>0.44</td>
<td>0.43</td>
<td>0.42</td>
</tr>
<tr>
<td>3</td>
<td>Hausner’s ratio</td>
<td>1.22</td>
<td>1.25</td>
<td>1.23</td>
</tr>
<tr>
<td>4</td>
<td>Angle of repose (°)</td>
<td>25.74</td>
<td>25.55</td>
<td>26.58</td>
</tr>
<tr>
<td>5</td>
<td>Compressibility Index (g)</td>
<td>18.29</td>
<td>19.25</td>
<td>19.07</td>
</tr>
</tbody>
</table>

**Table No 4: Preformulation studies on Sustained release layer granules**

<table>
<thead>
<tr>
<th>S.NO.</th>
<th>TESTS</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bulk density (g/ml)</td>
<td>0.41</td>
<td>0.44</td>
<td>0.42</td>
</tr>
<tr>
<td>2</td>
<td>Tapped density (g/ml)</td>
<td>0.5</td>
<td>0.51</td>
<td>0.51</td>
</tr>
<tr>
<td>3</td>
<td>Hausner’s ratio</td>
<td>1.21</td>
<td>1.22</td>
<td>1.2</td>
</tr>
<tr>
<td>4</td>
<td>Angle of repose (°)</td>
<td>25.12</td>
<td>26.22</td>
<td>26.17</td>
</tr>
<tr>
<td>5</td>
<td>Compressibility Index (g)</td>
<td>17.80</td>
<td>18.2</td>
<td>18.2</td>
</tr>
</tbody>
</table>

**3.5 Evaluation of Tablets**

The following tests were performed on the prepared bilayer tablets:

**General Appearance**\(^{[13]}\)

The tablets prepared were of two colours. Glibenclamide (immediate) layer was red in colour and the Metformin (sustained) layer was white in colour. They were smooth, uniform and free from cracking and chipping.

**Thickness and Diameter**\(^{[13]}\)

Thickness depends mainly upon die filling, physical properties of materials to be compressed force. There is bound to be a small variation in the thickness of individual tablet in a batch, but it should not be apparent to the unaided eye.
The thickness and diameter were measured by using Vernier Caliper. The thickness should not vary beyond ±5% of standard value.

![Vernier Caliper BIT08VC001](image)

**Fig 5: Vernier-Caliper-BIT08VC001**

**Hardness:**[13]

Hardness of the tablet is indicative of its tensile strength and is measured in terms of load/pressure required to crush it, when placed between plungers. The hardness of about 5kg is considered minimum for uncoated tablets for mechanical stability.

Hardness of the tablet was determined using Monsanto Hardness Tester. The tester consists of a barrel containing a compressible spring held between two plunger. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

![Monsanto Hardness Tester](image)

**Fig. 6: Monsanto Hardness Tester**

**4. Weight variation:**[13]

It is desirable that every individual tablet in a batch is uniform in weight and weight variation or any is within permissible limits (±10% for tablets weighing 80mg or less, ±7.5% for the tablet weighing between 80mg and 250mg, ±5% for tablets weighing between 250mg or more).
Non-uniformity in weights may lead to variation in dosing. All finished batches of tablets should be sampled and tested for weight uniformity.

20 tablets were weighed collectively and individually and form the collective weight, average weight was calculated. Each tablet weight was compared with average weight to ascertain whether it is within permissible limits or not. The tablets meet the I.P tests if not more than 2 tablet are outside the percentage limit and if no tablets differs by more than 2 times the percentage limit.

5. Disintegration time\textsuperscript{[13]}

This test determines whether dosage forms such as tablets, capsules, boluses pessaries and suppositories disintegrate within a prescribed time when placed in a liquid medium under the prescribed experimental conditions. For the purpose of this test, disintegration does not imply complete solution of the dosage unit or even of its active constituent. Disintegration is defined as that state in which no residue of the unit under test remains on the screen of the apparatus or, if a residue remains, it consists of fragments of disintegrated parts of tablets component parts such as insoluble coating of the tablets or of capsule shells, or of any melted fatty substance from the pessary or suppository or is a soft mass with no palpable core. If discs have been used with capsules, any residue remaining on the lower surfaces of the discs consists only of fragments of shells. One tablet was introduced into each tube and a disc was added to each tube. The assembly was suspended in the beaker containing the 0.1N HC and the apparatus was operated for the specified time. The assembly was removed from the liquid. The tablets passes the test if all of them have disintegrated. If 1 or 2 tablets failed to disintegrate, repeat the test on 12 additional tablets; not less than 16 of the total of 18 tablets or capsules tested disintegrate. If the tablets adhere to the disc and the preparation under examination fails to comply, repeat the test omitting the disc. The preparation complies with the test if all the tablets or capsules in the repeat test disintegrate.

![Fig. 7: Tablet Disintegration Test Apparatus](image)
Friability\cite{12}

Friability refers to the loss in weight of tablets in the containers due to removal of particles from the surface. In a wider sense chipping and fragmentation can also be included in friability. Friability reflects cohesion of tablet ingredients.

The Roche Friability Test Apparatus consists of a circular plastic chamber, divided into 2 compartments. The chamber was rotated at a speed of 25 rpm and the tablet were dropped 15cm distance. Pre-weighted tablets were placed in the apparatus which was given 100 revolutions after which tablets were weighed once again. The difference between the two weights represents friability. The weight loss should not be more than 1%.

![Tablet Friability Test Apparatus SP-115674](image)

Assay\cite{3}

20 tablets were taken and weighed. These tablets were then crushed using a mortar and pestle to get a fine powder. 500 mg powder was weighed accurately and dissolved in 30 ml of phosphate buffer (pH 6.8) in a 50 ml volumetric flask and made up the volume with the buffer. The solution was filtered and 1 ml of solution was diluted to 100 ml. The absorbance of the resulting solution was measured at 229.5 nm and 237 nm in a Schimadzu UV-1601 Spectrophotometer. Results are found in Table No. 5.

**Table No.5: Evaluation of bilayer tablets**

<table>
<thead>
<tr>
<th>S.NO.</th>
<th>TESTS</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Appearance</td>
<td>Round, bilayer - red and white</td>
<td>Round, bilayer - red and white</td>
<td>Round, bilayer - red and white</td>
</tr>
<tr>
<td>2</td>
<td>Thickness (cm)</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diameter (cm)</td>
<td></td>
<td>Hardness (Kg/cm)</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>1.3</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>1.3</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>4</td>
<td></td>
<td>3.3%</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>3.2%</td>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

Fig. 9: UV SPECTROPHOTOMETER 1650PC

Invitro Dissolution Test[14]

a. Acid Stage
750ml of 0.1N hydrochloric acid was placed in the vessel, and the apparatus was assembled. The medium was allowed to equilibrate to a temperature of 37±0.5°. 1 dosage unit was placed in the apparatus, the vessel was covered and the apparatus was operated at specific rate. An aliquot of fluid was withdrawn at an intervals of 30 minutes upto 2 hours. The aliquot was filtered and necessary dilutions were made with 0.1N HCl. The drug content was determined using Schimadzu UV-1601 Spectrophotometer.

b. Buffer Stage
250 ml of 0.2M tri basic sodium phosphate was added to the fluid in the vessel that was equilibrated to 37±0.5°. 2 N Hydrochloric acid and 2 N sodium hydroxide were added to adjust the pH to 6.8±0.005. The apparatus was continued to operate for 24 hours. An aliquot of the fluid was withdrawn every one hour till 24 hours. The aliquots were filtered and necessary dilutions were made and analyzed for drug content using Schimadzu UV-1601 Spectrophotometer.

Results are tabulated in Table No. 6 and represented graphically in Fig. 11 and 12.
5. RESULTS AND DISCUSSION

Granules are generally known to possess better flow properties than powdered materials. The angles of repose are 25-26° and 30.3 ° for the granules and powdered mixtures respectively. Although angle of repose is used as an index of flow ability of powdered materials, no relationship exists between flow rate and angle of repose of powders. But generally, angle of repose values between 21° and 35° indicate good flow ability. High angles of repose are due to the cohesiveness of powders which results to poor flow. Powders having low angles of repose are usually not available for capsule filling or tableting.

The bulk density of the granules and powdered mixtures are 0.33-0.36 g/ml and 0.41-0.44 g/ml for immediate release granules and sustained release granules respectively, while the tapped densities are 0.42-0.44 g/ml and 0.5-0.51 g/ml for immediate release granules and sustained release granules respectively. A high bulk density for powdered materials is good because of increased fill weight achieved.

The Hausner’s quotient values obtained for the granules and powdered mixtures are 1.2 an. Hausner's quotient value of 1.20 or less indicates good flow. High values may be due to interparticulate friction which impedes flow.

The results indicate that the powders are more cohesive than the granules, probably due to inter particulate friction which results in poor flow, while the granules are less cohesive resulting in good flow properties. The physical properties of the granules and powdered mixtures show that the results are adequate for purposes of tabletting.
The physical properties of bilayer tablets are shown in Table No. 5. All batches of tablets passed the weight uniformity test. Values of standard deviation from the mean weight are low. This indicates little weight variation within each tablet batch. The hardness of tablets was found to be 4 – 5 kg/cm. Friability was 0.7%, and the assay was 99.73% ± 0.636% and 99.90% ± 0.559% for glibenclamide and metformin respectively.

The percentage cumulative release of glibenclamide for formulation F1 was found to be 99.18%±0.229% at the end of second hour, for formulation F2 it was found to be 99.91%±0.225% at the end of two hours. But for formulation F3 it was found to be 100% at the end of one and half hour.

The percentage cumulative release of metformin for formulation F1 was found to be 77.99%±0.253% at the end of twenty one hour, for formulation F2 it was found to be 80.22%±0.732% at the end of twenty one hours. But for formulation F3 it was found to be 95.25%±0.694% at the end of twenty one and hour. It was seen as the ratio of polymer increased the rate of drug release decreased. All the three formulation showed a percentage cumulative release of metformin equal to 100% at the end of twenty four hour.

Table No 6: Drug release profile of the bilayer tablets

<table>
<thead>
<tr>
<th>Time (in hours)</th>
<th>Cumulative Percentage Drug Release</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>GLB</td>
<td>MET</td>
</tr>
<tr>
<td>0.5</td>
<td>77.94±0.924</td>
</tr>
<tr>
<td>1.0</td>
<td>90.00±0.733</td>
</tr>
<tr>
<td>1.5</td>
<td>98.99±0.773</td>
</tr>
<tr>
<td>2.0</td>
<td>99.64±0.433</td>
</tr>
<tr>
<td>2.5</td>
<td>99.18±0.229</td>
</tr>
<tr>
<td>3.0</td>
<td>100.00±0.00</td>
</tr>
<tr>
<td>4.0</td>
<td>19.27±0.253</td>
</tr>
<tr>
<td>5.0</td>
<td>22.48±0.544</td>
</tr>
<tr>
<td>6.0</td>
<td>27.11±0.453</td>
</tr>
<tr>
<td>7.0</td>
<td>31.05±0.911</td>
</tr>
<tr>
<td>8.0</td>
<td>35.54±0.534</td>
</tr>
<tr>
<td>9.0</td>
<td>39.21±0.779</td>
</tr>
<tr>
<td>10</td>
<td>41.67±0.644</td>
</tr>
<tr>
<td>11</td>
<td>48.05±0.645</td>
</tr>
<tr>
<td>15</td>
<td>56.05±0.791</td>
</tr>
<tr>
<td>18</td>
<td>63.25±0.663</td>
</tr>
<tr>
<td>21</td>
<td>77.99±0.253</td>
</tr>
<tr>
<td>24</td>
<td>100.00±0.00</td>
</tr>
</tbody>
</table>
6. CONCLUSION

Usually conventional dosage forms produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factor such as repetitive dosing and unpredictable absorption led to the concept of controlled
drug delivery systems. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance. Bi-layer tablet is suitable for sequential release of two drugs in combination, in which one layer is immediate release and second layer is for sustained release.

The sustained release layer is formulated by matrix technique. Matrix technique is gaining an importance in current days as a simplest technique for a controlled release of drugs. If a drug has right mix of physical chemistry and pharmacology, matrix tablets have a wide range of advantages. Many researches are aimed to discover an economical and effective polymer to release drug by this system.

In this study two anti-diabetic drugs, metformin and glibenclamide were chosen to form bilayer tablets. After preparation of bilayer tablets, physicochemical studies, in vitro release studies and in vivo release studies were performed. A satisfactory attempt was made to develop matrix tablets by using economical and easily available method. The release of glibenclamide was found to be satisfactory. The different grades of HPMC were found to be effective in sustaining the release of metformin for up to 24 hours.

7. ACKNOWLEDGEMENT
I take this opportunity to express my sincere thanks and foremost gratitude to my revered guide Dr. GRACE RATHNAM, M.Pharm., Ph.D., Principle, C.L Baid Metha College of Pharmacy and Head, Department of Pharmaceutics, C. L. Baid Metha College of Pharmacy, Chennai-97 for her valuable suggestions, constant inspiration and encouragement during the course of my project. Her exemplary guidance, optimistic approach, advices and help were of great importance to improve the outcome of the presented work. I am thankful to M/s FOURTS INDIA LTD., for providing me the drug sample at appropriate time in order to complete my project work successfully.

8. REFERENCES


