

ISOLATION OF MUCILAGE FROM THE FRUITS OF *Momordica charantia* AND INVESTIGATION OF ITS PHARMACOLOGICAL PROPERTIES



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Declaration

It declared that this thesis entitled “**Isolation of mucilage from the fruits of *Momordica charantia* and investigation of its pharmacological properties**”, prepared for submission for the degree of Masters in Chemistry are the original research works of my own under the supervision of **Professor Dr. Rajia Sultana**, Department of Chemistry, Chittagong University of Engineering and Technology (CUET), Chattogram - 4349, Bangladesh.

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Dedication

To my beloved parents

Publication(s)

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Mucilage as Novel Pharmaceutical Excipient

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Declaration by the Supervisor

I hereby certify that **Tahamina Momtaz Chowdhury (Student ID No. 19MSCHEM005F)** has completed her thesis work for Masters in Chemistry on the topic “**Isolation of mucilage from the fruits of *Momordica charantia* and investigation its pharmacological properties**”. I further certify that this thesis work was carried out under my supervision and guidance at Department of Chemistry in Chittagong University of Engineering and Technology (CUET) during academic Session 2019- 2020. This research work is up to our satisfaction.

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Tahamina Momtaz Chowdhury

Abstract

Momordica charantia is a plant belonging to the Cucurbitaceae family, also known as 'Bitter gourd', and 'Usta' in bangle. It contains alkaloids, insulin-like polypeptides, and charantin, a combination of steroidal sapogenins. It is an effective hypoglycemic agent. *Momordica charantia* is the most common plant used in alternate medicines as an anti-diabetic agent. Metformin hydrochloride is derived from the class of compounds from biguanide family, is an oral anti-hyperglycemic agent and is widely used as an anti-diabetic drug in the treatment of non-insulin-dependent diabetes mellitus (NIDDM). The action of Metformin is the alteration of the energy metabolism of the cell. By blocking hepatic gluconeogenesis and glucagon's action, metformin has its predominant effect of lowering blood glucose levels. Metformin has 50-60% bioavailability and 1.5–4.5 hours for plasma half-life. Initial dose (800 mg) required orally once a day. Therefore, in the case of higher diabetes, higher doses are required, there is a need to take this medicine 2–3 times in a day.

In the current study, the mucilage isolated from *Momordica charantia* fruits and used in the tablets formulations as a binding agent. Different phytochemical test of isolated mucilage showed that only carbohydrates is present in it. We have designed nine batch tablets containing 500 mg of Metformin HCl with different compositions of mucilage (1%, 2.5%, 5%, and 10%) for 800 mg of each tablet. The pre-compressional and post-compressional pharmacological properties of different formulated granules and tablets are evaluated. The granules showed good to excellent flow properties based on the values of bulk density, tap density, carr's index, hausner's ratio and angle of repose. The weight of the tablets is close to the standard and shown good hardness properties. Among all the formulations, the tablets batches of formulation 4 (F4) and formulation 8 (F8) have good disintegration properties. From *in vitro* dissolution profile analysis, formulation batch F 4 composed of 10% mucilage and F-8 composed of 10% mucilage along with 10 % starch, released 40.8% and 31.63% of the drug, respectively in 60 minutes. Drug Release Kinetics Study showed that F4 showed the first-order release kinetics and F-8 showed the zero order and the Higuchi-s release kinetics. Hence, mucilage from *Momordica charantia* can be used as excipients or tablet binders for low cost, available, nontoxic in pharmaceutical tablet formulations.

সারসংক্ষেপ

Momordica charantia হল Cucurbitaceae পরিবারের অন্তর্গত একটি উদ্ভিদ, যা করলা এবং উস্তা নামেও পরিচিত। এতে রয়েছে অ্যালকালয়েড, ইনসুলিন-সদৃশ পলিপেপটাইড এবং কারেন্টিন, স্টেরয়েডাল স্যাপোজেনিনের সংমিশ্রণ, এটি একটি কার্যকর হাইপোগ্লাইসেমিক এজেন্ট। *Momordica charantia* হল সবচেয়ে সহজ উদ্ভিদ যা অ্যান্টি-ডায়াবেটিক ঔষধের বিকল্প হিসাবে ব্যবহৃত হয়।

মেটফরমিন হাইড্রোক্লোরাইড (Metformin HCl) বিণ্ডুয়ানাইড পরিবারের শ্রেণীর অন্তর্ভুক্ত একটি ঔষধ। ইহা অ্যান্টি-হাইপারগ্লাইসেমিক বৈশিষ্ট্য প্রকাশ করে এবং ইহা নন-ইনসুলিন-নির্ভর ডায়াবেটিস মেলিটাস (NIDDM) এর চিকিৎসায় ডায়াবেটিক-বিরোধী ঔষধ হিসাবে ব্যাপকভাবে ব্যবহৃত হয়। মেটফরমিনের প্রধান ক্রিয়া হল মানব কোষের শক্তি বিপাকের বা হজমের পরিবর্তন করা। মেটফরমিন সাধারণত হেপাটিক গ্লুকোনোজেনেসিস এবং গ্লুকোজনের ক্রিয়াকে বাধা দান করে, আর রক্তে গ্লুকোজের মাত্রা কমিয়ে দেয়। মেটফরমিনের জৈব উপলভ্যতা হলো ৫০ - ৬০% এবং প্লাজমা অর্ধ-জীবন রয়েছে ১.৫ -৪.৫ ঘন্টা, যা উভয়ই তুলনামূলকভাবে কম। সাধারণত মেটফরমিন হাইড্রোক্লোরাইড ৪০০ mg ট্যাবলেট দিনে এক বার সেবন করা হয়। তবে ডায়াবেটিস এর ক্ষেত্রে যখন উচ্চ মাত্রার প্রয়োজন হয়, দিনে দুই বা তিনবার ঔষধ সেবনের প্রয়োজনীয়তা দেখা দেয়। *Momordica charantia* ফল থেকে মিউসিলেজ পৃথক করা হয় এবং এটি ট্যাবলেটের ফর্মুলেশনে বাইন্ডিং এজেন্ট হিসেবে ব্যবহার করা হয়। পৃথককৃত মিউসিলেজের বিভিন্ন ফাইটোকেমিক্যাল পরীক্ষায় দেখা গেছে যে এতে শুধুমাত্র কার্বোহাইড্রেট রয়েছে। আমরা ৫০০ mg মেটফরমিন হাইড্রোক্লোরাইড সমন্বিত নয়টি ব্যাচ ট্যাবলেট ডিজাইন করেছি, যেখানে প্রতিটা ট্যাবলেটের ওজন ৪০০ mg নির্ধারণ করা হয় এবং যার মধ্যে বিভিন্ন পরিমাণ এ মিউসিলেজ (১%, ২.৫%, ৫% এবং ১০%) রয়েছে। তৈরিকৃত বিভিন্ন গ্রানুলস এবং ট্যাবলেটগুলির pre- compressional এবং post- compressional ফার্মাকোলজিকাল বৈশিষ্ট্যগুলি পরীক্ষা করা হয়। গ্রানুলস ক্ষেত্রে দেখা যায় যে, গ্রানুলাসগুলির Bulk density, Tap density, Carr's index, Hausner's ratio এবং Angle of repose মানগুলির উপর ভিত্তি করে ভাল থেকে চমৎকার প্রবাহ বৈশিষ্ট্যগুলি (flow properties) দেখিয়েছে। post- compressional পরীক্ষায় দেখা যাই যে, সমস্ত ট্যাবলেটের ওজন স্ট্যান্ডার্ডের কাছাকাছি এবং তাদের ভালো হার্ডনেস বৈশিষ্ট্য রয়েছে। ট্যাবলেটগুলির সমস্ত ফর্মুলেশনগুলির মধ্যে, ব্যাচ Formulation ৪ (F4) এবং Formulation ৮ (F8) এর ভাল ড্রাগ রিলিজ বৈশিষ্ট্য (drug release properties) দেখিয়েছে। *In vitro* ড্রাগ রিলিজ

প্রোফাইল বিশ্লেষণ থেকে দেখা যায়, Formulation ব্যাচ F4, 10% মিউসিলেজ এবং Formulation F8, 10% মিউসিলেজ এবং 10% স্টার্চের সমন্বয়ে গঠিত, যাহা 60 মিনিটে যথাক্রমে 40.8% এবং 31.63% ওষুধ অবমুক্ত করেছে। ওষুধ অবমুক্তকরণ গতিবিদ্যা অনুসন্ধান (Drug Release Kinetics Study) থেকে দেখা যায় যে, Formulation ,F4 প্রথম-ক্রম রিলিজ গতিবিদ্যা অনুসরণ করেছে এবং Formulation , F8 শূন্য ক্রম এবং হিগুচি মডেল -এর রিলিজ গতিবিদ্যা অনুসরণ করেছে। প্রাপ্ত ফলাফল থেকে বলা যায় যে, *Momordica charantia* থেকে প্রাপ্ত মিউসিলেজ সহজ লভ্য, ব্যয় সাশ্রয়ী ও বিষহীন হওয়ায় ইহা Tablet formulation এ ট্যাবলেট বাইন্ডার বা excipient হিসাবে বাণিজ্যিকভাবে ব্যবহারের উপযুক্ত।

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Abbreviation

BSM	Basil Seed Mucilage
DPP- 4	Dipeptidyl Peptidase-4
e.g.	For example
<i>et al</i>	And Others
etc.	Etcetera
FACS	Fluorescence-Activated Cell Sorting
FDA	Food and Drug Administration
Fig.	Figure
G6PD	Glucose-6-Phosphate Dehydrogenase
GLP-1	Glucagon-Like Peptide-1
GLUT- 4	Glucose Transporter Protein Type-4
HDAC	Histone Deacetylase
HIV	Human Immune Virus
HPLC	High Performance Liquid Chromatography
IC ₅₀	Half-Maximal Inhibitory Concentration
IVIVC	<i>In Vitro</i> and <i>In Vivo</i> Correlations
MAP30	<i>Momordica charantia</i> Antiviral Protein-30
MC	<i>Momordica charantia</i>
MCC	Micro Crystalline Cellulose
MCL	<i>Momordica charantia</i> Lectin
MCP	<i>Momordica charantia</i> Polysaccharides
MDA	Maleic Dialdehyde
MetS	Metabolic Syndrome
NIDDM	Non-Insulin-Dependent Diabetes Mellitus
NPC	Nasopharyngeal Carcinoma
PCOS	Polycystic Ovary Syndrome
PMBs	Plant-Made Biologics
PMMA	Polymethyl Methacrylate
PMPs	Plant-Made Pharmaceuticals
PPARs	Peroxisome Proliferator-Activated Receptors

PPI	Proton Pump Inhibitor
PTP1B	Protein Tyrosine Phosphatase 1B
RIP	Ribosome Inactivating Protein
SOD	Superoxide Dismutase
SRDDS	Sustained Release Drug Delivery System
TGF- β	Transforming Growth Factor- β
TNF	Tumor Necrosis Factor
USP	United State Pharmacopeia
WBG	Wild Bitter Gourd
WHO	World Health Organization

Chapter 1: INTRODUCTION

1.1 General introduction

For thousands of years, people from various civilizations have used medicinal plants to treat diseases as traditional medicine practices and maintain health condition. In ancient civilizations, including the Chinese, Egyptians, Greeks, Romans, and Indians were used different kinds of plants e.g. Turmeric, Bitter melon, Garlic, Lavender etc. for their medicinal properties. Plants produce hundreds of different chemical and biologically active compounds for a variety of purposes, such as defense against pathogens, insects, fungi, and herbivorous mammals. Plants contain a wide range of phytochemicals that have been found to have biological activity, either known or unknown. In some countries, health professionals advise the employment of medicinal plants as an alternate treatment (Awuchi, 2019). The World Health Organization (WHO) has observed that a significant percentage (80%) of the world's population uses ancient medicine traditionally for their initial health care treatment, which includes remedies derived from medicinal plants. (Smith *et al.*, 2012). Approximately seventy thousand medicinal plants have been used therapeutically. In India, about 20% of the plant species are used medicinally. Plants produce compounds and molecules that provide them with evolutionary advantages, like defence against herbivores or, in the case of salicylic acid, hormone in plant. Approximately 25% of the medicines prescribed to patients in modern medicine are derived from medicinal plants, and these substances and compounds are subjected to rigorous testing (Ahn *et al.*, 2017). The biochemical constituents of phytochemicals and their known pharmacological activities support their potential for use as medicines and serve as a framework for their applications and uses in modern medicine. To obtain compounds for drug discovery, a variety of techniques have been used, such as combinatorial chemistry, synthetic chemistry, and isolation from plants molecular modeling and other sources of natural origin. Drug development is the process of isolating and separating therapeutically useful, physiologically active ingredients from medicinal plant extracts. The use of plants to generate therapeutic proteins for the development of pharmaceuticals and biotech-drugs for the treatment of lethal illnesses has been made possible by advances in biotechnology. Instead of using more expensive facilities and

traditional methods based on animal cell cultures and microbial fermentation to produce therapeutic proteins, these plant-made pharmaceuticals (PMPs) or plant-made biologics (PMBs) offer a more effective, safe, and economical platform. Plants are the fastest-growing classes of pharmaceutical products and an excellent platform, because of their low risk of infection human or animal by pathogens. The pharmacy or apothecary shops of 1800s, In European pharmaceutical sectors, some pharmacists treated patients with traditional medicines and it remedies from the area, including plant extracts like quinine, strychnine, and morphine. In addition to morphine, early drugs like quinine, cocaine, codeine and digitoxin were isolated as a result of drug discovery from medicinal plants. At its efforts to discover new drugs, the pharmaceutical remains very much interested about discovering the traditional applications of different plants (Saleem *et al*, 2020). The bioactive ingredients in these plant extracts must be separated and identified using a bioactivity-guided fractionation process. When the pharmacological effect is not controlled by a single component but rather results from the synergistic action of multiple compounds, bioactive standardized extracts are crucial. The majority of experimental clinical applications of plant secondary metabolites and their derivatives over the last half-century have been focused on achieving this objective. In the fight against cancer, the developing of medications derived from medicinal plants has proven crucial with their actions.

1.2 Plant-derived gum and mucilage

Natural plants have an important role preserving our health. Natural polymers are large molecular weight compounds derived from natural sources such as plants, microbes, and animals. Proteins, cellulose, starch, resins etc. are example of natural polymers. Due to various biological characteristics, including biochemical adaptability, metabolic biodegradability, cell localization and interactions, and resemblance to the extracellular matrix, natural polymers are organic molecules and can be used as drug delivery mechanisms (Rajeswari *et al.*, 2021). Natural gums and mucilage are less expensive, less toxic, and biocompatible properties. Different pharmaceutical dosage forms, such as coatings for film substances, sublingual products, small particles, micron-sized particles and polymers that are natural in viscous fluids such as eye solutions and suspensions products, have been investigated for the use of plant-based polymers. Their efficacy and suitability have been established. Alterations of polymers that are useful components in

developed drug delivery systems has been produced through modification of natural gum or mucilage. These modifications have increased the uses of natural gum as cutting-edge drug delivery methods in nanomedicine and gene delivery (Awuchi, 2019). Mucilage is a polymeric polysaccharide complex that also contains glycoprotein and a variety of bioactive components like carbohydrates, glycosides, alkaloids, tannins, and steroids. Plant-derived mucilage can be obtained from the particular mucilage cells present in different plant parts, including fruits, leaves and seeds (Mahmud *et al.*, 2021). Plant mucilage is admired for its capacity to hold onto water, produce a gel-like consistency, and offer a number of health advantages. It is frequently used in food and cosmetic products as a natural, plant-based substitute for artificial thickeners and gelling agents (Bahadur *et al.*, 2017). Plant mucilage's characteristics make it a flexible and sustainable component for a range of uses. Because of the bio-incompatibility, toxicity, and carcinogenic activity of synthetic polymers rather than plant-based, naturally generated biopolymers like mucilage have received more attention as crucial constituents for sustainable, available, and essential products. They are the material of choice for efficient medication administration due to their unique biological characteristics and chemical flexibility. Mucilage is a form of polysaccharide that has several different physical and chemical characteristics and is frequently utilized in pharmaceutical applications (Tosif *et al.*, 2021). Mucilage are used as tablet binders and disintegrates, as well as mucilage sustains, suspends, thickens, emulsifies, gels, and stabilizes tablets to get suitable form. Mucilage has been used for centuries to treat speed wound healing, obesity, diabetes disease, and increase immune system. Because of its great water absorption capacity, mucilage is in high demand for water filtration. Mucilage-based processed foods are now gaining popularity in the food production because of its thickening, gel formation and emulsifying activity (Munir *et al.*, 2021).

Plant-derived polymers such as mucilage are widely utilized in the pharmaceuticals, paper, and cosmetic sectors because of their film coating, emulsifier, binding agents, and gelling agent's properties. As a result, they are in great demand in the food business and other industries. Many different types of living systems, including plants, algae, animals, bacteria, and fungus, are enable of biosynthesizing of polysaccharides (Kumar *et al.*, 2022).

1.2.1 Classification of gum and mucilage

There are different kinds of gums and mucilage as following (Nokhodchi *et al.*, 2012; Jania *et al.*, 2009) following in table 1.1:

Table 1.1: Classification of gum and mucilage

Sl No.	Name	Class
1.	Based on charge	a. Non-ionic seed gums (e.g.: Guar, tamarind, xanthan, amylose, locust bean etc.). b. An-ionic gums (e.g.: Arabic, gellan, agar, algin, carrageenans, pectic acid, karaya, tragacanth etc.).
2.	Based on source	a. Marine origin, (eg. Agar, carrageenans, alginic acid) b. Animal origin (eg. Chitin and chitosan, chondroitin) c. Microbial origin (eg: Xanthan, pullulan, zanflo, emulsan , schizophyllan, lentinan ,dextran, curdian etc.)
3.	Based on semi-synthetic source	a. Starch derivatives (eg.: Hetastarch, starch acetate etc.) b. Celluloses derivatives (eg.: Carboxymethy)
4.	Based on shape	a. Linear (eg.: Algins, amylose, cellulose, pectins etc.) b. Branched (eg.: Short branches- xanthan, xylan etc.)
5.	Based on monomeric unit	a. Homoglycans (eg.: Amylose, arabinanas, cellulose) b. Diheteroglycans (eg.: Algins, carragennans) c. Tri-heteroglycan (eg.: Arabinoxylans) d. Tetra-heteroglycans e. Penta-heteroglycans

1.2.2 Advantages of mucilage and gums in pharmaceutical sciences

Several uses of gums and mucilage in pharmaceuticals are (Jania *et al.*, 2009) -

- **Hydrophilic characteristics:** They are extremely hydrophilic in nature, many natural gums and mucilage work effectively to hydrate the skin or provide

moisture to other products. Topical treatments like moisturizers, gel-like substances, and cream benefit greatly from this.

- **Biocompatible and biodegradable:** The carbohydrates found in all of these plant mucilage are composed of consisting of recurrent molecules of glucose (monosaccharide). They are therefore not harmful. Biodegradable polymers are naturally occurring and created by all living things. They are genuinely renewable and are not harmful to the health of people or other living things.
- **Less side effects:** Mucilage are preferred in preparations for sensitive individuals, including children, elders, and people with weakened immune systems, because they are natural compounds and typically cause fewer reactions than synthetic excipients or polymers.
- **Regulated drug dispensation:** In controlled-release drugs formulations, natural gums and mucilage can be utilized to help control the release of active pharmaceutical ingredients (APIs) over time. By keeping the drug's bloodstream concentration constant, this increases therapeutic efficacy and lowers adverse reactions.
- **Cost effective:** Natural sources are always less expensive to utilize, and their production costs are also considerably lower than those of synthetic materials and cost effective for pharmaceutical manufacturing.

1.2.3 Disadvantages of mucilage and gums

- **Microbiological interaction:** At least 10% moisture is present in gums and mucilage. And due to their structural interaction with the environment, there is a higher risk of microbial contamination during manufacturing, if they are not properly processed, handled and stored in suitable place (Bahadur *et al.*, 2017).
- **Reduced viscosity after storage:** Viscosity of formulations containing gums and mucilage increases when they come into contact with water moisture. It has been found that the viscosity of gums and mucilage's reduces with storage, indicating their complexity (Bahadur *et al.*, 2017).

- ***Solubility limitations:*** The use of certain gums and mucilage's in particular formulations may be limited by their limited solubility in water or particular solvents.

1.2.4 Applications of gum and mucilage

- ***Applications in pharmaceutical products manufacturing***

Gums and mucilage's have a range of uses in the pharmaceutical sector. They have growth-promoting activities or demulcent properties that are used in medicine to reduce coughs. As ingredients in dental and other adhesives, they can also be utilized as bulk laxatives. These hydrophilic polymers can be used as tablet binders, microcapsule coating agents, gelling agents, disintegrates, thickening agents, emulsifiers, suspending agents, stabilizing agents, film forming agents in transdermal and periodontal films, buccal tablets, sustaining agents in matrix tablets and microcapsules for drug delivery and protein delivery (Malviya *et al.*, 2011).

- ***Applications in the food manufacturing and processing***

Gums and mucilage's are extensively utilized in the production of many foods and food-related products. Guar gum and locust bean gum, stabilizers for ice-cream, meat products, instant pudding such as carrageenan, dairy, confectionery, confections, beverages, backing goods, and sauces are uses various gums like gum arabic, tragacanth, pectin's, alginates, and xanthan gum (Stephen *et al.*, 2016).

- ***Industrial application***

Mucilage, a gelatinous substance obtained from various plants, has a variety of industrial applications due to its unique properties such as its ability to form thick gels, water retention, and adhesive qualities (Malviya *et al.*, 2011).

1.2.5 Applications of plant-based mucilage's in Nanomedicine

Plants are widely used in science and medicine in modern science for a wide range of purposes, and this has drawn significant attention due to the growing interest in using natural components. Mucilage's or polysaccharide hydrocolloids, have unique functional and medicinal properties along with significant structural, chemical, and physical

variations. They serve as binding, thinning, sustaining and humidifying agents. Encapsulating food ingredients and pharmaceuticals has benefits for delivery properties, but it also presents a significant opportunity to boost the stabilization of bioactive compounds. Using mucilage for drug delivery represents one of its many potential uses. A significant amount of research has been reported on the creation of new methods for delivering drugs employing both natural and synthetic polymers. It is evident that using natural polymers in pharmaceutical formulations has additional advantages and is important drug delivery methods for developing new drugs. Natural polymers have the ability to change their functional properties and are less toxic than synthetic polymers. They are also more affordable, readily available, biocompatible, sustainable, and biodegradable (Amiri *et al.*, 2021).

1.3 *Momordica charantia*

A species of flowering plant in the Cucurbitaceae family, *Momordica charantia* L. is also referred to as a bitter gourd, bitter apple, bitter squash, balsam-pear, karala, usta, and others (Jia, 2017). It is grown in India, China, Japan, Thailand, Singapore, Vietnam, Malaya, Middle East, East Africa, Brazil, Colombia, Cuba, Ghana, Haiti, Mexico, New Zealand, Nicaragua, Panama, and South America (Grover *et al.*, 2004). In addition to being cooked and eaten as green vegetables, *Momordica charantia* fruit and leaf extracts are used to make tea (Ahmad *et al.*, 2016). It has incredibly bitter taste, which are frequently used in cooking as a vegetables and as a natural treatment. Around the world, *Momordica charantia* is a commonly grown medicinal plant. Because it contains a variety of bioactive compounds, its pharmacological activities and nutritional properties have been associated with therapeutic effects. It is used to treat ulcers, wounds, colic, cough, diabetes, fever (malaria), gout, helminthiases, and other inflammatory conditions. It is one of the most promising plants for the treatment of diabetes (Ahmad *et al.*, 2012).

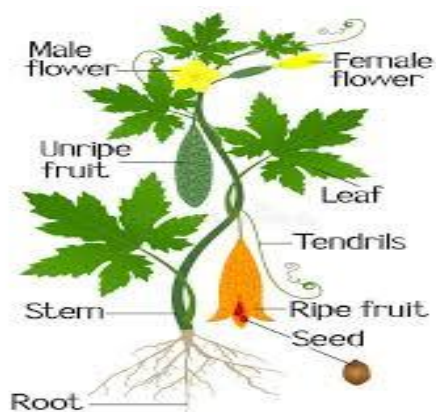


Fig.1.1: Whole plants



Fig.1.2: Cross section of fruits



Fig.1.3: Line drawing



Fig.1.4: Chopped dry fruits

Fig: *Momordica charantia* Linn

1.3.1 Scientific identification

The group of *Momordica charantia* contains approximately sixty species of herbaceous, annual, or perennial climbers, occasionally small plants that are members of the Cucurbitaceae family (Ahmad *et al.*, 2016).

Kingdom: Plantae

Subkingdom: Viridiplantae

Division: Tracheophyta

Subdivision: Spermatophytina

Class: Mangnoliopsida

Suborder: Rosanae

Order: Cucurbitales

Family: Cucurbitaceae

Genus: *Momordica*

Species: *Momordica charantia* L.

1.3.2 Botanical description

Momordica charantia Linn is a flowering climber in the Cucurbitaceae family. It is an annual growing plant that often reaches a height of 5 meters. It's long, and produce knobby fruits. It has 4–12 cm wide, alternate, simple leaves with 3–7 deeply divided lobes. The lobes feature a few tiny border tips but are mostly blunt. There are no stipulated terms. Actinomorphic and usually unisexual, flowers short (for females) or long (for males) peduncles with short-lived epigenous zones that are yellow in colour (Ganguly *et al.*, 2000). Fruit is oblong in shape with an ovoid, ellipsoid, or spindle-shaped exterior that is typically warty. Its cross section is hollow, with a thin layer of flesh surrounding a core seed chamber that contains large, flat seeds and pith that is 12.8–13 mm long, compressed, corrugated, and sculptured on both sides. Initially, the fruits are green; upon ripening, they transition to orange and subsequently to yellow. The fruit releases numerous reddish-brown or white seeds that are encased in scarlet arils by splitting into three irregular valves and curling backward. (Mantipelly *et al.*, 2020).

1.3.3 Traditional name of *Momordica charantia* in different countries

Various names of *Momordica charantia* in different countries including

Table 1.2 : Traditional name of *Momordica charantia*

Country	Name	Country	Name
Bangladesh	Korolla, Usta	India	Karela, Karilla
Pakistan	Karela	Sri Lanka	Karavila
Vietnam	Muóp Đắng, Khỏ Qua	Indonesia	Pare, Peria Katak
Thailand	Mara	Philippines	Ampalaya
China	Kǔguā	Japan	Nigauri, Gōyā
Dutch	Springkomkommer	French	Balsambirne
Africa	Margose , Margoze	Jamaica	Ceracea
Trinidad And Tobago	Caraille , Carilley	Nigeria	Ejirin, Garafun
United State	Bitter Gourd, Bitter Cucumber, Balsam-Pear, Balsam-Apple, Bitter Melon, Paria		

1.3.4 Phytochemistry

A potent plant with high nutritious content and a wide variety of advantageous components is *Momordica charantia*. These include antioxidants, vitamins, minerals, and bioactive compounds, all of which contribute to its remarkable flexibility in the treatment of a wide range of disorders. The main chemical constituents of *Momordica charantia* are flavonoids, isoflavones, terpenes, anthroquinones, vicine, charantin, momordicius, momordenol, momordin, momorchanins, momordicilin, and momordolol (Ahmad *et al.*, 2016). Cryptoxanthin, cycloartenols, cucuritanes, erythrodiol, elaeostearic acids, galacturonic acid, gentisic acid, goyaglycosides, goyasaponin, guanylate cyclase inhibitors, gypsogenin, hydroxytryptamines, multiflorenol, lanosterol, linoleic acid, linolenic acid, momordenol, momordicinin, momordicosides, and glucosinolates (Ahmad, 2016) etc. Vitamins B1, B2, B3, B9, C, A, and E are present in the different parts of the fruits. The fruit has a high dietary fiber content and is also a good source of iron, zinc, phosphorus, magnesium, potassium, and calcium (Kumar, 2022).

- **Charantin**

Charantin is a unique triterpenoid compounds that is present in *Momordica charantia* and may have anti-diabetic properties. Charantin utilized to treat diabetes and possibly take the place of other medications. It is a combination of stigmasteryl glycoside and sitosteryl glycoside (Krawinkel *et al.*, 2006). Kuguacins which are cucurbitane triterpenoids were discovered in the vines and leaves of *Momordica charantia*. They include two pentanercucurbitacins, one octanorcucurbitacin and two trinorcucurbitacins. By using a high performance thin layer chromatographic technique, the charantin was extracted and quantified from the fruits of *Momordica charantia*. According to studies, the substance is used to the oral hypoglycemic drug tolbutamide in terms of effectiveness (Joseph *et al.*, 2013). In a study, sitosterol and stigmastadienol glycosides, two aglycones of charantin, were separated; however, when evaluated individually for hypoglycemic activities through *in vivo* experiment, these two elements did not significantly shown alter blood glucose levels. This implies that other distinct, as yet unidentified components of charantin may be causing the hypoglycemia effects observed in diabetics (Harinantenaina *et al.*, 2006).

- **Polypeptide – p**

Momordica charantia has a particular form of protein called polypeptide-p, sometimes referred to as p-insulin. Its activity may have insulin like effects on blood sugar regulation for people with diabetes or those trying to control their blood sugar levels (Oyelere *et al.*, 2022). By assisting cells in absorbing glucose from the circulation, polypeptide-p has been suggested to work similarly to insulin in reducing blood sugar levels (Ahmad *et al.*, 2012). According to report, *Momordica charantia* extracts high in polypeptide-p may improve glucose tolerance and insulin sensitivity. (Krawinkel *et al.*, 2006). Since it reduces the activity with type 1 diabetes, P-insulin can be used as an alternative to insulin produced from plants. In rats with type 1 diabetes produced by streptozotocin (STZ), the extract from *Momordica charantia* seeds shown hypoglycemic effects when taken orally. This shows that compounds contained in *Momordica charantia* seeds other than p-insulin may be helpful in the management of type 1 diabetes (Wehash, 2010).

- **Vicine**

Vicine is a bitter taste of chemical compound found in bitter *Momordica charantia*. It is a type of glycoside, which consist of a sugar molecule attached to a non-sugar component. Vicine, along with its related compound called convicine, which are responsible for the bitter taste of fruits (Ham *et al.*, 2009). People with glucose-6-phosphate dehydrogenase (G6PD) deficiency are advised to avoid consuming foods that have high in vicine and related compounds, such as certain legumes and plants like bitter gourd (Joseph *et al.*, 2013) . Many *in vivo* studies confirmed the hypoglycemic potential and treatment of diabetes with hypoglycaemic agent's vicine which present in the plants (Mahwish *et al.*, 2021).

1.3.5 Biological activities

The *Momordica charantia* fruit increases the production of insulin to maximize the hormone's effects. In diabetic rats, both fresh and dried fruit extract lower blood sugar levels. Alloxan-induced diabetic rats show hypoglycemia, anti-diabetic, hypolipidemic, and hepato-renal protective benefits from its extracts. It controls micro vascular dysfunction, a frequent consequence of diabetes, by decreasing capillary permeability at the capillary and arteriolar levels (Raman *et al.*, 1996).

A steroidal saponin and a hypoglycemic substance is called charantin. In order to create charantin, stigmasteryl glucoside and sitosteryl glucoside were combined. The polypeptide P-insulin has 166 amino acids in it and has a molecular weight of about 11,000 Da (Dalton), is another bitter guard of hypoglycemic drug that causes hypoglycemia in rabbits when given orally or intravenously to the patients. Experimental testing has demonstrated that polypeptide-pZnCl₂ is responsible for the blood sugar-lowering action. The vicine pyrimidine nucleoside present in seeds and fruits can induce hypoglycemia in rats when given intra peritoneal. Charantin-rich *Momordica charantia* extracts increase the sensitivity of type 2 diabetic's insulin receptors.

- ***Modes of action of Momordica charantia in anti-hypoglycemic activity***

Several psychological, pharmacological, and biological mechanisms are responsible for the hypoglycemic effects of *Momordica charantia* and its different extracts and constituents has been suggested. The potential hypoglycemic effects of *Momordica charantia* and its different extracts and different compounds include preservation of islet cells and their functions, lowering intestinal glucose uptake (Cummings, 2004), resistance of adipocyte differentiation, activation of key enzymes of the HMP pathway, reduction of key gluconeogenic enzymes, and stimulation of peripheral and skeletal muscle glucose uptake (Sărăndan, 2010). *Momordica charantia* preserves pancreatic beta-cells by inhibiting MAPKs and NF- κ B in MIN₆N₈ cells. According to the study, *Momordica charantia* increases serum glucose levels and improves liver lipid profiles and serum lipid profiles through altering the expression of the Peroxisome Proliferator Activated Receptor-gene (PPAR-gene). Clerosterol and 5-stigmasta-7-en-3-ol, two sterols with notable hypoglycemic effects, were isolated from *Momordica charantia* fruits. In diabetic rats, it was found to exhibit potent neuroprotective effects against neurological deficits brought on by systemic cerebral ischemia and reperfusion injury. Protein tyrosine phosphatase 1B (PTP_{1B}) has been suggested as a potential therapeutic target for the management of type 2 diabetes because it functions as a regulator of insulin signaling (Hoang *et al.*, 2010). Many physiological and biochemical pathways are hypothesized to be responsible for the hypoglycemic effects of *Momordica charantia*, its extracts, and isolated components. The preservation of pancreatic islet cells and their functions, the stimulation of peripheral cells and skeletal muscle to absorb glucose, the inhibition of intestinal glucose absorption, the decrease in the expression of adipocyte differentiation, the inhibition of vital gluconeogenic enzymes,

the stimulation of significant enzymes, and effects similar to those of an insulin secretagogue are some of these (Sărăndan, 2010).

- ***Management of production of insulin and the cells of the pancreas***

Insulin may be secreted by endocrine pancreatic cells when *Momordica charantia* is taken orally. The daily oral administration of *Momordica charantia* fruit juice and the distribution of *Momordica charantia* present in the pancreas cells of diabetic rats induced by STZ. The islets of Langerhans significantly improved after receiving ethanolic extract from *Momordica charantia*. Additionally, physiological tests have suggested *Momordica charantia* can cause the liver to absorb glucose by increasing the release of insulin from the pancreatic endocrine glands (Ahmed *et al.*, 2004). Accordingly, current research indicates that *Momordica charantia* may have a variety of mechanisms of action, such as recovery, an increase in the number of cells that produce insulin, and the secretion of insulin, to achieve its hypoglycemic effects. *Momordica charantia* and its extracts may have characteristics of insulin-like cell proliferation and growth. However, additional research is necessary, at the molecular level, to determine the exact mechanisms through which *Momordica charantia* can either prevent or cure cells that are damaged (Liu *et al.*, 2021).

- ***Glucose metabolism***

A key biological function of insulin is to facilitate the body's different cells' absorption of glucose for energy production. *Momordica charantia* may directly cause a drop in blood glucose levels is crucial because of its various extracts and constituents have hypoglycemic effects. The aqueous and ethanolic extracts of *Momordica charantia* fruit can stimulate glucose-6-phosphatase dehydrogenase while inhibiting glucose-6-phosphatase enzymes and fructose-1,6-diphosphatase (Shetty, 2005). Different *Momordica charantia* extracts can promote peripheral cell glucose absorption in both age-matched control and STZ-induced diabetic rats, the effects of chloroform extract of *Momordica charantia* powder compared to insulin on the skeletal L6 myotube's capacity to absorb glucose and amino acids, as well as the uptake of Na⁺ and K⁺ glucose by jejunum brush border membrane vesicles. A phosphatidylinositol 3-kinase inhibitor which known as Wortmannin, significantly decreased the uptake of 3H-deoxyglucose by L-6 myotubes when *Momordica charantia* juice or insulin were incubated (Joseph *et al.*, 2013).

Momordica charantia has characteristics similar to V-insulin, a phytochemical component of *Momordica charantia* that has lower blood glucose capabilities. Over a 10-week period, daily oral consumption of *Momordica charantia* fruit juice considerably decreased the amount of Na⁺ and K⁺-dependent 1, 4 C-D-glucose absorbed by rat jejunum brush border membrane vesicles on skeletal muscle cells when compared to vesicles derived from rats with STZ-induced diabetes. With its various extracts, *Momordica charantia* can directly regulate blood sugar levels via two distinct mechanisms. It can regulate the amount of glucose that is absorbed into the bloodstream by the gut after eating a meal. Secondly, they function similarly to insulin in order to enhance the uptake of glucose into skeletal muscle cells. Furthermore, it is believed to regulate the body's metabolism of glucose by utilizing the same intracellular signaling pathways as insulin. (Jia *et al.*, 2017).

1.3.6 Traditional and medicinal uses

Momordica charantia Linn. has been administered for long time. Asian traditional medical systems as a beneficial drug for both disease prevention and treatment. *Momordica charantia* fruits are used to treat ulcers, wounds, colic, cough, diabetes, fever (malaria), gout, helminthiases, and other inflammatory conditions (Bortolotti *et al.*, 2019). In both animal and human trials, it has also been demonstrated to have hypoglycemic (anti-diabetic) characteristics. *Momordica charantia* leaf juice is used to completely treat piles. *Momordica charantia*'s bitter taste properties is used to purify blood and other skin-related blood issues, such as anemia, can also be treated. Hepatic disease can be prevented and treated with *Momordica charantia* juice. The leaves are used to treat a variety of conditions including colitis, transmission, parasitic organisms, influenza, liver disease, and helminthiases. Gastrointestinal parasitic organisms, high cholesterol levels, digestive gas, metabolic syndrome, liver and spleen problems, discomfort in the stomach, and ulcers can all be treated with seeds. Roots can be used to treat syphilis, arthritis, boils, ulcerations, septic enlargements, ophthalmia, and Prolapsus vaginae. Juice from *Momordica charantia* helps to reduce the problem of pyorrhea.

Traditional medicine uses of *Momordica charantia* in Asia: Tribal people use *Momordica charantia* to treat leprosy, respiratory tract infections, hemorrhoids, hydrophobia, dermatitis, obesity, problems with menstruation, discharge from the vagina, bowel movements, nutrition, diabetes, high blood sugar levels, jaundice, obstructions,

intestinal parasites, kidney, liver, fever (malaria), gout psoriasis, osteoarthritis, scabies, snakebite, piles, tonic, anthelmintic, and purgative (Ahmad *et al.*, 2016).

1.4 Tablet

Tablet is a solid dosage form which contains one or more medications in a unit dose, with or without excipients or binders. 90% of all drugs are administered orally for systemic action in the body and dose accurately placed hence less errors. They are ground in a specified form and size, such as round, cylindrical, triangular, and rectangular and are also intended to be ingested. For the oral administration of drugs, tablets are the most widely used dosage form. Tablets can be chewed or consumed orally. Some dissolve or disperse in water in advance of administration. With some, the active ingredient is administered at an appropriate rate while being placed in the mouth. These are made by either compression or molding methods to give their proper shape (Manju *et al.*, 2023).

1.4.1 General properties of tablets

The characteristics of the production process and the constituent materials have an impact on the tablet's qualities. In most cases, a formulation requires excipients such as diluents, binders, and lubricants to make manufacturing easier and ensuring that the final tablets have the appropriate qualities and good tablets properties. In the content release process, reproducibility and reliability are essentials for the tablet. The following characteristics define an excellent tablet (Ubhe *et al.*, 2020):

- An elegantly designed tablet should be free of discoloration, chips, cracks, and contamination.
- The active pharmaceutical ingredient must be released into the body in a manner that is obvious
- It must possess the necessary mechanical strength and not break when being transported
- It must not change or alter its chemical or physical properties in any way; and it must have the right amount of chemical stability over time.

1.4.2 Classifications of tablets in pharmaceuticals

The amount of different pharmaceutical ingredients and the intended method of administration that determine the shape, size, and weight of the various tablet forms. Different types of tablets are as follows (Manju *et al.*, 2023) –

1. Based on Route of Administration

- i. Oral Tablets
- ii. Buccal Tablets
- iii. Sublingual Tablets
- iv. Chewable Tablets
- v. Effervescent Tablets
- vi. Vaginal Tablets

2. Based on Drug Release Characteristics

- i. Immediate-Release Tablets
- ii. Sustained-Release Tablets
- iii. Controlled-Release Tablets
- iv. Delayed-Release Tablets
- v. Orally Disintegrating Tablets (ODTs)

3. Based on Manufacturing Method

- i. Compressed Tablets (CTs)
- ii. Molded Tablets - Hypodermic Tablet and Dispensing /soluble Tablet

4. Based on Coating

- i. Uncoated Tablets
- ii. Coated Tablets -Sugar Coated, Gelatin Coated and Film Coated
- iii. Enteric-Coated - Layered Tablet and Inlay Tablet

5. Based on Dissolution/Disintegration

- i. Fast-Disintegrating Tablets
- ii. Slow-Disintegrating Tablets

6. Based on Patient-Specific Needs

- i. Pediatric Tablets
- ii. Geriatric Tablets
- iii. Fixed-Dose Combination Tablets

7. According to Action

- i. Modified Release Tablet
- ii. Unmodified Release Tablet

8. Based on Purpose

- i. Conventional Tablets
- ii. Specialty Tablets
- iii. Diagnostic Tablets
- iv. Placebo Tablets

1.4.3 Advantage of tablets

There are many types of solid dosage forms manufactured. According to patients' safety and consuming of drugs, tablets are easily available. It has many advantages. The advantages of tablets are as follows (Ubhe *et al.*, 2020) -

- Within terms of physical, chemical, and microbiological characteristics, most stable.
- Simple to handle, utilize, and carry out with a beautiful appearance.
- Easy to consume, and no additional processing procedures are needed during manufacture.
- Unit Dosage Form with precise and consistent Dosing.
- Offer medication protection from environmental factors like air, moisture, and light.
- Compared to other solid dosage forms, large production runs can be easily accomplished at cheap manufacturing costs. The uncomfortable exams could be covered up by sugar.
- It may be prepared with two or more medicinal ingredients, even ones that are physically and chemically incompatible, therefore it is best to avoid taking multiple pills at once.
- They are well suited for some products with unique release profiles, like enteric or delayed release products.

1.4.4 Disadvantage of tablets

While tablets have a lot of advantages, they also have quite a few disadvantages. It's important to carefully consider these disadvantages for a tablet. Disadvantage of tablets are as follow (Ubhe *et al.*, 2020) -

- Increased product loss as a result of manufacturing processes with several levels.
- Cefpodoxime proxetil is an amorphous, low density, or medication in the form of floppy powder that is difficult to compress during the compression stage.
- It is not advisable to compress hygroscopic drugs. A specific coating may be required for oxygen-sensitive medications because it absorbs moisture and causes issues during compression.
- Physiological factors like stomach empty time affect drug absorption, which differs from patient to patient.
- A broken, crushed, or split tablet may cause the active ingredient to be distributed poorly, which could lead to incorrect dosing. With extended-release or coated tablets, this is particularly problematic because changing the tablet can alter the rate at which the drug is released.
- The availability of some tablets can be an issue.

1.4.5 Ingredients used in tablets

In addition to the active ingredients, the tablet also contains a number of inert substances known as excipients or additives. Different excipients are as follow (Manju *et al.*, 2023)

- **Diluent:** To make handling tablets easier during fabrication and to understand the intended content's consistency.
- **Binder and adhesive:** Employed as a binding agent in tablets, giving powdered materials cohesive strength. Granules are formed by adding binder in both dry and wet forms e.g.: Acacia.
- **Disintegrates:** Increase the tablet fragments surface area and eliminate the cohesive forces holding the tablet's constituent particles together.
- **Lubricants:** Used for preventing tablets from sticking to dies and punches and decrease friction between the die wall and tablet. Facilitates the easy removal of tablets from the die cavity. Example: Insoluble- Stearic acid.
- **Glidants:** Supports in the granules easy movement from the hopper to the die cavity and reduces particle friction. Example: Talc.
- **Coloring agents:** Improve patient acceptance, support identity, and prevent counterfeiting. Make a light sensitive medication more stable.

- **Flavoring agents:** Enhance the texture and taste of oral disintegrable and chewable tablets. It is possible to incorporate flavors as oils, aqueous (water-soluble), solids (spray dried flavors) or solids.
- **Anti-adherents:** Prevent the tablets surface from adhering to the die walls and punches.
- **Absorbents:** Minimize moisture from these liquid or semi-solid ingredients that could damage tablets or affect the cohesiveness of tablet granules or powder, enabling proper tablet compression during formulation.

1.4.6 Importance of binding agents in tablets

The integrity and quality of a tablet are greatly dependent on the binding agent, which is also referred to as a binder or adhesive in tablet formulation. The powdered or granulated ingredients are held together by the binding agent, which keeps the tablet's shape and structural strength unchanged. Poly vinyl pyrrolidone (PVP), starches, certain gums, and cellulose derivatives of all kinds—including microcrystalline cellulose—are frequently utilized as binding agents. Binding agents are crucial in the formulation of tablets for the following basic reasons (Vaishnavee *et al.*, 2021)

- **Tablet cohesion:** By effectively holding the powdered or granulated ingredients together, binding agents provide the tablet formulation cohesion. The cohesiveness of the tablet is crucial in avoiding crumbling or shattering during production, packaging, shipping, and user handling.
- **Tablet hardness:** The tablet's hardness is partially caused by the binding agent. One important factor that influences a tablet's capacity to sustain mechanical stress during handling and transportation without shattering or crumbling is its hardness. The tablet will have the necessary hardness for stability, if the binding agent is properly used.
- **Disintegration and dissolution:** The properties of tablet dissolution and disintegration can be affected by binding agents. They play a role in regulating, how quickly the tablet disintegrates into smaller particles when it comes in contact with liquids or moisture in the digestive system. This ensures the active pharmaceutical ingredient (API) is released for absorption in a timely and effective manner.

- **Uniformity of dosage:** In order to make sure that the active ingredient and other excipients are distributed uniformly throughout the tablet, binding agents are important. Since each tablet should contain the prescribed amount of the active ingredient, uniformity is essential for achieving consistent dosing.
- **Ease of manufacturing:** Binding agents facilitate the compaction process, which makes tablet manufacturing simpler. They facilitate the formation of tablets with uniform size, weight, and hardness by assisting the powder or granules in sticking together during compression.
- **Stability and shelf life:** By keeping the tablet's structure from breaking down over time, binding agents can help increase the stability and shelf life of tablets. This is essential to maintaining the drug's quality and efficacy for the entirely recommended shelf life.

1.4.7 Tablets manufacturing

There are three types of tablets manufacturing methods.

- i. Wet granulation methods
- ii. Direct compression methods
- iii. Dry granulation methods

i. Wet granulation methods

Wet granulation is the technique was using the most frequently in the pharmaceutical industry. Powders are mixed with a liquid solution to create a wet mass (with or without a binder), or they are mixed with an adhesive to create granules without compacting them in machine. Granules are made after the moist material is dried and sized. The moist powder particles are joined together by capillary and viscous forces when liquid is added. Further drying results in the formation of agglomerates because it strengthens. The active ingredient, diluent, and disintegrating substances are thoroughly combined. Twin shell, double cone, placatory, sigma blade, ribbon, and other types of blenders are commonly used in large-scale production. The moist mixture can be forced through using a 6 or 8 mesh screen or a number of mills. Drying chambers with thermo stable heat controllers and circulating air current are equipped with large trays that contain wet materials from wet milling procedures. Dryers like fluidized beds and tray dryers are

widely used. After drying, the granulation is sent through a smaller mesh screen to minimize the size of the particles (Bhowmik *et al.*, 2014).

ii. Direct compression methods

Active pharmaceutical ingredients (APIs) and excipients are compressed properly into tablets using the direct compression method, which eliminates the need for an additional granulation procedure. Compressed tablets are produced by single compression using tablet machines. The tablet punching machine has upper and lower punches which crush the powdered or granulated tableting material under required force once it has entered the crushing chamber (Bhowmik *et al.*, 2014).

iii. Dry granulation methods

Dry granulation, also known as pre-compression or double compression, is applied to improve the flow and compression properties of powders that aren't otherwise appropriate for compression. To make powder granules, powder particles are compressed into large compact particles, which are subsequently broken up into smaller granules. Later on, these granules can be used to manufacture dosage forms. If the formulation ingredients are too fluffy or highly susceptible to flow ability problems for direct compression to be a sustainable processing option, or if they are too sensitive to degradation from heat and/or moisture for wet granulation to be a practical processing option for increasing density, dry granulation is usually used in the production of tablets. When wet granulation cannot be employed, the method may be used in place of direct compression. Because dry granulation is more effective and because wet granulation is more costly and time-consuming for the maker, this is not frequently done. Some unit operations, such as medication grinding or micronization, weighing, mixing, slugging, dry screening, lubrication, and compression into tablets, are retained after using the dry granulation method to prepare tablets, but others are eliminated. For dry granulation to successfully produce tablets, either the active ingredient or the diluent must possess sufficient inherent cohesive or binding characteristics (Bhowmik *et al.*, 2014).

1.5 Diabetes

Diabetes is a metabolic conditions or disorder in which glucose levels in the blood remain elevated for an extended period of time and it occurs either the pancreas does not create enough insulin or cells within the body do not respond efficiently to the insulin produced. As a result, the amount of glucose in the blood might rise, leading to a range of diseases over time (Roglic, 2016).

1.5.1 Classification of diabetes

i. Type 1 diabetes

An autoimmune disease is type 1 diabetes. In this situation, the body's insulin-producing beta cells in the pancreas are purposefully and inadvertently destroyed by the immune system. Although the specific cause of this immune response is unknown, it is thought to be a combination of environmental and genetic factors. Genetic predispositions and some viral infections can cause the immune system to attack pancreatic cells (Ria, 2008).

ii. Type 2 diabetes

When the body develops resistant to the effects of insulin or the pancreas is unable to produce enough insulin to maintain blood sugar levels within normal ranges, type 2 diabetes develops. Type 2 diabetes is also referred to as insulin-resistant diabetes and adult-onset diabetes. Type 2 diabetes is caused by a number of factors including Genetics, Lifestyle, Age, High Blood Pressure, Gestational Diabetes, Polycystic Ovary Syndrome (PCOS), and Ethnicity etc. (Tyagi *et al.*, 2018).

iii. Signs and symptoms of type 2 diabetes

Hunger and thirst increased, regular urination, exhaustion, vision distortion, wounds heal slowly, hands or feet that tingle or feel numb, skin infections or itching, recurring yeast infections, loss of weight without effort etc.

iv. Medication of type 2 diabetes

Sl No	Name	Mode of action	Example
1.	Sulfonylureas	Reduce blood sugar levels by stimulating to produce more insulin from the pancreas.	Glyburide, glipizide , glimepiride and chlorpropamide
2.	Glinides or meglitinides	Reduce blood sugar levels by stimulating to produce more insulin from the pancreas.	Repaglinide and nateglinide
3.	Biguanides	Reduce the amount of glucose produced by the liver, slow down the body's conversion of carbs to sugar, and improve insulin's efficiency.	Metformin , proguanil and buformin
4.	Alpha-glucosidase inhibitors	Decrease blood glucose levels by prolonging the degradation of carbohydrates and decreasing the absorption of glucose from small intestines.	Acarbose, miglitol and voglibose
5.	Thiazolidinediones	Increase the amount of glucose that penetrates the muscles, fat, and liver to enhance the way insulin functions in the body.	Pioglitazone and rosiglitazone
6.	GLP-1 analogs (also called incretin mimetics or glucagon-like peptide-1 receptor agonists)	Increase insulin production, decrease the liver's release of glucose after meals, and prolong the stomach's emptying.	Exenatide, liraglutide, albiglutide, semaglutide and dulaglutide
7.	SGLT 2 inhibitors or sodium-glucose	Reduce the body's glucose through urine.	Canagliflozin, dapagliflozin and empagliflozin.

Sl No	Name	Mode of action	Example
	cotransporter 2 inhibitors		
8.	Bile acid sequestrants	Reduce glucose and cholesterol or triglyceride levels.	Colestipol, cholestyramine and colesevelam.
9.	Dopamine agonist	Decrease the percentage of glucose that the liver produces	Apomorphine hydrochloride, bromocriptine and pramipexole
10.	DPP-4 inhibitors or dipeptidyl peptidase-4 inhibitors	Reduce the amount of glucose that the liver produces.	Alogliptin, sitagliptin, saxagliptin and linagliptin

v. *Gestational diabetes mellitus*

It typically develops during pregnancy when a woman's body may become less sensitive to insulin due to hormonal changes. Although gestational diabetes typically goes away after giving birth, women who have had it are more likely to get type 2 diabetes in the future (Riaz *et al.*, 2008).

vi. *Less common types of diabetes include*

Some women witness this type of development while pregnant. After gestation, gravid diabetes generally disappears. Still, if you have gravid diabetes, ultimately acquire type 2 diabetes.

It is estimated that up to four out of every four cases of diabetes are caused by monogenic diabetes. Neonatal diabetes and diabetes with onset in childhood are two examples of these types of diabetes.

Diabetes patients are the individuals who can develop fibrosis, a type of the disease which referred as drug or substance-related diabetes. The examples are including HIV/AIDS treatment, Organ transplantation, and glucocorticoid function. Diabetes insipidus is a unique and unusual condition that causes patients to produce a lot of urine. Diabetes associated with cystic.

1.6 Metformin

An oral antihyperglycemic drug called metformin is frequently used to treat type 2 Diabetes Mellitus (DM). It is a biguanide medication and the drugs of choice and used in combination with other diabetes medications. In pharmaceutical tablets formulations the salt form of metformin is used. For over ten years, it has been among the most prescribed medications worldwide (Wadher , 2011).

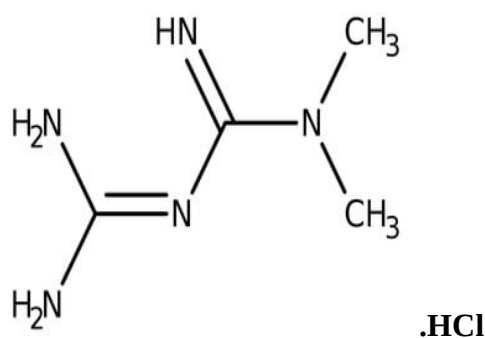


Fig. 1.5 : Metformin HCl

1.6.1 Physicochemical properties

Formula for the molecule: $C_4H_{11}N_5 \cdot HCl$

Chemical name: N, N-Dimethylimidodicarbonimidic diamide

Mass of molecules: 165.2 g/mole

Class: Biguanides derivatives

Protein binding: Minimal

Nature: Powdered white granules

Melting Point: 222 °C - 226 °C.

Half-life: 4 to 8.7 hours

Excretion: liver does not excrete

Routes: parenteral and oral

1.6.2 Solubility profile

Slightly soluble in alcohol, highly soluble in water, and nearly insoluble in methanol, ethanol and acetone.

1.6.3 Doses

500mg, 800mg, and 1000mg of Metformin for oral administration for each tablets.

1.6.4 Brand name of Metformin HCl in Bangladesh

In Bangladesh, metformin is available as single-ingredient preparations.

The following brand are -

Brand name	Brand name	Brand name
Bigmet®	Comet®	Centomin®
D-Met®	Deformin®	Formet®
Glunor®	Glymin®	G-Metformin®,
Insimet®	Informet®	Met®
Metform®	Metarin®	Nobesit®

1.6.5 Pharmacokinetics properties

The absorption of metformin hydrochloride after oral treatment is delayed and partial. After taking 500 mg of metformin once, its absolute bioavailability is between 50 and 60 percent. Ingestion of food reduces its bioavailability. The maximum plasma concentration (C_{max}) of type 2 diabetic patients with good renal function was higher (2.09 mg/L) than that of healthy subjects (1.32 mg/L) when 1000 mg of an immediate release metformin tablet was taken orally twice a day. Peak plasma concentration (1.0–1.6 mg/L) was reached within 3 hours of taking a 500 mg oral immediate-release metformin hydrochloride tablet. On the other hand, diabetic patients' overall clearance (781 mL/min vs. 1265 mL/min) was nearly 30% lower than that of healthy individuals (Fayfman *et al.*, 2017). After absorption, metformin binds to human plasma proteins minimally. After a single oral dosage of 850 mg, 654 ± 358 L is the average estimated amount in the distribution for metformin (FDA, 2015). Serum glands, the kidney, and the small intestine walls are all affected by metformin accumulation. Metformin's half-life in the plasma is approximately 2-4 hours following oral dosages. Metformin is subsequently

eliminated by the kidneys unaltered in the urine with the help of both active tubular secretion and filtration (Lipska *et al.*, 2011).

1.6.6 Pharmacological properties

Metformin decreases the hepatic gluconeogenesis process, decreases hepatic glucose synthesis, and acts systemically to improve glucose absorption. Metformin lowers postprandial plasma glucose concentrations during daytime glucose profiles, especially after the midday meal. Through the glucose-fatty-acid cycle, metformin inhibits fatty-acid oxidation by 10% to 20%, lowering plasma glucose concentrations. It increases the oxidation of glucose and decreases the oxidation of fatty acids, according to the indirect calorimetric process, suggesting that glycogen synthesis plays a significant role in the improved glucose disposal. Acutely insulin-insensitive tissues, such as the skin, brain, and renal medulla, appear to be immune to metformin. The blood lactate concentrations for postprandial and basal is slightly elevated with metformin medication. But it's important to remember that diabetes and obesity both modestly increase blood lactate concentrations when interpreting these increases. The higher blood lactate levels are likely brought on by metformin's ability to cause the intestinal mucosa to convert glucose to lactate (Rena , 2017). After entering the portal circulation, the lactate is mostly removed by the liver, where it serves as a substrate for the gluconeogenic process. More lactate enters the systemic circulation after a meal when the liver is overloaded with fuel. (Sundelin *et al.*, 2017). Because the liver produces less very-low-density lipoprotein, metformin long-term therapy contributed to a moderate (10% to 20%) reduction in plasma triglyceride concentrations, especially in patients with severe hyperglycemia (Sundelin *et al.*, 2017).

In vivo, Metformin increases the levels of phosphorylation and tyrosine kinase enzyme activity of insulin receptors in addition to the binding of insulin to its receptors. They may be the result of decreased plasma glucose levels. Additionally, in cultured hepatocytes and adipocytes exposed to high insulin concentrations for prolonged periods of time, metformin inhibits the development of insulin resistance and encourages the movement of the GLUT-4 and GLUT-1 isoforms of glucose transporters in a variety of cell types. While patients with hyper insulinemia may experience a decreased or unchanged plasma insulin response to glucose when taking metformin, oral glucose tolerance is improved. The decrease in fasting plasma glucose levels often reflects the reduction in the gradual increase in plasma glucose levels after oral glucose

administration. Decreased blood glucose levels with metformin medication may have contributed to decreased platelet sensitivity to aggregating drugs. While fibrinolytic activity increased, the plasma concentrations of the fibrinolytic inhibitor plasminogen-activator inhibitor type 1 diabetes slightly decreased (Herman , 2022).

1.6.7 Side effects

The common side effects include nausea, abdominal bloating, heartburn, headache, agitation, chills, loss of appetite, asthenia, myalgia, flatulence, vomiting, diarrhoea or constipation, dizziness, tiredness, abdominal cramps or pain, upper respiratory tract infection and an altered or metallic taste (Zhou *et al.*, 2014).

1.7 Drug delivery for oral route of system

The largest and most established submarket within the entire administration of medication industry is oral delivery of medicines. It is the most popular and quickly growing method of administering therapeutic drugs, a useful way to achieve both local and systemic effects, and it has been used to treat a variety of diseases. The administration of these route have some limitations, including first-pass metabolism, patients with mental illnesses and obstinate patients, among others. Many patients preferred oral dosage forms and new oral drug delivery methods over other dosage forms. The tablet-shaped oral formulation that is most popular on the market. The therapeutic range of plasma medication concentration can be maintained for a long period of time because of the prolonged release technique (Nokhodchi *et al.*, 2012).

1.8 Sustained release drug or Extended release drug

The Sustained Release Drug Delivery System (SRDDS) aims to minimize side effects by maintaining a consistent drug level for a specified amount of time while releasing a drug at a predetermined rate. To maximize a drug's biopharmaceutical, pharmacokinetic, and pharmacodynamics properties in order to reduce side effects, increase effectiveness and treat a condition, is the basic premise underlying sustained release drug delivery systems. In comparison to conventional dosage forms, sustained release drug delivery has a number of advantages, including better patient compliance because medications are administered less frequently, maximum drug utilization, increased potency safety margin, decreased steady-state drug level fluctuations, lower

healthcare costs because of better therapy, and quicker treatment times (Diksha *et al.*, 2019).

1.8.1 Advantages of sustained release drug

Increase in the drug's safety margin and uniform drug release across time. Stable medication levels that fluctuate less. The medicine is used to its fullest potential action. Minimize adverse effects and improved patient adherence. Reduce the variability of the plasma level and to prolong the drug's period of action. Additionally, drug administration could be made more effective (Dixit *et al.*, 1978).

1.8.2 Disadvantages of sustained release drug

Further individuals knowledge is necessary to ensure appropriate medication administration. The formulation has a high cost, toxicity brought on by cost increases and dose dumping, raise the possibility of first-pass metabolism, less dose modification (Dixit *et al.*, 1978).

RESEARCH GAP

Literature review on *Momordica charantia* has revealed that a very small number of researches have been done on isolation, characterization, biological and pharmacological activities of isolated compounds and mucilage i.e. Germacrene, Momordicin I, Kuguacin A etc. Research on Bangladeshi origin of this plant has not been done well enough. Best of our knowledge, on publication have not found on mucilage of *Momordica charantia* as excipients in tablet formulation for sustained release properties. This research gap makes me interest to give concentration study on isolation, characterization and pharmacologically active mucilage from Bangladeshi origin of this plant.

OBJECTIVE OF THE STUDY

The objective of the present study are -

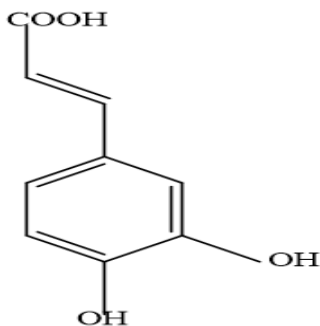
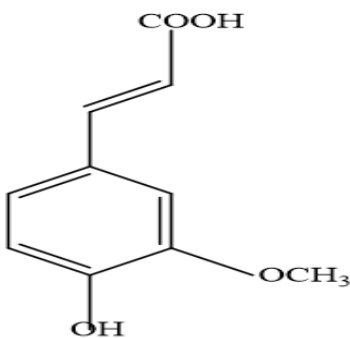
- to isolate the mucilage from the extract of *Momordica charantia* fruits.
- to phytochemical screening of isolate mucilage.
- to formulate tablets with isolate mucilage and Metformin HCl at different composition.
- to evaluate the pre-compressional and post-compositional pharmacological properties of all formulated granules and tablets.
- to evaluate the percentage of release of drug after periods of time with different concentration of mucilage and observe the drug release properties by using kinetics modelling of formulated tablets prepare from fruits mucilage.

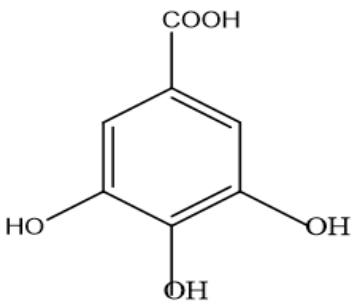
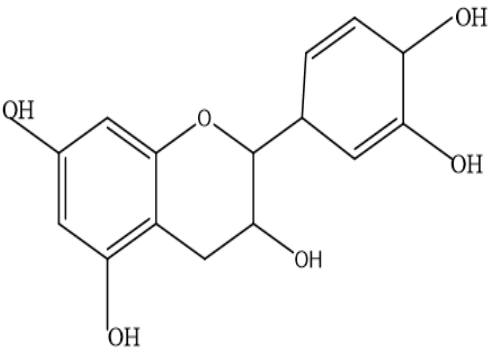
Chapter 2: LITERATURE REVIEW

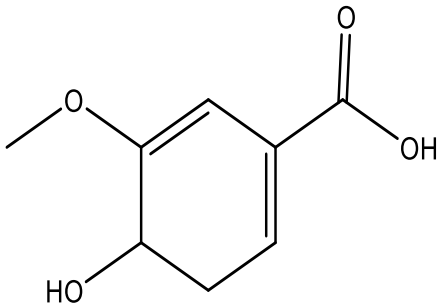
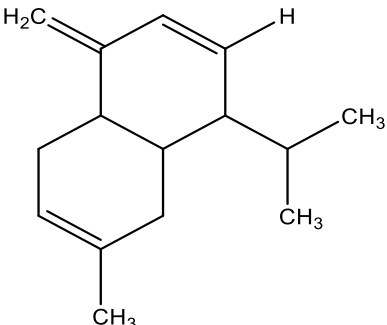
Momordica charantia Linn. is a medicinal plant used for the treatment of various diseases. A number of researcher have done their research on different parts, like fruits, leaves, roots etc. of this herb and their research findings describes shortly in this chapter. This literature survey divided into two section, the first section contain the compounds isolated from the *Momordica charantia* and the second section contain biological evaluations of *Momordica charantia*.

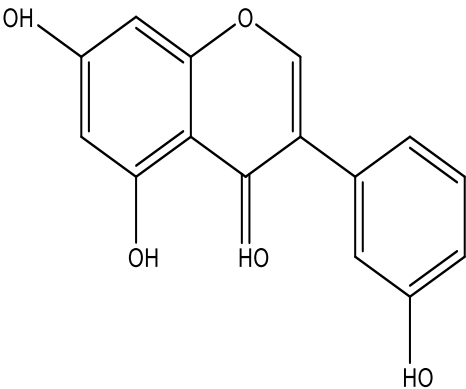
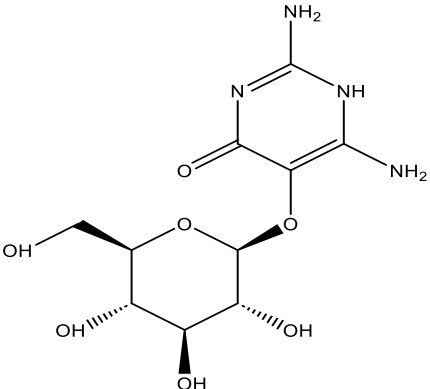
2.1 Chemical constituent isolation from *Momordica charantia*

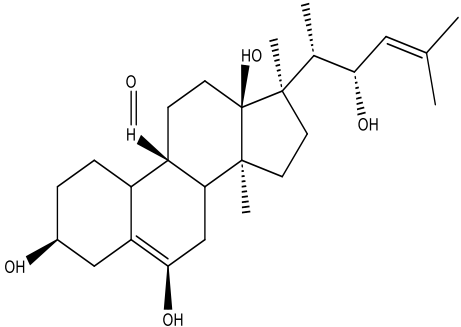
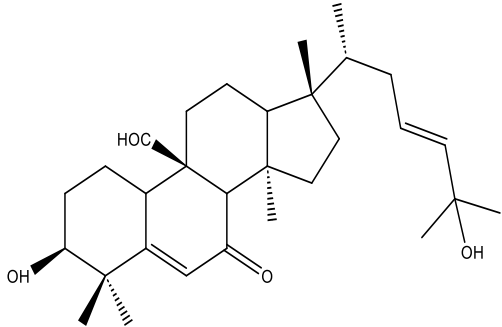
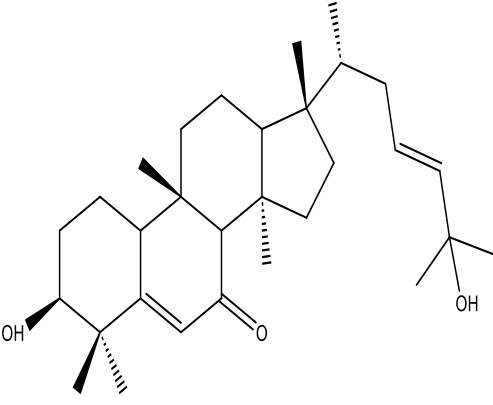
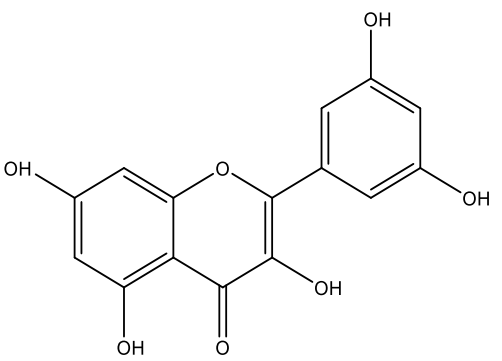
Phenolic compounds Caffeic acid (1), Ferulic acid (2), Gallic acid (3) found in the *Momordica charantia* plant (Horax *et al.*, 2005). High performance liquid chromatography (HPLC) analysis was also used to isolate the phenolic constituents from *Momordica charantia* (Kubola , 2008). Charantin (4), a natural cucurbitane type triterpenoid isolates from *Momordica charantia*. The fruits of *Momordica charantia* have resulted in isolation of essential amino acids e.g. Vanillic Acid, (5) (Oyelere *et al.*, 2022; Desai *et al.*, 2015). Germacrene (6), Genistein (7), Vicine (8) (Mahwish *et al.*, 2021), Momordicin I (9), kuguacins A (10), Kuguacin J (11), Quercetin (12), Momordicine (Sur *et al.*, 2021), kuguacins B (Haque *et al.*, 2011) and kuguacins I many more compound are isolated and separated from leaves and vines of *Momordica charantia* (Chen *et al.*, 2009).

	
Caffeic acid (1)	Ferulic acid (2)

	
Gallic acid (3)	Charantin (4)

	
Vanillic acid (5)	Germacrene (6)

	
Genistein (7)	Vicine (8)

	
Momordicin I (9)	Kuguacin A (10)
	
Kuguacin J (11)	Quercetin (12)

2.2 Pharmacological properties of *Momordica charantia*

Momordica charantia is also known as bitter guard which have potential pharmacokinetics and pharmacodynamics characteristics and contains different bioactive compounds which have nutritional properties. This plant rich in carbohydrates, proteins, lipids compounds including Momordicin, Momordicoside, Vicine, Kuguacin J, Karavilagenin, vanillic acids , Kuguacin A, Galic acids, Karaviloside, and Kuguacin, all of these reported to contribute for its biological properties including antiparasitic, anti-inflammatory, antiviral, anticancer, antifungal, and antibacterial infections (Jia *et al.* 2017). The important pharmacological properties of *Momordica charantia* plant in detail given below –

2.2.1 Anti-hypoglycemic activity of *Momordica charantia*

Momordica charantia has good medicinal properties and use for treatment of a number of diseases, its anti-diabetic characteristics are more widely recognized (Garau *et*

al., 2003). Charantin is one of the active ingredients that reduce the blood sugar levels, furthermore, lectin also reduce the blood glucose levels, present in *Momordica charantia*, and those are key component of the hypoglycemic effect (Joseph *et al.*, 2013). A combination of steroids charantin found in alcohol-extracted of *Momordica charantia*, it improved glucose tolerance level in animal model of diabetes, compare to the effects of tolbutamide an oral hypoglycemic compound. Blood glucose levels were statistically significantly lower than those following a control clinical trial with people who had been diagnosed with type 1 diabetes, after receiving a subcutaneous injection of *Momordica charantia* extract which contains crystallized p-insulin (Sarkar *et al.*, 1996). When *Momordica charantia* fruit extract was tested on streptozocin (STZ)-induced type 2 diabetic rats, it decreased blood glucose levels in contrast to glibenclamide, which raised rats' serum insulin levels (Abdollahi *et al.*, 2011). Fresh *Momordica charantia* fruit juice is administered orally to lower blood sugar levels in both alloxan-diabetic and healthy rabbits. When alcoholic plant extracts were given orally to certain diabetic patients, no hypoglycemic effect were found (Abdollahi *et al.*, 2011).

It has been demonstrated that juice preparations of the fruits of *Momordica charantia* improve glucose tolerance. Type 2 diabetes can be effectively treated with *Momordica charantia* (Raman, 1996). The hypoglycemic action of *Momordica charantia* is caused by mechanisms like extra pancreatic effects or the effect of stimulating or recovering beta cells. The extract's various fractions have the capacity to stimulate insulin secretion and repair beta cells (Xiang *et al.*, 2007; Wang *et al.*, 2014). Extracts from *Momordica charantia* may have an anti-diabetic effect by promoting insulin production by the islets of langerhans, decreasing hepatic glycogenesis, improving peripheral glucose consumption, and raising serum protein levels. *Momordica charantia* extracts may have an anti-diabetic effect which improve peripheral glucose utilization, increase serum protein levels, improve insulin secretion by the islets of Langerhans cells and decrease the production of glycogen in liver tissue (Joseph *et al.*, 2013; Ouassou *et al.*, 2018). It has been shown that *Momordica charantia* increases the number of beta cells, which can either stimulate the secretion of insulin or act similarly to insulin (Mahmoud *et al.*, 2021). Additionally, some research indicates that hypoglycemic activity to an extra-pancreatic effect (Desai, 2015), which includes enhanced muscle GLUT-4 transporter protein (Çakici *et al.*, 1994), Fructose-1,6-bisphosphatase and glucose-6-phosphatase inhibition in the liver, increased liver and muscle glucose utilization, and increased hepatic (Fuangchan *et al.*, 2011. Polypeptide with pZnCl₂ molecules has been shown blood sugar-

lowering effect in clinical studies. Insulin sensitivity improve diabetes patients are shown in presence of charantin, *Momordica charantia* extracts (Banerjee *et al.*, 2019).

2.2.2 Antioxidant activity of *Momordica charantia*

Polysaccharides from *Momordica charantia* showed significant antioxidant properties (Jia *et al.*, 2017). A pectin type's polysaccharide were found after isolating and purifying from *Momordica charantia* fruits, researchers discovered that the polysaccharide could inhibit lipid peroxidation. After being separated from the *Momordica charantia* fruits by precipitation with alcohol, BP1, BP2, and BP3 are three water-soluble fractions of polysaccharides were assessed for their antioxidant activity using the scavenging of superoxide and hydroxyl radicals (Jia *et al.*, 2017). *Momordica charantia* polysaccharide inhibited lipid peroxidation and had direct scavenging effects on NO and O₂. Its antioxidant activity may be linked to its neuron protective effects through inhibiting kinases (JNK₃) signal transduction and oxidation resistance (Gong *et al.*, 2015). Ferric reducing antioxidant activity and free radical activity were demonstrated by a pectin-like bioactive polysaccharide (MCBP) at a rate of 31.9% (Tan *et al.*, 2016; Sathishsekar *et al.*, 2005). The impact of chemical modification, particularly sulfated modification, on the antioxidant activities of *Momordica charantia* polysaccharides has been tested (Kobori *et al.*, 2007). Administration of *Momordica charantia* polysaccharides lowered maleic di aldehyde (MDA) in liver, brain, and serum activities of different catalase and superoxide dismutase enzymes were markedly increased in mice (Xie *et al.*, 2015). The scavenging or phagocytic activity of hydroxyl radicals was caused by the inhibition of hydroxyl radicals produced by chelating ions, such as Fe²⁺ and Cu²⁺ (Zou *et al.*, 2008). The phytochemicals are mostly polysaccharides, saponins, and phenolic has antioxidant activity. According to analysis, Strong antioxidant properties linked to phenolic compounds are found in *Momordica charantia* and its ethanolic extracts. By raising catalase activity and lowering glutathione levels, *Momordica charantia* extracts have been shown to have greater antioxidant capacity than other solvent-based extracts and to reduce stress-induced lipid peroxidation (Guan *et al.*, 2012).

2.2.3 Anti-inflammatory activity of *Momordica charantia*

Chronic inflammation is influenced by dietary practices, and that can change the immune system and gut microbiotics balance. Many research investigations have explored *Momordica charantia*'s possible hypoglycemic and lipid-lowering properties in

connection with the management of various illnesses, such as cancer, obesity, cardiovascular disease, and neurodegenerative diseases (Minihane *et al.*, 2015; Garau *et al.*, 2003; Bai *et al.*, 2016). Beneficial properties of *Momordica charantia* have showed antioxidant activities, anti-inflammatory and anti-glycaemic activities. The main way it controls inflammation is by blocking the NF- κ B signaling pathway, which reduces TNF- α production (Biswas, 2016). An important enzyme that induces hyperuricemia and gout, xanthine oxidase, is implicated in numerous inflammatory diseases (Battelli *et al.*, 2016). In separate test systems, it was successfully demonstrated that a methanolic extract of the seeds from the unripe fruits of *Momordica charantia* produces a significant dose-dependent analgesic effect in mice but a much weaker effect in rats (Xu *et al.*, 2022; Matsuur *et al.*, 2002).

2.2.4 Anti-cancer activity of *Momordica charantia*

Anti-leukemic and anti-cancerous action of *Momordica charantia* has been documented in several *in vitro* investigations in a wide range of cell lines, including human leukemia, liver cancer or hepatic carcinoma, solid sarcomas, and melanoma (Mantipelly *et al.*, 2020; Ru *et al.*, 2011). Numerous investigations revealed that activated AMP-activated protein kinase (AMPK) was essential for apoptotic cell death (Kwatra *et al.*, 2013). It was found that *Momordica charantia* extract activates AMPK. Several cancer cell lines' AMPK pathway was activated by the cell and its extract, depending on the cell's origin, resulting in either autophagy or apoptotic cell death (Guan, 2012). Studies performed *in vitro* investigation shows *Momordica charantia* extract affected the volume of mouse pancreatic cancer xenografts (Kaur *et al.*, 2013) and crude extract from *Momordica charantia* can stop the cell cycle (Nerurkar *et al.*, 2010). According to Fluorescence-Activated Cell Sorting (FACS) analysis, the *Momordica charantia* extract-treated breast cancer cell line MCF-7 displayed cell cycle arrest at the G2-M phase (Ray *et al.*, 2010). *Momordica charantia* Lectin (MCL) is a type 2 Ribosome Inactivating Protein (RIP) that has been shown to be both anti-tumor and extremely toxic. In addition to reducing cell viability, MCL has been found to induce autophagy, cell death, and cell cycle arrest and decrease cell viability in the nasopharyngeal carcinoma (NPC) cell lines CNE-1 and CNE-2 (Zhang *et al.*, 2015; Fang *et al.*, 2012). Histone deacetylase (HDAC) activity was reduced by *Momordica charantia* Antiviral Protein-30 (MAP-30). HDACs are overexpressed in a variety of tumour types and are understood to interact with mutant proteins that cause cancer (Xiang *et al.*, 2007).

2.2.5 Anti-viral activity of *Momordica charantia*

Alpha Momorcharin was found in *Momordica charantia* which having abortifacient, tumor-suppressive, and anti-HIV characteristics. Several *in vivo* and *in vitro* investigations demonstrated the anti-HIV activity of MAP³⁰, recombinant MAP³⁰, and proteolytic fractions of MAP³⁰ (Lee-Huang *et al.*, 1995). The effectiveness of anti-HIV therapy was increased when MAP³⁰ was combined with low dosages of indomethacin and dexamethasone. In an *in vivo* investigation, *Momordica charantia* leaf extract showed promise in boosting viral infection resistance and producing immunostimulant effects in both clinical and experimental contexts. The salt-precipitated fraction of MRK²⁹ resulted to an 82% reduction in the expression of the viral core protein p²⁴ in HIV-infected cells (Joseph *et al.*, 2013). In HIV-infected cells, the salt-precipitated fraction of MRK²⁹ resulted to an 82% decrease in the expression of the viral core protein p²⁴ and an increase in TNF activity. MAP³⁰ and *Momordica charantia* ribosome-inactivating proteins were shown to have antiherpes activity against HSV- 1 and HSV-2 in two *in vitro* investigations (Lee *et al.*, 2015). *Momordica charantia* leaves and stems have shown strong antiviral activity in ethanolic extracts. It has been proposed that *Momordica charantia* root exhibits mild anti HIV-1 activity. These substances, *Momordica charantia*, offer defense against viral infections (Abad *et al.*, 2000). It has been demonstrated that taking *Momordica charantia* orally decreases the progression of HIV in infected people. Leaf extracts can be used to treat a variety of viral diseases because they have immunostimulant qualities against viral infections, including HIV (Jiratchariyakul *et al.*, 2000).

2.2.6 Immunomodulatory activity of *Momordica charantia*

Momordica charantia polysaccharides have been demonstrated to have strong immunomodulatory effects both *in vitro* and *in vivo*. According to the research's observations, *Momordica charantia* polysaccharides have strong immune-boosting qualities and may improve immune function by triggering the activation of lymphocytes and macrophages (Deng *et al.*, 2014). Through the immune system's NK cell, cellular, and mononuclear macrophage functions, *Momordica charantia* polysaccharides have significant immunomodulatory activity. It has the ability to stimulate both thymocytes and spleenocytes (Wang *et al.*, 2021). *Momordica charantia*'s polysaccharides could restore normal levels of NK cell cytotoxicity, spleen index, thymus index, serum haemolysin production, and carbolic particle clearance index (Deng *et al.*, 2014).

2.2.7 Anti-parasitic (anti-anthelmintic) activity of *Momordica charantia*

Momordica charantia also has anthelmintic effects involving acetyl cholinesterase inhibitors, oxidative phosphorylation inhibition, micro-nicotinic agonists, β -tubulin binding, increased calcium permeability, and suppression of arachidonic acid metabolism (Pereira *et al.*, 2016).

2.2.8 Antihyperlipidemic activity of *Momordica charantia*

Significant antihyperlipidemic effects shown in *Momordica charantia*. An alternative mechanism of *Momordica charantia* has reported, indicating that it enhances insulin levels and sensitivity by repairing damaged β -cells (Chaturvedi *et al.*, 2012). When diabetic rats were given *Momordica charantia* extract, their blood lipid levels were considerably reduced (Bai *et al.*, 2016). The hyperlipidemic effect of HIV-1 protease inhibitors, which block lipoprotein instead of elimination of it from the body, is caused by triglyceride synthesis in the liver (Panda *et al.*, 2010). *Momordica charantia* compounds increase Apo lipoprotein A-1, a basic protein component essential to HDL synthesis (Mahwish *et al.*, 2017). A hyperinsulinemic high-fat diet that reduced visceral fat mass was examined, when it came to *M. charantia*. As a result of its anti-hyperlipidemia properties, *Momordica charantia* can lower body weight, visceral fat, and the buildup of excess fat (Saad *et al.*, 2017). Another study found the formulations and the anti-hyperglycemic and anti-hyperlipidemic action of various parts of *Momordica charantia* (Dar *et al.*, 2020).

2.2.9 Trypanocidal activity and Antiherpes activity of *Momordica charantia*

The ethanolic extract from *Momordica charantia* leaves has an effective concentration of 46.06 gm/mL G1 and was able to kill 50% of *Trypanosoma cruzi* parasites (Santos, 2012). The antiherpes effectiveness of *Momordica charantia* MAP³⁰ against HSV-2 and HSV-1 proteins and ribosome-inactivating proteins has demonstrated in two *in vitro* experiments (Upadhyay *et al.*, 2015).

2.2.10 Antifungal activity of *Momordica charantia*

Antifungal agents of alpha seed proteins and ribosome-inactivating proteins from *Momordica charantia* are important antifungal agents. MCha-Pr, an antifungal protein, extracted from the *Momordica charantia* which is strong antimicrobial proteins (Wang *et*

al., 2012) and exhibited inhibitory effects on a range of fungal species, including *Rhizoctonia solani*, *Fusarium oxysporum*, *Alternaria brassicae*, *Cercospora personata*, and *Mucor sp* and 50% inhibition of fungal growth (IC₅₀) was observed. *A. brassicae* spore germination can be inhibited by this antifungal protein at 12.5 µg/mL (Wang *et al.*, 2011). These findings imply that MCha-Pr in *Momordica charantia* leaves has a broad antimicrobial spectrum and serves as a protective factor against phytopathogens. The plant lysozyme demonstrated antifungal activity against *Rhizoctonia solani* and *Mucor racemosus* in addition to antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*. *Momordica charantia*'s recombinant napin-like protein (rMcnapin) has trypsin inhibitory properties and antifungal activity against *Trichoderma viride* (Ganguly *et al.*, 2000).

2.2.11 Anti-genotoxic activity of *Momordica charantia*

Momordica charantia inhibits the genotoxic activity of tetracycline, methanesulfonate, and methyl nitrosamine, as evidenced by a decrease in chromosome breakage (Guterres *et al.*, 2015). A sensitive test for determining the genotoxic and anti-mitotic properties of plant extracts is the *Allium cepa* L. assay (Paul *et al.*, 2010).

2.2.12 Adipocyte inhibition of *Momordica charantia*

In mice administered a high-fat diet, the adipose tissue may express lipogenic genes in a dramatically down-regulated manner, which could be associated with adipocyte enlargement and abdominal fat storage. *Momordica charantia* indicates to have a variety of effects on glucose and lipid metabolism, which seems to greatly neutralize the detrimental effects of a high-fat diet (Nerurkar *et al.*, 2010).

2.2.13 Anti-fertility activity of *Momordica charantia*

The *in vitro* spermicidal activity of *Momordica charantia* seed and hydro alcoholic pulp extracts was investigated. The abortifacients Mormorcharin are present in its seeds (Tsao *et al.*, 1990). Alkaloids and Triterpene glycosides have shown antifertility properties. Alcoholic seed extract's antispermatogenic activity *in vivo* has both antisteroidogenic and antiandrogenic properties. An immobilizing factor, possibly a flavonoid, is present in the hydro alcoholic pulp extract of *Momordica charantia* (Naseem *et al.*, 1998). This factor likely reduces motility by causing sperm nonviability through membrane disruption (Lohiya *et al.*, 1992). *Momordica charantia* extract demonstrated an

extended proestrous phase and a reduction in the length of the metestrous and estrous phases (Koneri *et al.*, 2007). The production of sperm can be decreased by consuming too much bitter gourd fruit and leaves. Male antifertility effects of bitter gourd ethanol seed extracts have shown in dogs and guinea pigs (Dixit *et al.*, 1978; Udoh *et al.*, 2001).

2.2.14 Antimalarial activity

An *in vitro* study on *Plasmodium falciparum* showed that *Momordica charantia* extract exhibited excellent antimalarial activity, while *in vivo* activity against *Rodent malaria* caused by *Vinckeia petteri* was moderate (Muñoz *et al.*, 2000).

2.3 Wound healing activity of *Momordica charantia*

Diabetes and delayed healing of wounds are both associated with neovascularization, growth factor deficiencies and anomalies including weakened immunological function and reduced collagen synthesis (Qing, 2017). It has been proposed that applying *Momordica charantia* fruit ointment to diabetic rats will improve wound closure and increase the expression of TGF- β in wound tissue, which is crucial for controlling cell growth and differentiation. Evidence suggests that *Momordica charantia* juice can be used to treat psoriasis, ringworm, and scabies. Rats utilized for investigating the potential of *Momordica charantia* fruit powder to heal wounds responded significantly to the powder ointment when measured by the length of time it took for the wound to close, the ability to contract the wound, and the duration of epithelization (Hussan *et al.*, 2014).

2.4 Toxicity and safety

Although no extensive research on the adverse effects of *Momordica charantia* could be found, years of use as an ethno medicine and dietary supplement in many nations do point to a high degree of safety (Basch *et al.*, 2003). While *Momordica charantia* fruit can cause decreased fertility and the induction of abortions in animals, *Momordica charantia* seeds have the potential to cause anaemia in humans who are deficient in glucose-6 phosphate dehydrogenase (Raman, 1996). Overuse of *Momordica charantia* fruit extract may have adverse impacts on lipid peroxidation and thyroid function (Abalaka *et al.*, 2009). Studies on humans, animals, and cell cultures have all shown the metabolic and hypoglycemic benefits of bitter gourd extracts.

Chapter 3: METHODOLOGY

Mucilage is a valuable natural polysaccharide source that has excellent potential for application in food and pharmaceutical applications. It can be extracted from any part of a plant. A number of studies have indicated that the functional, rheological, yield and characteristics of mucilage are significantly influenced by the conditions and methodology of extraction. The present chapter describes the isolation and extraction process of mucilage from *Momordica charantia* fruits. Later on, this mucilage use to formulate tablets with Metformin hydrochloride (Metformin HCl). Designed, formulation and preparation of new tablets with Metformin HCl and mucilage are briefly described in Experiment Section.

3.1 Fruits collection and identifications

The fresh, clean, mature but not over aged *Momordica charantia* fruits (3.0 kg) as research materials were collect from ‘Bohoddharhat’, a local vegetable market at Chittagong city in Bangladesh on the period of April 2022. The plant were collected from agricultural filed area of Patanga in Chittagong city. *Momordica charantia* Linn. plant and fruits identified and authenticated by Dr. Shaikh Boktar Uddin, Professor, Department of Botany, University of Chittagong. The plant specimen deposit at the herbarium in the same department with assigned accession number: TA-03122022-6443.

3.2 Materials

3.2.1 Chemicals

All the solvents were purchased intact jars from local vendor in Chittagong. These were analytical grade. *N-hexane*, acetone, methanol, and ethanol Solvents were used in experiments. The solvents purified by double distillation process and checked by their boiling points.

3.2.2 Equipment's

i. *Analytical Balance*

An analytical balance is a type of laboratory balance used to measure the mass or weight of an item precisely. FA2204 (Aurora Pro Scientific) are used in the experiment.

ii. *Hardness tester*

Monsanto Hardness tester B07LGC8126 (Lablink) is used in the experiments to evaluate a tablet's fragility and structural integrity before using it, as well as the way it will be handled and stored.

iii. *Friability tester*

Friability test is intended to measure the physical strength of tablet. Friability Tester LTFT-A10 (LABTRON) are used in the experiment. It was ensure the instrument that is clean and Calibrated before proceeding.

iv. *Disintegration tester*

The Disintegration Tester is used to develop precisely estimate the required time for tablets disintegrate. Mtandt MT-901(Mtandt Ltd), Digital Disintegration Test Apparatus (Two Baskets), Resolution 1 sec, Power 230VAC are used in the analysis.

v. *Dissolution tester*

Dissolution testing is an important analytical technique, as part of the final release investigation for solid oral dosage forms. White Dissolution Tester, Model: T70, (PG Instruments Ltd) are used in this analysis.

vi. *UV – spectrophotometry*

The method most commonly used in pharmaceutical analysis for estimating the amount of visible or ultraviolet light absorbed by a substance in solution is UV spectrophotometry. SCILOGEX SCI-UV1000 (SCILOGEX) UV/Vis Spectrophotometer (200 – 1000 nm) are used in this analysis. UV-blocking safety glasses or goggles are used when operating this device.it was ensure the instrument was clean and calibrated before proceeding.

3.3 Flow chart of experiment

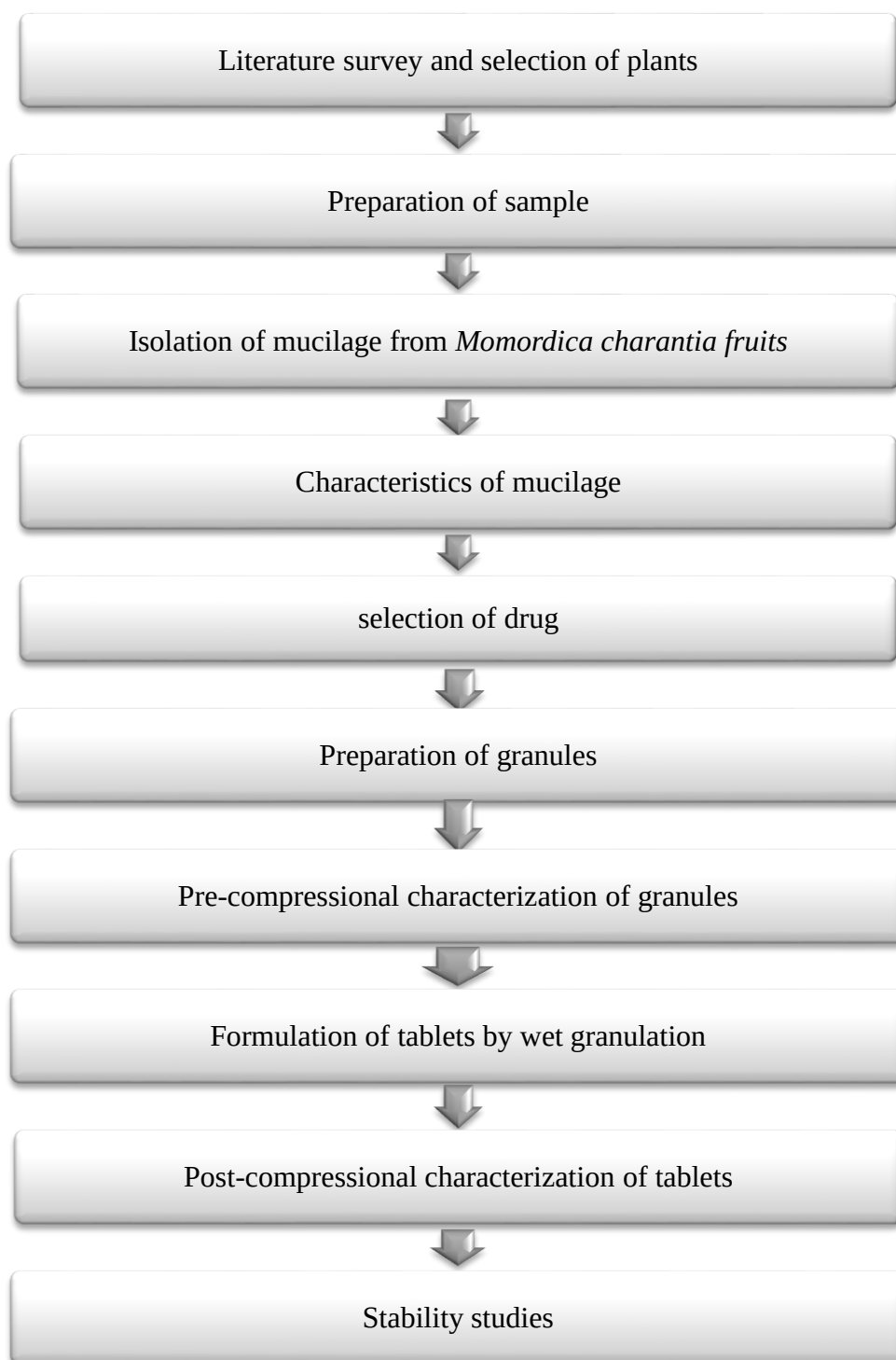


Fig. 3.1: Flow chart of studies

3.4 Sample preparation

Momordica charantia (5.0 kg) fruits collected from the market and washed with deionized water to remove dust and undesirable materials. Then the fruits were chopped into small piece and let it dry with subdued sunlight.

The fruits were dry in subdue sunlight at the room temperature and in a well-ventilated area. Direct sunlight sometimes damage many chemical compounds of fruits. This way show good results for isolations. 3.0 kg of dried fruits were found.

Then the dried fruits crushed into small pieces and by make powder used Electrical Grinder to for further use. The powder fruits put in air tight bag and stored in a cool, dry and well - ventilated places.

3.5 Isolation of mucilage

The isolation and extraction methods of mucilage were developed by Malyiva in 2011 (Malviya *et al.*, 2011). This procedure is slightly modified by using different plants for isolation (Barua *et al.*, 2019). We followed the procedure to isolate mucilage from *Momordica charantia* fruits:

Step 1: Extraction of mucilage

- *Momordica charantia* (3.0 kg) fruits were collected, washed and dried.
- The fruits were grinded into powder (600 gm). Then the powder was soaked in warm distilled water for 8 hours, than boiled for 2 hours, and then left to stand for an additional 2 hours where the mucilage allow for completing release in the water.
- Then the solution was filtrated by muslin cloths from the mixture and a solid particle was separated from the solution. The solutions collected for further used.

Step 2: Isolation of mucilage

- 450 mL of acetone added to the solution. The mucilage was extracted from the solution because it was insoluble in acetone.
- Two layers was formed. The upper thick layer was collected by muslin cloths, which called mucilage.
- Mucilage was washed in distilled water and separated by filter paper.

- After being separated, the mucilage was dried at 40°C in an oven. Ground the mucilage and passed through a # 80 sieve to form fine powder. Then we get 12.7 gram (gm) of Mucilage powder.
- For future usage, the mucilage powder was kept at room temperature in a desiccator.



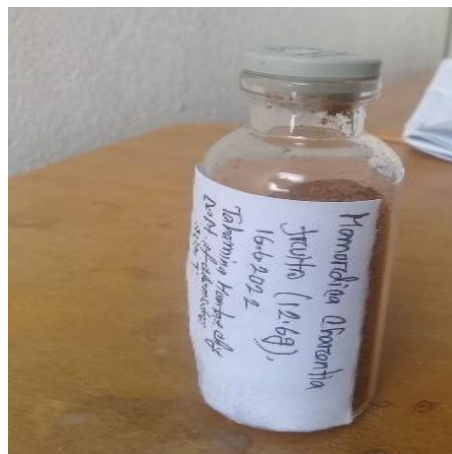
Dry fruits



Boiling



Mucilage



Dry mucilage

Fig. 3.2 : Isolation process of mucilage

3.6 Phytochemical characterization of isolate mucilage

3.6.1 Chemical Characterization

The isolated mucilage was chemically characterized using an aqueous solution. The standard procedure was followed in the testing of proteins, carbohydrates, alkaloids, phenolic compounds, and flavonoids:

i. Test for carbohydrates

Test	Observation	Results
Molish's test	Plant mucilage 2 mL was taken in a test tube. The test tube is filled with a few drops of concentrated sulfuric acid and two drops of an alcoholic solution of α -naphthol. A violet ring was observed.	Carbohydrates present.

ii. Test for amino acids

Test	Observation	Result
Ninhydrin test	Ninhydrin solution is composed of ninhydrin and acetone. Take 3 mL of mucilage in a test tube and two drops of Ninhydrin solution added in the test tube. No remarkable change were observed.	Amino acid absent.

iii. Test for alkaloids

Test	Observation	Result
Mayer's test	In a test tube, add 2 drops of Mayer's reagent to 3 mL of mucilage. No remarkable change were observed.	Alkaloids absent.
Wagner's test	Take 3 mL of plant mucilage in a test tube and few drops of Wagner's reagent added in a test tube. No remarkable change were observed.	

iv. Test for glycosides

Test	Observation	Result
Borntrager's test	3 mL of chloroform is added in 2 mL of mucilage solution and shaken. No remarkable change were observed.	Glycosides absent.
Legal's test	Using 10% NaOH, 50 mg of mucilage is dissolved in an alkaline solution of pyridine sodium nitroprusside. No remarkable change were observed.	

v. Test for phenolic compounds

Test	Observation	Results
Ferric chloride test	2 mg of mucilage dissolve in 5 mL of distilled water, a 5% ferric chloride solution was added. No remarkable change were observed.	Phenolic compound absent.

vi. Test for flavonoids

Test	Observation	Results
Alkaline reagent test	2-3 drops of sodium hydroxide solution and few drops of sulphuric acid added in mucilage. No remarkable change were observed.	Flavonoids is absent.

vii. Reducing sugar test

Test	Observation	Results
Fehling's test	1 mL of Fehling's solution added in the mucilage solution. No remarkable change were observed.	Reducing sugar absent.

The constituents in mucilage, at a glance

Table 3.1: Phytochemical screening of isolated mucilage

SI No.	Active constituents	Result
1	carbohydrates	+
2	Amino acids	-
3	Alkaloids compounds	-
4	Glycosides	-
5	Tannins	-
6	Flavonoids	-
7	Reducing sugar	-
Note: '+' sign indicates Present and '-' sign indicates absent		

3.6.2 Solubility test

Solubility of mucilage from the dried fruits of *Momordica charantia* was determined by dissolving in different following solvents.

Table 3.2 : Solubility profile of isolated mucilage

SI No.	Solvents	Result
1	Hot water	Soluble (Thicky solution)
2	Methanol	Insoluble
3	Ethanol	Insoluble
4	Acetone	Insoluble
5	<i>n</i> -Hexan	Insoluble

3.6.3 Organoleptic characteristics of isolated mucilage

Organoleptic character describes color, odor, taste and texture of any mucilage's.

i. Swelling Index

A 50 mL measuring cylinder containing approximately 1.0 g of the mucilage was mixed with 25 mL of distilled water, and then create suspension shaken every ten minutes

for an hour. After that, it stand for three hours. It was measured how much more water was occupied by the enlarged mucilage. The process was carried out twice more, and the following formulas were used to determine the swelling index (Dwivedi *et al.*, 2019).

$$\text{Swelling index} = \frac{\text{volume after swelling} - \text{volume before swelling}}{\text{volume before swelling}} \times 100$$

ii. Organoleptic properties

Table 3.3 : Organoleptic properties of isolate mucilage

SI No.	Parameters	Results
1	Colour	Brownish
2	Odor	Odorless
3	Taste	Characteristic
4	Yield	5.33%
5	pH	6.1
6	Swelling Index	13.6

3.7 Preparation of granules

Wet granulation is used granulation procedure for manufacturing of tablet. In order to produce a wet mass, a small amount of water and other liquid ingredients are alternately added to powders with or without a binder, the powder can be transformed into granules by adding an adhesive. Granules were formed by drying and sizing the wet material. The liquid uses a combination of capillary and viscous forces to bind the wet powder particles in the wet state. (Parashar *et al.*, 2012).

3.7.1 Functions of ingredients

- ‘Metformin Hydrochloride (HCl)’ used as model drug
- ‘Mucilage’ used as binder
- ‘Lactose’ used as a diluent
- ‘Maize starch’ used as a thickening agent
- ‘Povidone’ used as a synthetic polymer
- ‘Microcrystalline Cellulose (MCC)’ used as an anti-caking agent and an emulsifier

- ‘Mg stearate’ used as a lubricant
- ‘Talc’ used as a thickening agent and lubricant
- Distilled water

‘Active Pharmaceutical Ingredients (API)’ of Metformin HCl was obtained from Ibne Sina Pharmaceutical Ltd, Dhaka, Bangladesh as a gift sample

3.7.2 Preparation procedure of granules

Granules are important intermediate for preparation of pharmaceutical tablet. Granules with good properties gives more stability of tablets. In the experiments Granules were prepared by following two steps,

- **Step 1:** Metformin HCl, Lactose and Microcrystalline Cellulose (MCC) were weighted for 20 tablets 10,000 mg, 3648 mg and 1760 mg respectively for formulation of 20 tablets. Then the ingredients into a mortar and mixed them properly to form fine powder.
- **Step 2:** Mucilage, Povidone were weighted for 160 mg and 192 mg 20 tablets respectively. Mucilage was taken in a porcelain disc and a small amount of water was added onto the mucilage. Water was applied to dissolve the mucilage in water and form a thick solution. Povidone was added into the mucilage and mixed properly.
- **Preparation of mush for tablets:** Mucilage is slowly added to the mortar, where the pre-mixed ingredients are present, and a paste is formed with the ingredients.
- Then the mixture was sieved in 10 meshes to form big granules from the paste.
- The mixture dried at 60 °C for half hour. After drying, the granules was sieved in 20 mesh to form small granules.
- Then pre weighted Talc and Mg stearate 160 mg and 80 mg respectively added to the powder for 20 tablets mixed properly.
- The granules are prepared for compression and are stored for future use in an airtight container.



Balance machine



Weighted ingredients



Granules



Tablets

Fig 3. 3 : Preparation procedure of granules

3.7.3 Pre-compressional parameters

In order to create a stable, safe, and effective dosage form, pre-formulation studies detailed the chemical and physical characteristics of a drug molecule. The term "stage of research and development" to explains this. Various methods of pre-formulation are described below:

i. **Bulk density**

Bulk density determined by the ratio of total powder mass to bulk powder volume. A measured amount of powder was put into the measuring cylinder. Carefully leveling the powder in cylinder, V_0 , the unsettled apparent volume, was determined to the nearest evaluated unit. Calculation of bulk density gm/mL tabulated, by the following formula (Krishnarajan *et al.*, 2013):

$$\text{Bulk density } (V_b) = \frac{m}{V_0}$$

Where, m = Mass of powder of granules

V_o = Apparent volume of granules

ii. Taped density

It was calculated by adding the granules in a measuring cylinder and measure the initial tapped volume (V_i) before tapping and final tapping volume (V_f) after 100 tapping on the cylinder wall. The total granule mass was calculated. The tapped density was determined using the formula (Krishnarajan *et al.*, 2013):

$$\text{Tapped density } (V_t) = \frac{V_i}{V_f}$$

Where, V_i = Initial volume of granules

V_f = Final volume of granules

iii. Carr's index

The Carr index is commonly used in pharmaceuticals to determine the compressibility and the flowability of a powder. The bulk density and tapped density of the powder are used to determine how easily it can be compacted. Calculation of CI from the values of TD and BD with the following formula (Dwivedi *et al.*, 2019) :

$$\text{Compressibility index} = \frac{V_t - V_b}{V_t} \times 100$$

Where, V_t = Tapped density of granules

V_b = Bulk density of granules

iv. Hausner's ratio

Hausner's Ratio is an essential measurement for evaluating the flowability of powders in the food, pharmaceutical, and chemical sectors. This dimensionless number contrast a powder's bulk and tapped densities. The calculation tabulated using the following formula (Dwivedi *et al.* , 2019) :

$$\text{Hausner's ratio} = \frac{V_b}{V_t}$$

Where, V_t = Tapped density of granules

V_b = Bulk density of granules

v. ***Angle of repose***

The angle of repose is a common parameter used for the evaluation of interparticle force (0° - 90°) of practicals. A powder pile's angle of repose is the greatest angle between its surface and a horizontal plane. Flow characteristics are computed using the angle of repose. We used the fixed funnel method to determine it. Retaining lip is required. This will assist in leaving a coating of powder on the base. Change the funnel's height. This should be done in order to generate a symmetrical cone of powder. The height of the funnel needs to be controlled carefully. Keep a height between two and four centimeters above the powder pile's the top. Utilizing the formula for the greatest angle that can exist between a given powder heap's surface and the horizontal plane, determine the angle of repose (Dwivedi *et al.*, 2019) :

$$\text{Angle of repose, } \tan \theta = h/r$$

Where, h = Height of piles

r = Radius of base of the pile

θ = Angle of repose



Fig 3.4 : Angle of repose of granules

3.7.4 Compression of granules

Using 800 mg granules, the die volume was adjusted to compress tablets of uniform weight. The tablets were then sealed in airtight containers and stored in a desiccator until they were evaluated.

3.7.5 Post-compressional parameters

For each prepared tablet, the post-compressional parameters such as weight variation, friability, hardness, thickness, disintegration time, and dissolution studies were assessed:

i. Weight variation

Separately weighted 10 units of tablets selected randomly and average weights was calculated (Chettupalli, 2013):

$$\text{Average weight} = \frac{\text{weight of 10 tablets}}{10}$$

ii. Friability

A Roche Friabilator was used to rotate a plastic chamber at 25 rpm and drop the tablets six inches with each revolution, exposing them to abrasive and stress effects. The friabilator was loaded with 10 pre-weighed (W_1) tablets and turned on for 100 rotations. The tablets were powdered and weighed again (W_2). The following formula was used to compute the percentage lost during the test (Daharwal *et al.*, 2015):

$$\text{Friability} = \frac{W_1 - W_2}{W_1} \times 100$$

Where, W_1 = Weight of the tablet before test

W_2 = Weight of the tablets after test.

iii. Hardness

Tablet hardness testing is an analytical method used by the pharmaceutical industry to ascertain the breaking point and structural integrity of tablets, as well as how they change during handling, packing, shipping, and storage before use. The tablet hardness tester helps to improve the quality of drugs. Each sample tablet should be placed vertically in the anvil's supporting edges of the Monsanto Hardness Tester. By moving the screw in the forward direction, adjust the position of the pointer at the zero position on the scale. Then, turn the screw until the tablet breaks. In order to get an average reading, repeat the process for 8 - 10 tablets fracture. The value of pressure for fracture of tablets (kg/cm^2) are recorded from the tester (Dwivedi *et al.*, 2019).

iv. Disintegration studies

The disintegration test was carried out in accordance to USP 30 specifications by using Disintegration Tester. Each tube of the disintegration apparatus contained six tablets. The basket was filled with a pH 6.8 buffer solution, and the temperature was kept at $37^{\circ}\text{C} \pm 2^{\circ}\text{C}$. A pH meter was used to measure the solution's pH. At each time interval, a new amount of dissolving medium was added to replace the volume that was removed. It was recorded the amount of time it took for the tablets to completely dissolve (Naveed *et al.*, 2018). Cumulative percent of the drug released was calculated and plotted against time.

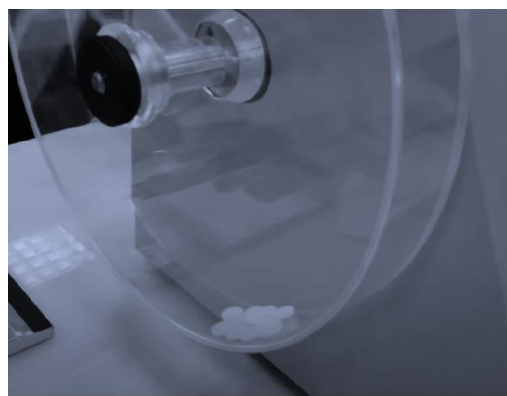
v. Dissolution studies

The BP paddle method was used to conduct the *in vitro* dissolution studies on the various batches of metformin tablets. This studies were done by the following methods (Dwivedi *et al.*, 2019; Kumar *et al.*, 2016):

- A dissolution apparatus employed with 900 mL of phosphate buffer at pH 6.8 solution was. It was warmed to 37°C and rotated at a speed of 50 rpm.
- The bottom of the jar filled with variously marked tablets containing 800 mg of metformin drug.
- At 0 minutes, 5 mL of sample were taken out and preserved in a correctly labeled test tube.
- Similar samples were taken at intervals of 5, 15, 30, 45, and 60 minutes. Watt-Man filter paper is used to filter all samples solutions.
- Every 10 minutes, samples were taken out the dissolving fluid and replaced with an equal volume kept at the same temperature, were filtered and diluted with the phosphate buffer solution accordingly.
- The solutions that were produced underwent spectrophotometric examination with a maximum wavelength of 233 nm.
- The equation of the standard calibration curve of the pure metformin powder was used to calculate the concentration and percentage of metformin released at the different in time. The observed curve used to determination the kinetics or drug release model.



Hardness tester



Friabilator



Buffer solution



Dissolution machine



Disintegration machine

Fig 3.5 : Post-compressional parameters

3.8 Drug release kinetics

The kinetic model following was fitted to the dissolution data obtained through dissolution investigations. This was to determine the mechanism of drug release mechanism.

i. Zero-order kinetics

It describes the process of continuous, concentration-independent drug release from a timely drug delivery system. It is frequently employed in pharmaceutical science to describe the release of drugs from controlled release dosage forms, including matrix tablets containing low-soluble medications, oral osmotic tablets, and transdermal systems. The zero-order release equation is expressed as follows (Giri *et al.*, 2012):

$$Q = Q_0 - kt$$

Where, Q = Amount of drug released at time t

Q_0 = Initial amount of drug in the dosage form

k = Zero-order release rate constant

t = Time.

With zero-order kinetics, the cumulative amount of drug released is represented by the term kt , which causes the drug content to decrease linearly over time. Linear graphs will be used to show how much of the drug dissolves over time. This characteristic is appropriate for a dose form and causes the least amount of variation in medication plasma levels (Lieberman, 2018).

ii. First order kinetics

First-order release kinetics in the design of a pharmaceutical formulation may result in a comparatively predictable and controllable release profile. The rate of drug release in first-order kinetics is proportional to the amount of drug still present in the dosage form. The release from a system with a concentration dependent release rate is described by first order kinetics. The first-order release equation is expressed as follows (Giri *et al.*, 2012):

$$Q = Q_0 \cdot e^{-kt}$$

Where, Q = Amount of drug released at time t

Q_0 = Initial amount of drug in the dosage form

k = First-order release rate constant

t = Time.

The exponential decay of the drug's remaining release over time is represented by the term e^{-kt} in this equation. The first-order release model depends on the assumption that

the release rate is directly proportional to the gradient in drug concentration within the dosage form. In order to create a straight line, the graph was created by taking the log of the cumulative percentage of drug release over time (Dwivedi *et al.*, 2019).

iii. Higuchi model

Enhancing therapeutic efficacy, ensuring safety, and improving patient compliance are the key objectives of controlled drug delivery systems. Higuchi proposed the Higuchi Model, a mathematical model that describes how pharmaceuticals are released from drug systems. This model may be used to investigate how water-soluble and low-soluble drugs that are incorporated into semisolid and solid matrices release. The Higuchi equation is typically expressed as follows (Giri *et al.*, 2012):

$$Q = K H \cdot t^{0.5}$$

Where, Q= Amount of drug released at time t

K= Higuchi release rate constant

H = Square root of time (t)

t = Time

The Higuchi and zero order models are used to characterize the time-dependent transport and medication release limits. The main advantages of this equation are that it allows for device optimization and a better understanding of the underlying drug release mechanisms. The equation is also applicable to various types of drug delivery systems, such as controlled drug release or oral controlled drug delivery films. According to Higuchi kinetics, the particles of the substance are smaller compared to that of a carrier, and the drug only spreads in one dimension. The drug's initial concentration in the formulation is greater than its solubility.

Chapter 4: RESULTS AND DISCUSSION

The mucilage was isolated from *Momordica charantia* fruits and used as binding agent to formulate Metformin HCl tablet due to its sustainable properties. The chapter describes the physicochemical characterization of mucilage from *Momordica charantia* fruits, formulation of tablets, evaluation of tablets, *in-vitro* release study with kinetic modelling and percent drug release.

4.1 Physicochemical characterization of mucilage

- The morphological and physical evaluation studies of mucilage from *Momordica charantia* show brownish coloured powder and an odourless test (Daharwal *et al.*, 2015).
- Molisch's test, that evaluates the presence of carbohydrates, yields a positive result in phytochemical analyses of isolated mucilage, but the mucilage does not have tannin, amino acids, alkaloids, reducing sugar, glycosides, and flavonoids (**Table 3.1**).
- Solubility test of isolated mucilage showed when dissolve in water at room temperature form a colloidal solution, and when dissolved in hot water shows a thick solution.
- Isolated mucilage is insoluble in organic solvents like methanol, ethanol, acetone, *n*-hexane etc. (**Table 3.2**).
- The pH of this mucilage show 6.1 and swelling index value 13.6% (**Table 3.3**).

4.2 Formulation of tablets

Metformin hydrochloride tablets were formulated by wet granulation method using mucilage of *Momordica charantia* as excipients. We designed and formulate nine batches of tablets (F1- F9) containing 500 mg of Metformin HCl with different concentrations (1%, 2.5%, 5%, and 10%) of mucilage and usual other ingredients as required to prepare 800 mg weight of each tablets. Here formulation, F1-F4 contains only mucilage as binder and Formulation, F5-F8 contains mucilage with maize starch as binders. The formulation of tablets with others ingredients given below:

Table 4.1: Formulation of tablets weight in mg

Formulation									
Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metformin HCl	500	500	500	500	500	500	500	500	500
Mucilage	8 (1%)	20 (2.5%)	40 (5%)	80 (10%)	8 (1%)	20 (2.5%)	40 (5%)	80 (10%)	-
Maize starch	-	-	-	-	80	80	80	80	80
Povidone	9.6	9.6	9.6	9.6	9.6	9.6	9.6	9.6	9.6
MCC	88	88	88	88	88	88	88	88	88
Mg stearate	4	4	4	4	4	4	4	4	4
Talc	8	8	8	8	8	8	8	8	8
Lactose	182.4	170.4	150.4	110.4	102.4	90.4	70.4	30.4	110.4
Water	1 μ l	-	-	-	-	-	-	-	-
Total weight	800	800	800	800	800	800	800	800	800
Note: All data represent as Mean $\pm$ SD									

4.3 Evaluation of tablets

4.3.1 Pre-compressional evaluation

The pre-compressional parameters of prepared granules evaluate were evaluated in this study of Bulk density, Tapped density, Carr's index, Hausner's ratio and Angle of repose. Results of the pre-compressional parameters show in **Table 4.2**.

- The tapped density and bulk density for all formulation within the range of 0.31 $\pm$ 0.01 (F1) to 0.44 $\pm$ 0.03 (F8) g/cm³ and 0.33 $\pm$ 0.03 (F1) to 0.52 $\pm$ 0.03 (F7)

g/cm³, respectively. Values <1 indicating good flow properties of granules and all of both density in the formulations show acceptable limit (Mishra *et al.*, 2010).

- Hausner's ratio found in the ranged from 1.06±0.01 (F1) to 1.23±0.06 (F7). Values <1.25 indicating good flow properties of granules (Alothaid *et al.*, 2021). All the values of Hausner's ratio found an acceptable limit.
- Carr's index values shows range from 6.14±0.01 (F1) to 16.85±0.06 (F7). Values less than 15 indicating good flow properties of granules (Parashar *et al.*, 2012). Formulation F1, F2, F5, F8, F9 shown the value in the range.
- The value of angle of repose observed from the range 22.22±0.02 (F8) to 24.35±0.02° (F4). This values within the limit of 25° – 30° indicates excellent flow of granules (Alothaid *et al.*, 2021) and also <40° values indicating better flow characteristics (Raddy *et al.*, 2013). All the formulation shown excellent flow properties.

The above results for formulations (F1 to F9) possess excellent flow properties. It observe that the granules show good to excellent flow properties based on the values of Hausner's ratio, bulk density, compressibility index tap density, and angle of repose.

Table 4.2: Pre-compressional evaluation of granules

Formulation	Bulk density (g/cm³)	Tapped density (g/cm³)	Hausner's ratio	Carr's index (%)	Angle of repose (°)
F1	0.31±0.01	0.33±0.01	1.06±0.01	6.14±0.01	22.78±0.02
F2	0.34±0.01	0.38±0.01	1.12±0.02	10.41±0.01	23.73±0.08
F3	0.35±0.04	0.41±0.02	1.13±0.01	16.74±0.77	23.32±0.03
F4	0.42±0.02	0.52±0.02	1.19±0.01	16.63±0.74	24.35±0.02
F5	0.37±0.03	0.43±0.02	1.16±0.01	13.87±0.06	24.23±0.02
F6	0.40±0.01	0.47±0.01	1.19±0.01	15.99±0.06	22.57±0.03
F7	0.41±0.01	0.52±0.03	1.23±0.06	16.85±0.06	23.76±0.03
F8	0.44±0.03	0.51±0.01	1.14±0.01	12.79±0.07	22.22±0.02
F9	0.33±0.03	0.37± 0.01	1.12±0.01	13.73±0.03	23.75±0.01
Note: All data represent as Mean ± SD					

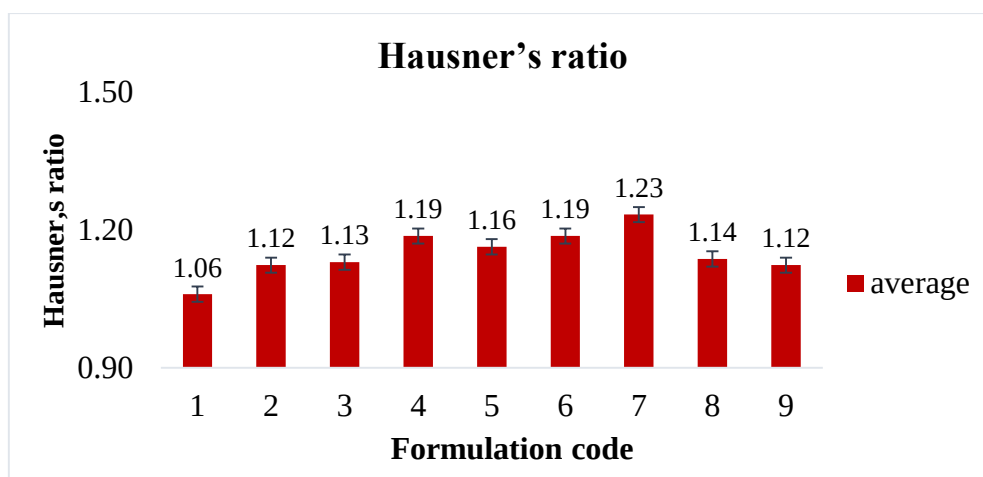
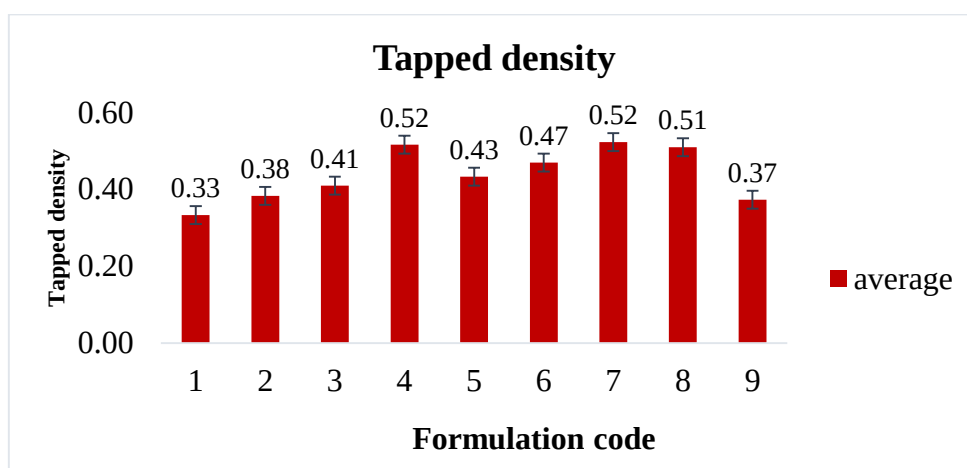
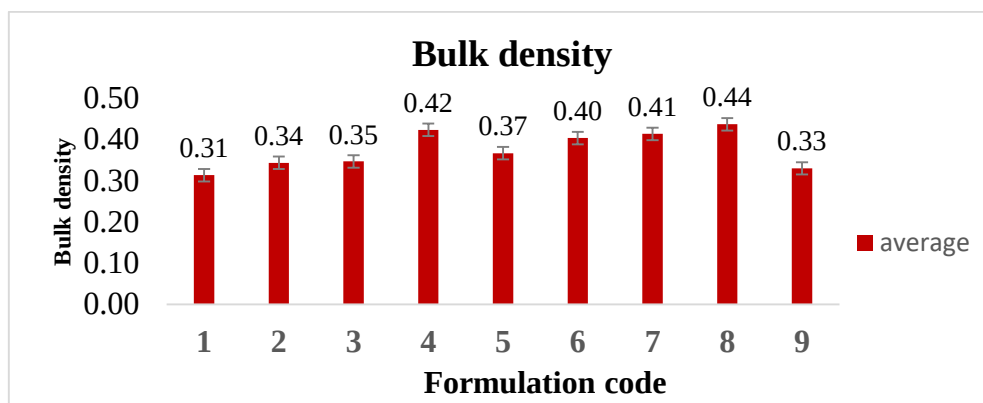


Fig 4.1: Graphical representation of pre-compressional values

4.3.2 Post-compressional evaluation

The prepared tablets observe and found smooth texture with free from any cracks or defects. For all the batches test for their physical parameters such as average weight, hardness, and friability and disintegration time. The compressed tablets and the results discuss below

- The average weight of twenty tablets calculated for each batch, which varied from 796.14 ± 1.07 (F9) mg to 796.86 ± 1.86 (F5) mg which are very close to standard 800 mg (Raddy *et al.*, 2013). So average weight of prepared tablets are excellent.
- Hardness found in the range from 2.17 ± 0.29 (F1) kg/cm² to 7.83 ± 0.29 (F8) kg/cm² within acceptable limit of 3–8 kg/cm² (Dulla *et al.*, 2018; Karmakar *et al.*, 2012). The experiment results shown excellent values.
- The prepared tablets have friability values that range from $0.61 \pm 0.01\%$ (F1) to $0.21 \pm 0.01\%$ (F8). All formulations showed less than 1% (w/w) friability, which within the acceptable limits (Chandre *et al.*, 2012).

Disintegration time found from 2.00 ± 0.45 (F1) to 8.23 ± 0.79 (F8) in minutes for all formulations (Parashar *et al.*, 2012). The present study shows that among all the formulations of tablets, batches F4 show good result without starch and F8 with mucilage with starch have good disintegration properties.

Table 4.3: Post-compressional evaluation of tablets

Formulation	% of mucilage	Average weight (mg)	Hardness (kg/cm ²)	Friability (%)	Disintegration time (min)
F1	1	796.86 ± 1.46	2.17 ± 0.29	0.61 ± 0.01	2.00 ± 0.45
F2	2.5	797.57 ± 1.81	3.33 ± 0.29	0.52 ± 0.01	3.06 ± 0.46
F3	5	797.71 ± 1.11	3.83 ± 0.29	0.46 ± 0.01	4.26 ± 0.18
F4	10	797.86 ± 1.35	5.17 ± 0.29	0.38 ± 0.01	5.03 ± 0.40
F5	1	796.86 ± 1.86	3.83 ± 0.29	0.52 ± 0.01	4.17 ± 0.15
F6	2.5	797.29 ± 1.11	5.00 ± 0.50	0.42 ± 0.01	5.55 ± 0.44
F7	5	797.43 ± 1.51	6.50 ± 0.50	0.30 ± 0.01	6.31 ± 0.87
F8	10	797.57 ± 1.62	7.83 ± 0.29	0.21 ± 0.01	8.23 ± 0.79
F9	-	796.14 ± 1.07	4.00 ± 0.87	0.35 ± 0.13	4.99 ± 0.59
Note: All data represent as Mean $\pm$ SD					

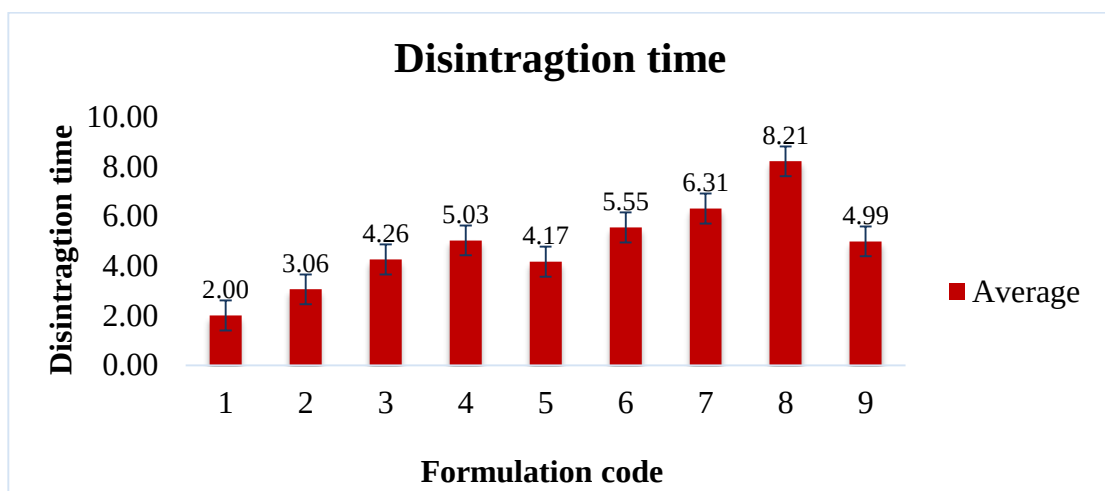
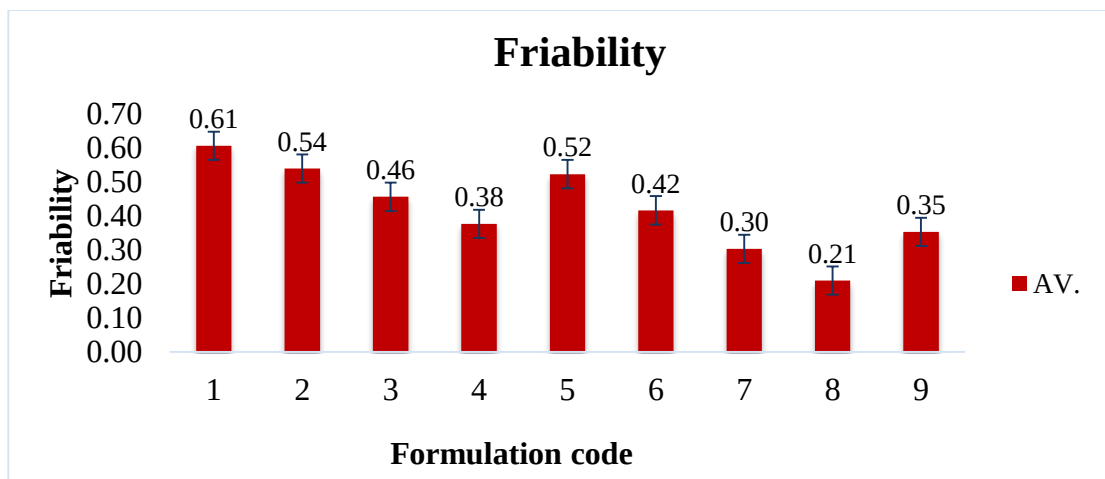
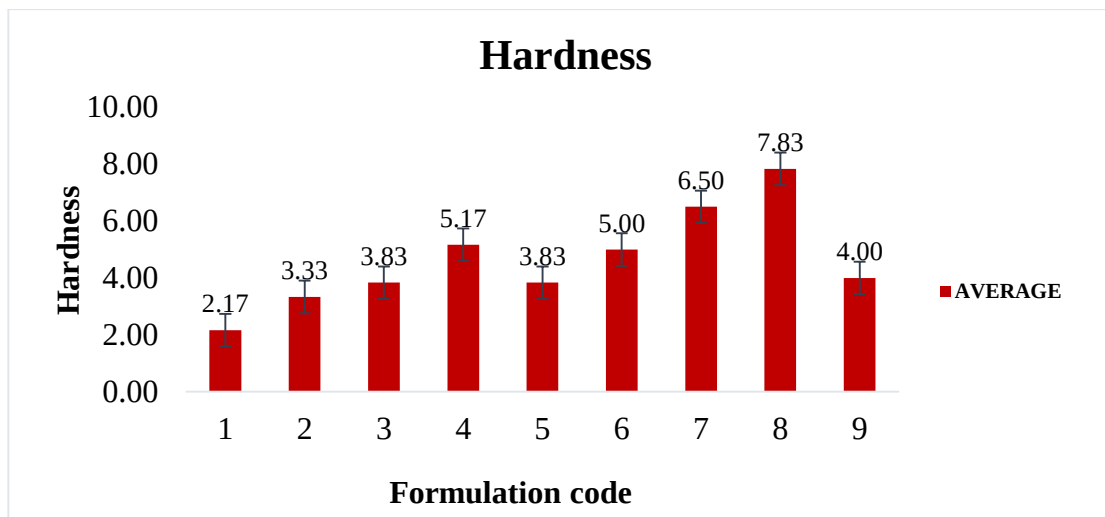


Fig 4.2: Graphical presentation of post-compressional values

4.3.3 *In -vitro* drug release study with kinetic modeling

From pre-compressional and post-compressional evaluation of all batches of tablets, formulation F4 and F8 showed good flow properties, hardness, friability and disintegration time. For that, the tablets of these two batches (F4 and F8) consider for an *in vitro* drug dissolution test. It observed from *in-vitro* dissolution profile analysis that formulation **F4** release 40.8% of drug which contain 10% of mucilage and formulation **F8** released 31.63% of drug which contain 10% mucilage and 10% starch together in time 60 minutes (Chandre *et al.*, 2012).

Table 4.4: Percent drug release (%)

Time	F4	F8
5	8.96	5.21
15	15.33	10.46
30	23.96	19.33
45	28.83	26.96
60	40.8	31.63

4.3.4 Kinetic modeling drug release

To understand the mechanism of drug release properties, the percentage of drug release data obtained from experiments were plotted to zero order, first order, and Higuchi's square root of time equations (Paarakh *et al.*, 2019; Guerra-Ponce *et al.*, 2016; Heredia *et al.*, 2022). Fig No. 4.3, 4.4 and 4.5, gave idea on the release rate and the mechanism of release of drugs.

In zero-order kinetics, the drug rate at which drugs release from dosage forms for drugs is independent of the drug concentration. The rate in first-order kinetics depends on the concentration, indicating that the higher the concentration, the more quickly the process. Higuchi plots are frequently used in evaluation of controlled-release drug formulations' release kinetics. Drugs with controlled-release formulations are developed to release the drug gradually over time, which can increase the drug's effectiveness and minimize its adverse effects.

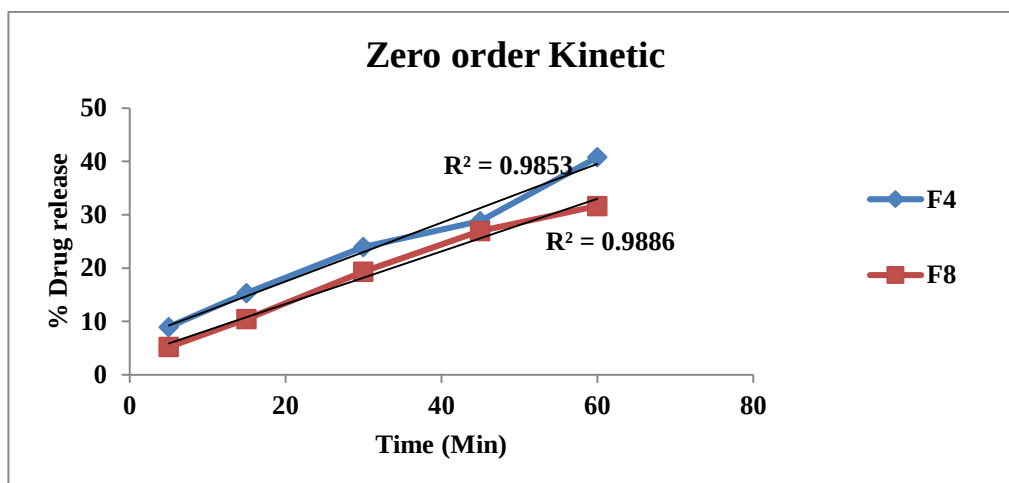


Fig 4.3 : Zero order release of F4 &F8

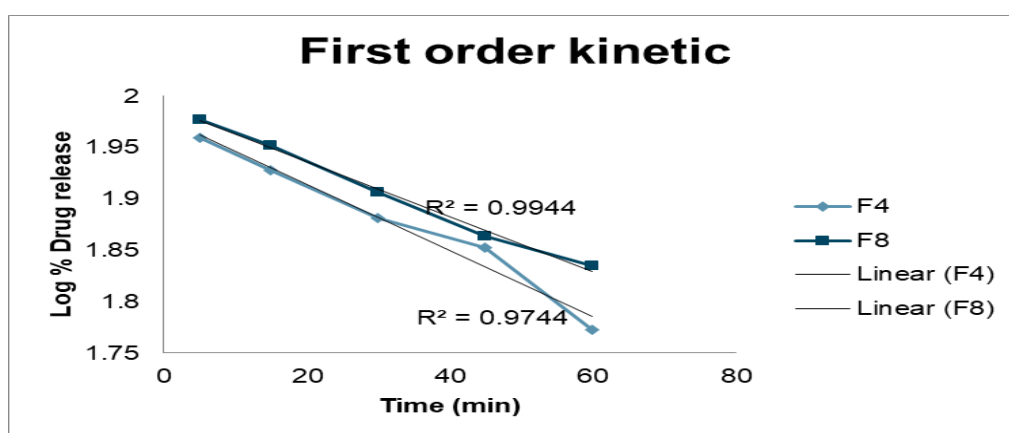


Fig 4.4 : First order release of F4 &F8

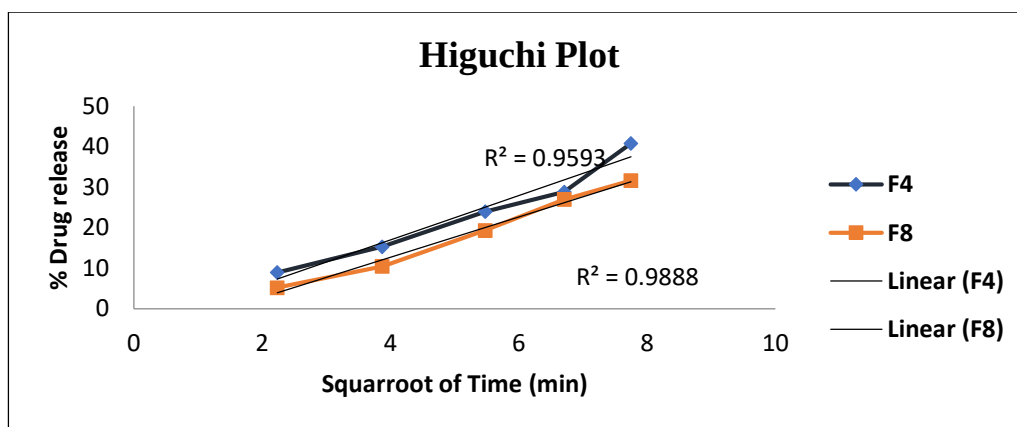


Fig 4.5 : Higuchi's release of F4 &F8

The regression coefficient (R^2) value obtained from the log %ARR (Amount Remaining to be released) v/s time was examined to find out the release mechanism. The regression coefficient value R^2 indicate the appropriate kinetic model for the release of drug (Dash *et al.*, 2010). The regression coefficient values for Zero order, First order and Higuchi's plot from the fig. 4.3, 4.4, 4.5 and **Table 4.4**, found for formulation F4 are

0.985, 0.994 and 0.959 and for formulation **F8** are found 0.988, 0.974 and 0.988 with high linearity

From kinetics plots, R^2 value of formulation **F4** is 0.994, which is very close to 1, and the plot (**Fig 4.4**) shows linear drug release properties which follow first order release kinetics. The R^2 value of formulation **F8** is 0.988, which close to 1, that follows zero order kinetics. Higuchi's plots kinetics (**Fig 4.5**) shows linear drug release properties with R^2 values 0.959 and 0.988 for formulation of **F4** and **F8**, respectively, indicate that formulation **F8** has more sustain drug release property then formulation **F4** (Patil *et al.*, 2021). It indicates that for highly water soluble drugs, concentration has a significant impact on drug release.

Table 4.4: Regression coefficient (R) of drug release kinetics of different formulation

Formulation (F)	Zero order	First order	Higuchi's plot
F4	0.985	0.994	0.959
F8	0.988	0.974	0.988
F4 = 0.994 = First order kinetics F8 = 0.988 = Zero order & Higuchi kinetics			

Chapter 5: CONCLUSIONS

5.1 Conclusions

The mucilage isolated from *Momordica charantia* fruits and used in the tablets formulation as a binding agent. Nine batches of metformin HCl tablets was designed with different concentration of mucilage (1%, 2.5%, 5%, and 10%) for 800mg.

From this present research we have found that -

- Pre-compressional flow properties by the tablet (F1 to F8) granules have showed good (F4) to excellent (F8) results.
- Good binding properties have been revealed by the formulation F4 and F8 (Table 4.2 and Table 4.3).
- *In vitro* drug release kinetics studies showed the formulation F4 (10% mucilage without Mg-starch) exhibited good binding properties and intermediate level of sustained drug release properties, among the formulations F1 to F4,
- *In vitro* drug release kinetics studies showed that formulation F8 (10% mucilage with 10% Mg-starch) exhibit the highest tablet binding properties, as well as exhibit excellent level of sustained drug release properties, among the formulations F5 to F8.

From this following study it has been concluded that mucilage from *Momordica Charantia* showed significant binding properties and sustain drug release properties of Metformin HCl or any other drug will stay in the body for a prolong time.

Hence, mucilage from *Momordica charantia* be used as excipients or tablets binders for cost, available and non-toxic in pharmaceutical formulation.

5.2 Recommendation

The present research demonstrates an effort to separate mucilage from *Momordica charantia* and using different concentrations of mucilage as natural binding agents, to formulate and assess sustained-release tablets of Metformin HCl.

The manufacturing of dosage forms for drugs now depends on the use of polymers to maintain drug release. Due to its natural characteristic's and numerous advantages over synthetic polymers, *Momordica charantia* mucilage can be used in drugs formulation to produce sustained release. Natural polymers are attractive primarily because they are capable of chemical modification, have a high drug holding capacity, and have thermal stability. In sustained-release drug delivery systems, natural polymers are readily available and offer numerous advantages, including nontoxicity, bioacceptability, biocompatibility, and biodegradability.

The study showed that natural mucilage could be a better alternative to synthetic polymers in terms of its utility and cost. To determine these formulations' effectiveness, more detailed in vivo bioavailability studies are required performed.

For explore these types of natural polymers and mucilage for low cost, available and non-toxic in pharmaceutical excipients from other natural source can be extended.

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Appendices A

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Appendices B

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Exploring the Potential of *Momordica charantia* Fruits Mucilage as a Novel Pharmaceutical Excipient

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: The discovery and developments of new drug formulations are inspired by medicinal plants. Polysaccharides, such as mucilage or gum from medicinal plants, have a variety of physicochemical properties and are commonly used in pharmaceutical applications.

Objectives: The current study's objectives are to construct and assess Metformin HCl tablets employing *Momordica charantia* (MC) natural mucilage as a binder and release modifier.

Methods: The mucilage was isolated from the fruits of MC. The tablet was made using a wet granulation process, and the formulation included several mucilage ratios (1%, 2.5%, 5%, and 10%).

Results: It was found that the granules and tablets had good flow qualities based on results of the pre- and post-compression parameters. The release kinetic study showed that F4 showed the first order release kinetics and F8 showed the zero and the Higuchi's release kinetics. In low

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concentration of mucilage tablets showed good binding properties with immediate release properties. As the concentration was increased, tablets showed good binding properties with sustained release properties.

Conclusion: The isolated mucilage from *Momordica charantia* has the potential to be used as a tablet binder and as an intermediary in the development of a sustained-release drug

Keywords: *Momordica charantia*; mucilage; binder; metformin HCl; sustained release.

1. INTRODUCTION

Mucilage is a thick, sticky substance produced by almost all plants and some microorganisms [1]. It is a polymeric polysaccharide complex and water-soluble adhesive material that contains glycoprotein and a variety of bioactive components present in different parts of plants, such as seeds, leaves, and fruits [2]. Because of the bio-incompatibility, toxicity, and carcinogenic activity of synthetic polymers, plant-based, naturally generated biopolymers such as mucilage have received more attention as crucial constituents in the creation of sustainable, eco-friendly, and cost-effective goods [3,4]. Mucilage is used as tablet binders and disintegrates, as well as, suspending, emulsifying [5], thickening, gelling, stabilizing, and sustaining agents in tablets [1]. Nowadays, natural mucilage may be changed into synthetic or artificial excipients to satisfy the necessities of drug delivery systems [6]. In the manufacturing of tablets, binders, often referred to as adhesives and pharmaceutical excipients, are utilized. Improving the flow characteristics of granules by aggregating the powder of other ingredients in a tablet. The disintegration time increases in direct proportion to the binder concentration in a tablet. Binder is widely used in the wet granulation process [7]. The Cucurbitaceae family includes *Momordica charantia* (MC), often known as the bitter melon, bitter guard, karela, etc. Throughout the world, *Momordica charantia* fruits, seeds, and other parts have been used to treat both normal and diabetic individuals for diabetes[8]. By enhancing glucose absorption and glycogen synthesis in the liver, muscles, and fat cells, oral treatment with the fruit juice or seed of *M. charantia* decreases fasting blood glucose and improves glucose tolerance [9]. Metformin hydrochloride is an anti-diabetic drug that is taken orally, is derived from the biguanide family, and is widely used in the treatment of type II diabetes [10]. Metformin has a 50–60% bioavailability and a 1.5–4.5 h plasma half-life, which are both relatively short. Therefore, the requirement for administration 2-3

times a day when higher dosages are required can reduce patient compliance [11].

The objective of the current study was to manufacture oral sustained-release tablets of Metformin hydrochloride (HCl) using a wet granulation process, mucilage from *Momordica charantia* fruits, starch, and other ingredients with various concentration ratios and to evaluate the effects of polymer concentration on the duration of drug release.

2. MATERIALS AND METHODS

2.1 Plant Materials

The fruits of *Momordica charantia* were collected from Local Market at Chittagong division in Bangladesh and authenticated by Md. Boktear Uddin, Professor, Department of Botany, University of Chittagong, Bangladesh. A voucher specimen was deposited (Accession No.TA-03122022-6443) at the herbarium in the Department of Botany, University of Chittagong, Bangladesh.

2.2 Drug and Chemicals

Metformin HCl was obtained from Ibne Sina Pharmaceutical Limited, Barisal, Bangladesh as gift sample. All the other materials, such as Potato Starch, Lactose, Microcrystalline Cellulose (MCC), Talc and Magnesium stearate were of pharmaceutical grade and were purchased from Taj Chemical Store, Chittagong, Bangladesh.

2.3 Separation of Mucilage Fruits

For the purpose of isolating mucilage from the fruits of *Momordica charantia*, an established procedure previously reported by Barua et al., [12] was used with a few slight modifications, as will be explained below.

Step 1: Extraction of Mucilage

Momordica charantia fruits were collected, washed of any adhering dirt, and then dried in the sun. The dried fruits were mashed using a mechanical grinder. To release the mucilage into the water, the powdered fruits (150 g) was macerated in 400 mL of warm (50 °C) distilled water for 8 hours, boiled for 2 hours, and then left to stand for an additional 2 hours. The macerate was poured into a muslin bag, and 100 mL of the filtrate was obtained after filtering.

Step 2: Isolation of Mucilage

Acetone (450 mL) was added to the filtrate (150 mL) that was collected in the previous step. Due to the insolubility of mucilage in acetone, the mucilage was precipitated from the solution. Then the mucilage was washed into distilled water and precipitated by filter paper. The precipitated mucilage was filtered and dried in an oven at 40 °C. The dried mucilage was grounded and passed through an 80-mesh sieve. The sieved mucilage (11.85 g) was stored in desiccators until further use.

2.4 Physicochemical Identifications of Isolated Mucilage

2.4.1 Chemical characterization

An aqueous solution of the isolated mucilage was used for chemical characterization. Carbohydrates, proteins, mucilage, gums, alkaloids, fats, and tannins were tested according to standard procedure [13].

Solubility test: Solubility of the dried fruits mucilage of *Momordica charantia* was determined by dissolving in different solvents like acetone, methanol, ethanol, etc [13]

2.4.2 Organoleptic properties

The isolated mucilage was taken for organoleptic properties like color, odor, taste, and texture[13].

2.5 Swelling Index

About 1g of the mucilage powder with a tapped volume in a 25 ml glass-stoppered measuring cylinder was dispersed with 25 ml of distilled water and cylinder and shaken thoroughly every 10 minutes for 1 h. Then it was allowed to stand for 3 hours at room temperature. The increased volume of water that was occupied by the swollen mucilage was measured. The procedure was repeated twice more, and the swelling index was calculated [13].

2.6 Evaluation and preparation of Metformin Tablets with Mucilage

2.6.1 Preparation of granules

Wet granulation technique was used to uniform distribution of drug as well as improve flow property. So, this approach was carried forward for the formulation development of new metformin tablets. Metformin HCl was used as a model drug to formulate the granules. Microcrystalline cellulose was used as disintegrate, and lactose was used as a diluent in the composition. Tablets were prepared by using mucilage at 2.0%, 2.5%, 5.0%, and 10.0% w/v with 10.0% starch in concentrations [14].

2.6.2 Preparation of tablets compression

The granules were prepared by a wet granulation process with a single punch machine for tablet manufacturing. In vitro drug release, hardness

Table 1. Formulation of *Momordica charantia* tablets (mg)

Ingredients	Formulations (mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metformin HCl	500	500	500	500	500	500	500	500	500
Mucilage	1%	2.5%	5%	10%	1%	2.5%	5%	10%	-
Maize starch	-	-	-	-	10%	10%	10%	10%	10%
Povidone	9.6	9.6	9.6	9.6	9.6	9.6	9.6	9.6	9.6
Mcc	88	88	88	88	88	88	88	88	88
Mg stearate	4	4	4	4	4	4	4	4	4
Talc	8	8	8	8	8	8	8	8	8
Lactose	182.4	170.4	150.4	110.4	102.4	90.4	70.4	30.4	110.4
Water	qs	qs	qs	qs	qs	qs	qs	qs	qs
Total	800	800	800	800	800	800	800	800	800

(by Monsanto hardness tester), friability (Roche Friabilator), disintegration time, and average weight variation were just some of the parameters that the produced tablets were analyzed for [14].

3. RESULTS

3.1 Physicochemical Characterization

The results of Molisch's Test, which produced a purple color on powdered particles, and the Ruthenium Red Test, which produced a pink color on powdered particles, respectively, indicated the presence of carbohydrates and mucilage. The phytochemical analysis of natural mucilage showed the presence of polysaccharides in nature (Table 3). Mucilage's physical, chemical, and organoleptic characteristics were established. The results of the morphological and physical evaluation examinations showed a brownish powder that was odorless and tasted distinctive (Table 2). The mucilage was completely soluble in warm water, whereas all of the chemical solvents used to dissolve it were essentially insoluble (Table 4). The mucilage's pH was discovered to be 6.1, which is extremely close to neutral, with a swelling index of 13.6 and a yield of 5.33 %.

Table 2. Organoleptic properties of isolate mucilage

Parameters	Results
Colour	Brownish
Odour	Odourless
Taste	Characteristic
Yield	5.33%
pH	6.1
Swelling Index	13.6

Table 3. Phytochemical properties of isolated mucilage

Phytochemicals	Result
Carbohydrates	+
Tannins	-
Alkaloids	-
Glycosides	-
Flavonoids	-
Reducing sugar	-
Protein	-
Mucilage	+

Note: '+' sign indicates Present and '-' sign indicates absent

Table 4. Solubility profile of isolated mucilage

Solvent	Solubility
Water	Soluble (Colloidal solution)
Hot water	Soluble (Thicky solution)
Methanol	Insoluble
Ethanol	Insoluble
Acetone	Insoluble
n-Hexan	Insoluble

3.2 Pre-compression Evaluation of Granules

Granules were established to have an acceptable appearance. The formulation of the granules was done, and their bulk density (BD), tapped density (TD), Carr's index, Hausner's ratio, and angle of repose were all analyzed. With the funnel method, the angle of repose was calculated. By applying the cylinder method, the bulk density and the tapped density were calculated, and the Carr's index (CI) was then calculated by this formula: $(TBD-BD)/100$. Powder flow properties could be predicted using Hausner's ratio, which was connected to interparticulate friction [15]. The bulk density and tapped density for all formulations were found in the range of 0.31 ± 0.01 F (1) to 0.33 ± 0.03 F (9) g/cm³ and 0.33 ± 0.03 F (1) to 0.37 ± 0.01 F (9) g/cm³, respectively. Hausner's values ranged from 1.06 ± 0.01 F (1) to 1.12 ± 0.01 F (9) (<1.25) indicating good flow properties. The value of the angle of repose the range of 22.78 ± 0.02 F (1) to 23.75 ± 0.01 F (9) (<40°) which indicates a good flow property of the powder. It was observed that the granules showed good to excellent flow properties based on the values of angle of repose, bulk density, tap density, compressibility index, and Hausner's ratio as per Table 5.

3.3 Post-Compression Evaluations of Tablets

The physical appearance of the tablets was found to be satisfactory. The compressed tablet and reference standard were tested for hardness, thickness, percentage friability, weight variation, disintegration time, and dissolution. The hardness of the tablets was tested using a hardness tester. The thickness of the tablets was measured by a digital vernier caliper. Friability of the tablets was determined in a Roche friabilator (Electrolab). A weight variation test was performed according to the laboratory method [16]. The average weight of twenty tablets was calculated for each batch, which varied from

796.8±1.46 (F1) to 798.29±1.38F (9) mg. Hardness was found to be from 2.17±0.29 (F1) to 4.00±0.87 (F9). The friability values of the prepared tablets ranged from 0.61±0.01 (F1) to 0.35±0.13 (F9). All formulations showed less than 1% (w/w) friability, which was within the prescribed limits. Disintegration time for all formulations ranges from 2.00±0.45F (1) to 4.99±0.59 (F9) in minutes. The present study shows that among all the formulations of tablets, batches F4 and F8 have good disintegration properties (Table 6).

3.4 In vitro Drug Release Study

The mucilage of MC was used to prepare nine batches of tablets containing four different concentrations of the drug (1, 2.5, 5, 10% w/w). In in-vitro dissolution profile analysis, formulations F-4 to F-8 were composed of 10% of mucilage along or with 10% starch, released the 40.8% and 31.63 % of drug in 60 minutes respectively. It was found that varied ratios of mucilage were used in the release of drugs from tablets; as mucilage concentration

increased, so increased the extent of the drug release. Sustain released formulation were developed by using mucilage with starch (10%) and release were prolonged by increasing concentration of mucilage (Table 7).

3.5 Drug Release Kinetics

Release kinetics is crucial for new drug formulation as it directly impacts therapeutic efficacy, pharmacokinetics, patient compliance, safety, and intellectual property. To describe the kinetics of drug release from tablets, release data was analyzed according to different kinetics, e.g., zero order, first order, and Higuchi plots are shown in Figs 1, 2 and 3, respectively. The regression coefficient (R^2) value obtained from the first order, zero order and Higuchi plot were examined to find out the release mechanism [17,18]. In the release kinetic study (Table 8) showed that F4 showed the first order release kinetics and F8 showed the zero and the Higuchi's release kinetics as sustained release dosage form.

Table 5. Pre-compression evaluation of Metformin HCl granules

Formulations	Bulk density(g/cm ³)	Tapped density(g/cm ³)	Hausner's Ratio	Carr's Index (%)	Angle of repose (°)
F1	0.31± 0.01	0.33± 0.01	1.06± 0.01	6.14± 0.01	22.78± 0.02
F2	0.34± 0.01	0.38± 0.01	1.12± 0.02	10.41± 0.01	23.73± 0.08
F3	0.35± 0.04	0.41± 0.02	1.13± 0.01	16.74± 0.77	23.32± 0.03
F4	0.42± 0.02	0.52± 0.02	1.19± 0.01	16.63± 0.74	24.35± 0.02
F5	0.37± 0.03	0.43± 0.02	1.16± 0.01	13.87± 0.06	24.23± 0.02
F6	0.40± 0.01	0.47± 0.01	1.19± 0.01	15.99± 0.06	22.57± 0.03
F7	0.41± 0.01	0.52± 0.03	1.23± 0.06	16.85± 0.06	23.76± 0.03
F8	0.44± 0.03	0.51± 0.01	1.14± 0.01	12.79± 0.07	22.22± 0.02
F9	0.33± 0.03	0.37± 0.01	1.12± 0.01	13.73± 0.03	23.75± 0.01

Note: All data represent as Mean ± SD

Table 6. Post-compression evaluation of Metformin HCl tablets

Formulations	% of mucilage	Average weight(mg)	Hardness (kg/cm ²)	Friability (%)	DT(min)
F1	1	796.86 ± 1.46	2.17± 0.29	0.61± 0.01	2.00± 0.45
F2	2.5	797.57± 1.81	3.33± 0.29	0.52± 0.01	3.06± 0.46
F3	5	797.71 ± 1.11	3.83± 0.29	0.46± 0.01	4.26± 0.18
F4	10	797.86 ± 1.35	5.17± 0.29	0.38± 0.01	5.03± 0.40
F5	1	796.86 ± 1.86	3.83± 0.29	0.52± 0.01	4.17± 0.15
F6	2.5	797.29 ± 1.11	5.00± 0.50	0.42± 0.01	5.55± 0.44
F7	5	797.43 ± 1.51	6.50± 0.50	0.30± 0.01	6.31± 0.87
F8	10	797.57± 1.62	7.83± 0.29	0.21± 0.01	8.23± 0.79
F9	-	796.14 ± 1.07	4.00± 0.87	0.35± 0.13	4.99± 0.59

Note: All data represent as Mean ± SD

Table 7. *In vitro* percentage of drug release study

Time(min)	Percent of Drug Release	
	F4	F8
5	8.96	5.21
15	15.33	10.48
30	23.96	19.33
45	28.83	26.96
60	40.8	31.63

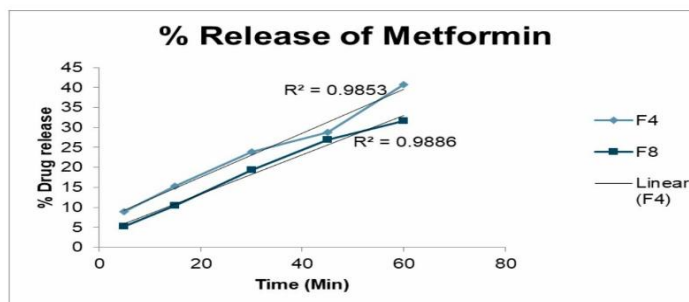


Fig. 1. Zero order release kinetics of formulation F4 and F8

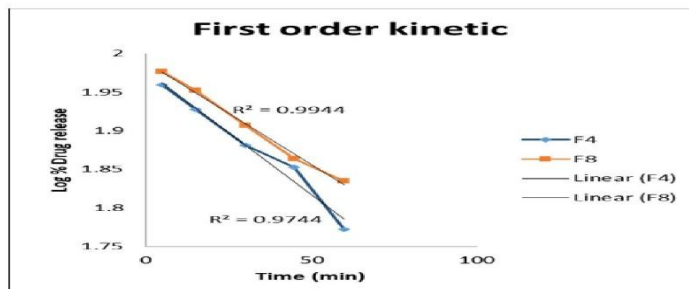


Fig. 2. First order release kinetics of formulation F4 and F8

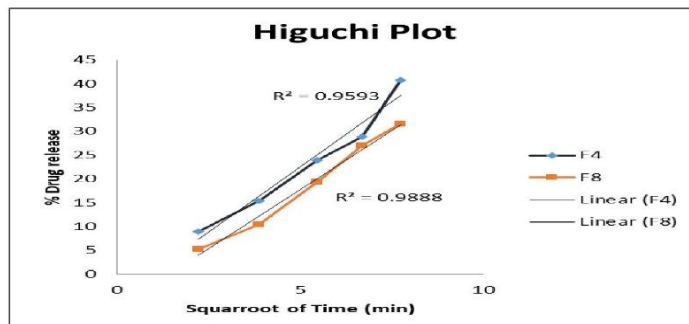


Fig. 3. Higuchi release kinetics of formulation F4 and F8

Table 8. Regression coefficient(R) of drug release kinetics of different formulation

Formulations	Zero order	First order	Higuchi's
F4	0.985	0.994	0.959
F8	0.988	0.974	0.988

4. CONCLUSION

In conclusion, natural mucilage can be easily isolated from *Momordica charantia* fruit with good yield. Metformin tablets containing a various concentrations of isolated mucilage alone and in combination with starch demonstrated promising outcomes as binder and release modifier. Formulations F4 and F8 exhibited commendable binding capabilities, while F4 showing excellent immediate release kinetics and F8 displaying sustained release characteristics. This research concludes that the mucilage extracted from *Momordica charantia* possesses noteworthy binding and drug release properties. Consequently, it has the potential to serve as a binder and/or release modifier in pharmaceutical formulations.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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