PREPARATION AND EVALUATION OF MUCOADHESIVE GASTRO RETENTIVE TABLETS OF GLICLAZIDE BY USING MUCOADHESIVE POLYMERS

DISSERTATION

Submitted to

THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI

In partial fulfillment of the award of degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

OCTOBER 2016

PADMAVATHI COLLEGE OF PHARMACY AND RESEARCH INSTITUTE

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CERTIFICATE

This is to certify that the dissertation entitled **"PREPARATION AND EVALUATION OF MUCOADHESIVE GASTRO RETENTIVE TABLETS OF GLICLAZIDE BY USING MUCOADHESIVE POLYMERS"** was carried out by **Reg.No: 261410857** under the guidance of **Dr. M.MUTHUKUMAR, M.Pharm, Ph.D., Professor & Head** in the Department of Pharmaceutics, Padmavathi College of Pharmacy and Research Institute, Dharmapuri, Affiliated to The Tamilnadu Dr. M.G.R Medical University, Chennai - 32.

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Dr.M.MUTHUKUMAR, M.Pharm, Ph.D.,

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DECLARATION

I hereby declare that the matter embodied in the dissertation entitled **"PREPARATION AND EVALUATION OF MUCOADHESIVE GASTRO RETENTION TABLETS OF GLICLAZIDE BY USING MUCOADHESIVE POLYMERS"** is a bonafide and genuine research work carried out by me under the guidance of **Dr. M.MUTHUKUMAR, M.Pharm, Ph.D.,** Professor & Head Department of Pharmaceutics, Padmavathi College of Pharmacy and Research Institute, Periyanahalli, Dharmapuri.

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EVALUATION CERTIFICATE

This is to certify that the work embodied in this thesis entitled **"PREPARATION AND EVALUATION OF MUCOADHESIVE GASTRO RETENTION TABLETS OF GLICLAZIDE BY USING MUCOADHESIVE POLYMERS"** submitted to the **Tamil Nadu Dr. M.G.R. Medical University**, was carried out by **B.PURUSOTHAMAN (Reg.No: 261410857)** in the partial fulfillment of the Degree of **"Master of Pharmacy" in Pharmaceutics** under the supervision of D**r.M.MUTHUKUMAR, M.Pharm**,Ph.D., Professor and Head, Department of Pharmaceutics, Padmavathi College of Pharmacy & Research Institute, Dharmapuri.

This work is original and has not been submitted in part or full for the award of any other degree or diploma of any other University.

Internal Examiner **External Examiner**

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CONTENTS

1. INTRODUCTION

The newer drug delivery systems have been developed from time to time with a goal of providing the therapeutic amount of drug to the proper site in the body and to increase the bioavailability of the drug. An appropriately designed controlled-release drug delivery system can be major advance towards solving the major issues like delivering drug to the site, controlling the rate of drug delivery. This can be achieved by better control of plasma drug levels and less frequent dosing[1].

Historically, oral drug administration has been the predominant route for drug delivery. Oral dosage forms capable of having prolonged retention time in the stomach to extend the duration of drug delivery have been receiving much attention in recent years[2]. More often, drug absorption is unsatisfactory and highly variable among and between individuals, despite excellent in vitro release patterns. The reasons for this are essentially physiological and usually affected by the GI transit of the form, especially its gastric residence time (GRT).[3]

Over the past three decades, the pursuit and exploration of devices designed to be retained in the upper part of the gastrointestinal (GI) tract has advanced consistently in terms of technology and diversity, encompassing a variety of systems and devices.Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. Also, longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease.

Furthermore, improved bioavailability is expected for drugs that are absorbed readily upon release in the GI tract. These drugs can be delivered ideally by slow release from the stomach. Many drugs categorized as once-a-day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the release time .[4]

Drugs that are having short half-lives are eliminated quickly from the systemic circulation. In order to achieve suitable therapeutic activity, the drug should be

administered frequently. This can be overcome by developing the drug in to controlled release formulations which will release the drug slowly into the gastrointestinal tract (GIT). This approachwill maintain an effective drug concentration in the systemic circulation for a longer durations. Thus the orally administered controlled drug will retained in the stomach and release the drug in a controlled manner supply the drug continuously to its absorption sites of the gastrointestinal tract (GIT) [5.]

1.1 GASTRORETENTIVE DRUG DELIVERY SYSTEMS

Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs.

1.1.1 Advantages[6]

- Improvement of bioavailability and therapeutic efficacy of the drugs and possible dose reduction e.g. Furosemide
- Enable constant therapeutic levelsover a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics. E.g. b-lactam antibiotics (penicillin and cephalosporins)
- For drugs with relatively short half-life, sustained release may result in a flip- flop pharmacokinetics and also enable reduced frequency of dosing with improved patient Compliance.
- They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET). As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of employing because of their bulk density is lower than that of the gastric fluids.

- Gastro retentive drug delivery can produce prolongs and sustains release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.

- The controlled, slow delivery of drug form gastro retentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. This site-specific drug delivery reduces undesirable side effects.
- Gastro retentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency.
- Reduction of fluctuation in drug concentration makes it possible to obtain improved selectivity in receptor activation.
- The sustained mode of drug release from Gastro retentive doses form enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the chemical outcomes.

1.1.2 NECESSITIES OF A DRUG FOR GASTRIC RETENTION[7]:

1. Physiological factors in the stomach,
2. The dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms.
3. To function as a gastric retention device, it must resist premature gastric emptying.
4. Furthermore, once its purpose has been served, the device should be removed from the stomach with ease.

1.1.3 LIMITATIONS OF GASTRO RETENTION[8]:

1. The floating systems in patients with achlorhydria can be questionable in case of swellable systems, faster swelling properties are required and complete swelling of the system should be achieved well before the gastric emptying time.
2. high turnover of mucus may affect the effectiveness of gastro retention
3. retention of high density systems in the antrum part under the migrating waves of the stomach is questionable.
4. Not suitable for drugs that may cause gastric lesions e.g. Non- steroidal anti inflammatory drugs. Drugs that are unstable in the strong acidic environment, these

systems do not offer significant advantages over the conventional dosage forms for drugs, that are absorbed throughout the gastrointestinal tract.

5. The mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.
6. In all the above systems the physical integrity of the system is very important and Primary requirement for the success of these systems

1.1.4 Factors Affecting Gastric Retention:[10]

- **Density:** GRT is a function of dosage form buoyancy that is dependent on the density.
- **Size:** Dosage form units with a diameter of more than 7.5mm are reported to have anIncreased GRT compared with those with a diameter of 9.9mm.
- **Shape of dosage form:** Tetrahedron and ring shaped devices with a flexural modulusof 48 and 22.5 kilo pounds per square inch (KSI) are reported to have betterGRT≈ 90% to 100% retention at 24 hours compared with other shapes.
- **Single or multiple unit formulation:** Multiple unit formulations show a morePredictable release profile and insignificant impairing of performance due to failure of units, allow co- administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.
- **Fed or unfed state: under fasting conditions:** GI motility is characterized by periodsof strong motor activity or the migrating myoelectric complex (MMC) that occursevery 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if thetiming of administration of the formulation coincides with that of the MMC, the GRTof the unit can be expected to be very short. However, in the fed state, MMC is delayedand GRT is considerably longer.
- **Nature of meal:** feeding of indigestible polymers or fatty acid salts can change themotility pattern of the stomach to a fed state, thus decreasing the gastric emptying rateand prolonging drug release.
- **Caloric content:** GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.

- **Frequency of feed:** the GRT can increase by over 400 minutes, when successive meals are given compared with a single meal due to the low frequency of MMC.
- **Gender:** Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.
- **Age: Elderly people, especially those over 70, have a significantly longer GRT.**
- **Posture:** GRT can vary between supine and upright ambulatory states of the patient.
- **Concomitant drug administration:** Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride.
- **Biological factors:** Diabetes and Crohn's disease.

1.1.5. DRUG CANDIDATES SUITABLE FOR GASTRORETENTIVE DRUG DELIVERY SYSTEM[12]

a. Drugs which act primarily in the stomach. E.g. antacids.

b. Drugs that are primarily absorbed from the stomach. E.g. amoxicillin

c. Drugs that are poorly soluble at alkaline pH. E.g. verapamil, diazepam, etc.

d. Drugs with a narrow window of absorption. E.g. levodopa, cyclosporine, etc.

e. Drugs which are rapidly absorbed from the GIT. E.g. tetracycline

f. Drugs that degrade in the colon. E.g. ranitidine, metformin, etc.

g. Drugs that disturb normal colonic microbes. E.g. Antibiotics against Helicobacter pylori.

1.1.6. Drug candidates unsuitable for gastroretentive drug delivery system[13]

a. Drugs that have very limited acid solubility e.g. phenytoin etc.

b. Drugs that suffer instability in the gastric environment e.g. erythromycin etc.

c. Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids etc.

1.1.7 Approaches for gastro retention[14,15,16]:

To improve the retention of an oral dosage form in the stomach various approaches have been developed, it includes floating systems and non-floating systems. Floating systems includes effervescent systems and non-effervescent systems, these systems have the bulk density lower than the gastric fluid and remain floating and releases the drug slowly in a desired rate. Non floating systems include bioadhesive systems, swelling systems, high densitysystems, expandable systems, raft forming systems, magnetic systems which utilizedifferent mechanisms to prevent the exit of drugs through pyloric sphincters.

1.2 TYPES OF GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS

The various types of gastro retentive drug delivery systems are basically classified in to two major classes based on the floating efficiency.

I. Floating systems

A. Effervescent systems

1. Volatile liquid containing systems

a. Intra gastric floating gastrointestinal drug delivery system

b.Inflatable gastrointestinal drug delivery systems

c. Intra gastric osmotically controlled drug delivery systems

2. Gas generating systems

a. floating capsules

b. floating pills

c. Floating system with ion exchange resins

B. I. Non – effervescent systems

1. Hydro dynamically balanced systems
2. Microballons/ microspheres
3. Alginate beads
4. Matrix layered tablets
5. Raft forming systems

II. Non floating systems

A. Swelling systems
B. Magnetic systems
C. Expandable systems
D. High density systems

1.2.1. FLOATING DRUG DELIVERY SYSTEMS [17]:

These are the low density systems having the bulk density less than the gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. When the drug delivery system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. This results in increased gastro retention time and a better control of fluctuations in the plasma drug concentration.

Based on the buoyancy mechanism, floating systems are classified as follows

A. Effervescent systems

B.Non effervescent systems

A. Effervescent systems[18]

These dosage forms are developed in such a way that, when they come in contact with gastric juices in the stomach , carbon dioxide gas is released due the reaction between sodium bicarbonate, citric acid and tartaric acid and is trapped in the swollen hydrocolloids. This provides buoyancy to the dosage form there by making it to float on the gastric fluids.

These systems may also contain liquids which gasify and evaporates at body temperature by which the specific gravity decreases and causes the dosage form to float.

These effervescent systems have been further classified into different types:

1) Volatile liquid containing systems[19]: These are further classified as

a) Intragastric floating gastrointestinal drug delivery systems: These systems are made to Float in the stomach because of the floating chamber, which may be filled with air or vacuum or harmless gas, and the drug reservoir is encapsulated inside a micro porous compartment. This micro porous compartment has pores on the top and bottom surfaces, whereas the peripheral walls of the reservoir compartment were completely sealed to prevent any physical contact of the undissolved drug with the walls of the stomach.

b) Inflatable gastrointestinal drug delivery system: These systems consist of inflatable chamber with liquid ether that gasifies at body temperature making the chamber to inflate in the stomach. This inflatable chamber contains a drug reservoir which is encapsulated in a gelatin capsule. After oral administration, the capsule dissolves and releases the drug reservoir together with the inflatable.

c) Intragastric osmotically controlled drug delivery system:

It consists of osmotic pressure controlled drug delivery device and an inflatable support in a biodegradable capsule. On reaching the stomach, inflatable capsule disintegrates and releases the osmotically controlled drug delivery. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. Osmotic pressure controlled drug delivery device consists of two components i.e. drug reservoir compartment and osmotically active compartment. The drug reservoir compartment is enclosed in a pressure responsive collapsible bag, which is impermeable to vapour and liquid and it contains a delivery orifice. The osmotically active compartment consists of a semi permeable membrane which encloses osmotically active salt. This device on reaching the stomach absorbs water from the gastro intestinal fluids through the semi permeable membrane into the osmotically active compartment and

dissolves the osmotically active salt and creates the osmotic pressure. The pressure developed acts on the collapsible bag which forces the drug reservoir compartment to activate the release of drug in the solution form through the delivery orifice. After the predetermined period of time the biodegradable plug in the floating support erodes and deflates the support, which is then emptied from the stomach

Gas generating systems[20]: In these systems floatability is achieved by generation of gas bubbles. Carbon dioxide is generated in situ by incorporation of carbonates or bicarbonates, which react with acid, either the natural gastric acid or co-formulated as citric or tartaric acids. The gas generated makes the systems to float on the gastric fluids and releases the drug at a predetermined rate. These are of different types

a. Floating capsules: Floating capsules are prepared by filling a mixture of sodium alginate and sodium bicarbonate, these float due to the generation of carbon dioxide which gets trapped in the hydrating gel network on exposure to an acidic environment.

b. Floating pills: These systems consist of two layers, inner effervescent layer containing sodium bicarbonate and tartaric acid and the outer swellable polymeric membrane. The inner layer is further divided into two sub layers to avoid physical contact between sodium bicarbonate and tartaric acid. When this pill is immersed in buffer solution at 37 °C, it settles down at the bottom and buffer solution enters into the effervescent layer through the outer Swellable membrane. Swollen pills or balloons are formed due the generation of carbon dioxide as a result of reaction between sodium bicarbonates and tartaric acid. The carbon dioxide generated is entrapped within the delivery system making the device to float.

These systems were found to float completely within 10 minutes and have good floating ability independent of pH, viscosity of the medium and the drug is released in a controlled manner.

c. Floating systems with ion exchange resins: These systems are formulated by using ion exchange resin that is loaded with bicarbonate by mixing the beads with sodium bicarbonate solution .These loaded beads were then surrounded by a semi permeable membrane to avoid the sudden loss of carbon dioxide. Upon coming in contact with

gastric contents there is an exchange of chloride and bicarbonate ions resulting in generation of carbon dioxide thereby carrying beads toward the top of gastric contents and producing a floating layer of resin beads, which releases the drug at a predetermined.

B .Non effervescent systems[21]: Non effervescent drug delivery systems are those which upon swallowing swells via imbibition of gastric fluids to an extent that it prevents their exit from the stomach. These systems may also be referred to as 'plug-type systems' since they have the tendency to remain lodged near the pyloric sphincter. Different types of non effervescent systems area. Hydrodynamic ally balanced systems (HBS): HBS are also called as 'colloidal barrier systems' these systems contains drug along with thegel forming hydrocolloids. When thecapsules containing the drughydrocolloid mixture comes in contact with the gastric fluids, the capsule shell dissolves and the mixture swells to form a gelatinous barrier, which imparts buoyancy in gastric fluids for a prolonged period of time due to the continuous erosion of the surface. This allows water penetration in to the inner layers maintaining surface hydration and buoyancy to the dosage form. This gel barrier controls the rate of fluid penetration into the device and consequent release of drug from the system.

1.**Microballoons / hollow microspheres[22]:** Micro balloons/ hollow microspheres are the lowdensity systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. These systems contain outer polymer shell loaded with drug. When they come in contact with gastric fluid the gel formers, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The airtrapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. These are considered as one of the most promising buoyant systems as they possess the unique advantage of multiple unit system as well as better floating properties because of central hollow space inside the microspheres.

2.Alginate beads: These are the freeze-dried calcium alginate beads of approximately 2.5 mm diameter prepared by dropping sodium alginate solution into

aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which helps in floating of

the system on the gastric contents. Due to the porous nature these can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence time of 1 hour, and these floating beads shows a prolonged residence time of more than 5.5 hours.

3.Matrix layered tablets[23]: These are the dosage forms which contain gel forming hydrocolloids which make the delivery system to float on the gastric contents. These may be single layered, bi layered and tri layered.

i. Single layered matrix tablets are obtained by intimate mixing of drug with gel forming hydrocolloids which swells in contact with gastric fluids and maintains bulk density less than gastric fluids.

ii. Bi layered tablets contain one immediate release layer and one sustained release layer. Immediate release layer releases the initial dose of drug and the sustain release layer absorbs the gastric fluids and produces the bulk density of less than that of GI fluids and remain in stomach for an extended period of time.

iii. Tri layered tablets consists of immediate release layer, sustained release layer and the gas generating layer, which helps the system to float.

4. Raft forming systems[24]: These systems contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of carbon dioxide to make the system less dense and float on the gastric fluid. The mechanism involved in the raft formation includes the formation of viscous cohesive gel on contact with gastric fluids, where in each portion of the liquid swells forming a continuous layer called as raft. This raft floats on gastric fluids and prevent the reflux of the gastric contents into esophagus by acting as a barrier between stomach and esophagus, thus these systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders.

1.2.2.Non Floating drug deliverysystems[25]:

These are the drug delivery systems which do not float but remain in the stomach for prolonged period of time. Different mechanism have been used to retain the device in the stomach which includes

A. Bioadhesive systems: The term bioadhesion is defined as adhesion of the delivery system to biological surface i.e. mucus and/or mucosal surface. Bioadhesive systems adhere to the mucosa of the stomach and remain in intimate contact with the membrane for longer period of time and hence retains in the stomach for its prolonged release. Bioadhesive polymers are used to formulate these systems.

B. Swelling system: Gastro retentivity of the dosage form can be enhanced by increasing its size above the diameter of the pylorus. Thus, thesedelivery system are formulated with swellable polymers which upon entering the stomach causes these polymers to swells to an extent the device cannot pass through the pyloric sphincter leading to the retention of the delivery device in stomach.

C.High density systems: These are the systems which have the density greater than the density of the gastric fluids as a result these systems sinks to the bottom of the stomach, thus retains in the stomach for prolonged period of time. These are usually formulated by coating the drug on heavy inert materials like zinc oxide, titanium dioxide, iron powder etc.

D. Expandable / unfolded systems[26, 27]: In these systems the size of the delivery system is increased beyond the diameter of pylorus there by the gastro retentive activity of the dosage form is achieved. Thus expandable or unfolded drug delivery systems were developed. These dosage forms are usually small enough to be swallowed. In the stomach after coming in contact with the gastric fluids, they get expanded to a larger size so that gastric retention is achieved. In these systems compressed systems are placed in the carriers such as capsules and then administered, upon contact with gastric fluid, these systems get unfolded into the forms which can retain in the stomach for longer time.

E.Magnetic systems: These are designed in such a way that the dosage form contains a small internal magnet. After the administration of the dosage for, a

small magnet is placed on the abdomen over the position of the stomach. By this technique the dosage form with an internal magnet is retained in the stomach region until the external magnet remains.

1.3.MUCOADHESIVE APPROACH FOR GASTRO RETENTION

Mucoadhesion can be defined as a state in which two components, of which one is of biological origin are held together for extended periods of time by the help of interfacial forces. Mucoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains.

ADVANTAGES

i. Improved patient compliance,
ii. Improved Drug compliance,
iii. Better control of disease condition,
iv. Better control of plasma levels,
v. Decreasing in total amount of dose administered,
vi. Short time require for disease treatment,
vii. Reducing in health care costs.

Several research groups have been reported different gastro intestinal mucoadhesive dosage forms such as microspheres, matrix tablets, discs etc[28].

1.4.TYPESOF BIO ADHESION[9]

The term bioadhesion refers to any bond formed between two biological surfaces or a bond between a biological and a synthetic surface. In case of bioadhesive drug delivery, the term bioadhesion is used to describe the adhesion between polymers, either synthetic or natural and soft tissues or the gastrointestinal mucosa. In cases where the bond is formed with the mucus the term mucoadhesion may be used synonymously with bioadhesion.

- **Type I:**Type I Bioadhesion is characterized by adhesion occurring between biological objects without involvement of artificial materials.
  Example: Cell fusion and cell aggregation

- **Type II:**Type II Bioadhesion can be represented by cell adhesion onto culture dishes or adhesion to a variety of substances including metals, woods, and other synthetic materials.
- **Type III:**Type III Bioadhesion can be described as adhesion of artificial substances to biological substrates such as adhesion of polymers to skin or other soft tissues.

1.5. MECHANISM OF MUCOADHESION

Mucoadhesion is the attachment of the drug along with a suitable carrier to the mucous membrane. Mucoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains. Mucoadhesion has the following mechanism.[29]

1. Intimate contact between a bioadhesive and a membrane (wetting or swelling Phenomenon) [30, 31]
2. Penetration of the bioadhesive into the tissue or into the surface of the mucous membrane (interpenetration)[30,31]

1.6. THEORIES OF MUCOADHESION[29]

1. Wetting Theory:

Wetting theory is predominantly applicable to liquid bioadhesive systems. It analyzes adhesive and contact behavior in terms of the ability of a liquid or paste to spread over a biological system. The work of adhesion expressed in terms of surface and interfacial tension, Y, is defined as the energy per square centimeter released when an interface is formed.

The work of adhesion is given by:

$W_a = Y_A + Y_B - Y_{AB}$

Where, A and B refer to the biological membrane and the bioadhesive formulation respectively. The work of cohesion is given by:

$W_C = 2Y_A$ or Y_B

For a bioadhesive material B spreading on a biological substrate A, the spreading coefficient is given by:

SB/A = YA – (YB + YAB)

SB/A should be positive for a bioadhesive material to adhere to a biological membrane.

2. Electronic theory:

The electronic theory depends on the assumption that the bioadhesive material and

the target biological material have different electronic surface characteristics. Based on this,

when two surfaces come in contact with each other, electron transfer occurs in an attempt to

balance the Fermi levels, resulting in the formation of a double layer of electrical charge at

the interface of the bioadhesive and the biologic surface. The bioadhesive force is believed to be present due to the attractive forces across this double layer.[32, 33]

3.Fracture Theory:

Fracture theory attempts to relate the difficulty of separation of two surfaces after adhesion. Fracture theory equivalent to adhesive strength is given by:

G = (E/L) l h

Where, E is the Young's modulus of elasticity 6 is the fracture energy, and L is the critical crack length when two surfaces are separated.

4. Adsorption theory:

This theory states that the bioadhesive bond formed between an adhesive substrate and the tissue is due to the weak van der waals forces and hydrogen bond formation. It is one of the most widely accepted theories of bioadhesion.[34,35]

1.7. POLYMERS USED IN THE MUCOADHESIVE DRUG DELIVERY SYSTEMS

A.NATURAL POLYMERS:

Examples: Na alginate, Pectin, Tragacanth, Gelatin, Carrageenan, Gum karaya, Gum ghatti

B.SYNTHETIC POLYMERS:

Examples: Polyvinyl alcohol, Polyamides, polycarbonates, Polyalkylene glycols, polyvinyl esters. Esters and halides, Polymethacrylic acid, Polymethyl methacrylic acid. Methylcellulose, Ethylcellulose, Hydroxypropyl cellulose, hydroxy propyl methylcellulose. Sodiumcarboxymethylcellulose.

C.BIODEGRADABLE POLYMERS:

Examples: Poly (lactides), Poly (glycolides), Poly (lactides-co-glycolides), Polycaprolactones. Polyalkyl cynoacrylates, Polyorthoestes, Polyphosphoesters, Polyanhydrids. Polyphosphaznes Chitosan, Polyethylene oxide.

D.BIOCOMPATIBLE POLYMERS:

Examples: Esters of hyaluronic acid. Polyvinyl acetate, Ethylene glycol

Ideal Properties of a mucoadhesive polymer[36]

- Not binding covalently with the mucus layer.
- Possess high chain flexibility.
- It must be loaded substantially by the active compound.

- ❖ Swell in the aqueous biological environment of the delivery–absorption site.
- ❖ Interact with mucus or its components for adequate adhesion.
- ❖ When swelled they allow, controlled release of the active compound.
- ❖ To be excreted unaltered or biologically degraded to inactive metabolites.

1.8. DIABETES MELLITUS

Diabetes mellitus (DM) is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. Insulin deficiency in turn leads to chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism.[37]It is one of the most common metabolic syndromes, since there are 200 million diabetic individuals in the world.

Several pathogenic processes are involved in the development of diabetes; these range from autoimmune destruction of the cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. Deficient action of insulin on target tissues and hyperglycemia are the basis of the abnormalities in carbohydrate, fat, and protein metabolism, causing diabetes 'characteristic clinical features, micro and-macro vascular complications and Increased risk of cardiovascular disease [38].

1.8.1 CLASSIFICATION OF DIABETES

The new classification system (American Diabetes Association 2004) identifies four types of diabetes mellitus:

1. TYPE 1,
2. TYPE 2,
3. GESTATIONAL DIABETES.
4. OTHER SPECIFIC TYPES

1.8.1.1. TYPE 1 DIABETES MELLITUS (INSULIN DEPENDENT DIABETES MELLITUS)

Type 1 diabetes mellitus (T1D) is characterized by β-cell destruction caused by an autoimmune process, usually leading to absolute insulin deficiency [39,40]. This form of diabetes, which accounts for only 5–10% of all diabetes, is a **juvenile-onset diabetes**; it results from a cellular-mediated autoimmune destruction of the β-cells of the pancreas by CD4 and CD8 T cells and macrophages infiltrating the islets.

In this case insulin therapy is required for survival, to prevent the development of ketoacidosis, coma and death[41].

1.8.1.2. TYPE 2 DIABETES MELLITUS (NON-INSULIN DEPENDENT DIABETES MELLITUS)

Type 2 Diabetes Mellitus (T2D) is a complex heterogeneous group of metabolic condition characterized by elevated levels of serum glucose; according to WHO, it is defined as resulting from a defect in both insulin secretion and in insulin sensitivity.β-cell dysfunction includes abnormalities in pulsatility and in kinetics of insulin secretion, quantitative and qualitative abnormalities of insulin, β-cell loss and its progression.

Type 2 Diabetes exerts a huge toll in human suffering and economy. The total number of people with diabetes is projected to rise from 171million in 2000 to 366 million in 2030, with India, China and USA being the top 3countries estimated to have the highest numbers of people with diabetes ([42,43,44]).

1.8.1.3. GESTATIONAL DIABETES. (45,46)

Gestational Diabetes (GD) mellitus refers to the onset or initial recognition of glucose intolerance during pregnancy, usually in the second or third trimester. It occurs in about4% of all pregnancies. Patients with GD have a 30% to 50%chance of developing DM, usually

Type 2 DM.

1.8.1.4. OTHER SPECIFIC TYPES [48,49]

- Genetic defects of ß-cell function
- Genetic defects in insulin secretion

- Diseases of the exocrine pancreas
- Endocrinopathies
- Drug-induced or chemical induced
- Infections (congenital rubella, cytomegalovirus and others)
- Uncommon forms of immune mediated diabetes
- Other genetic syndromes sometimes associated with
- Diabetes Gestational diabetes

1.8.2.ETIOLOGY [49]

Type 1 Diabetes

- Caused by the immune destruction of the beta cells of the pancreas.
- Antibodies to islet cells and insulin are present at diagnosis.
- Insulin secretion gradually diminishes.
- May present at any age, but most common in childhood and adolescence.
- Insulin by injection is necessary for survival.

Other factors

- Genetic
- Environmental triggers (infection or other stress)

Type 2 Diabetes

- Caused by insulin resistance in the liver and skeletal muscle, increased glucose production in the liver
- Over production of free fatty acids by fat cells and relative insulin deficiency.
- Insulin secretion decreases with gradual beta cell failure.
- Reductions in blood glucose levels often can be achieved with changes in food intake and
- Physical activity patterns. Oral medication and/or insulin injections are eventually required.

Contributing factors:

- Obesity

- Age (onset of puberty is associated with increased insulin resistance)
- Lack of physical activity
- Genetic predisposition
- Racial/ethnic background (African American, Native American, Hispanic and Asian/PacificIslander)
- Conditions associated with insulin resistance, (e.g., polycystic ovary syndrome)

1.8.3.SYMPTOMS OF DIABETES

- ❖ Polyuria
- ❖ Polydipsia
- ❖ Polyphagia
- ❖ Blurred vision
- ❖ genital itching
- ❖ slow wound healing
- ❖ weight loss

1.8.4. TREATMENT

The major components of the treatment of diabetes are:

- ✓ insulin treatment
- ✓ oral hypoglycemic therapy sa
- ✓ diet (combined with exercise if possible)

DRUGS USED IN TREATMENT[50]

There are many drugs used in the treatment of diabetes mellitus such as

- ❖ Sulfonylureas: Tolbutamide, Chlorpropamide, Gliclazide, Glipizide, and Glibenclamide.
- ❖ Bigunides: Metformine, Phenformine,
- ❖ Meglitinide analogues: Repaglinide, Nateglinide,
- ❖ α Glucosidase inhibitors: Acarbose, Miglitol and many others.

1.9. Anatomy and physiology of gastrointestinal tract.

1.9.1. **Anatomy of the gastrointestinal tract[51, 52]:**

The gastrointestinal tract categorizes into three mainparts:

a. Stomach

b. Small intestine- Duodenum, Jejunum and Ileum

c. Large intestine

The gastrointestinal tract is a long muscular tube, startingfrom the mouth and end at the anus, which capture thenutrients inside the body and eliminate waste by differentphysiological processes such as secretion, digestion,absorption and excretion. Figure 1 includes the basicconstruction of gastrointestinal tract from stomach tolarge intestine.

The stomach is a J-shaped organ which can be dividedinto four parts: cardia, fundus, body and antrum. Themain function of the stomach is to store and mix foodwith gastric secretions.

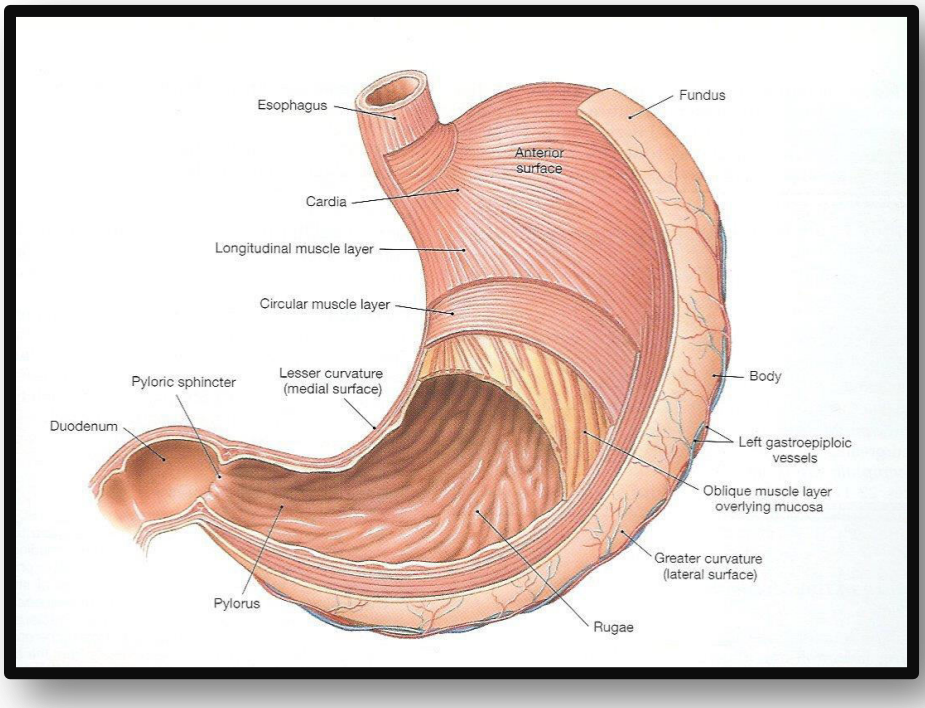


Figure no: 1.1: Anatomy of gastroretentive tract

1.9.1.1.Layers of the GI Tract

The GI tract is composed of four layers or also known as Tunics. Each layer has different tissues and functions. From the inside out they are called:

i. mucosa,
ii. submucosa,
iii. muscularis,
iv. Serosa.

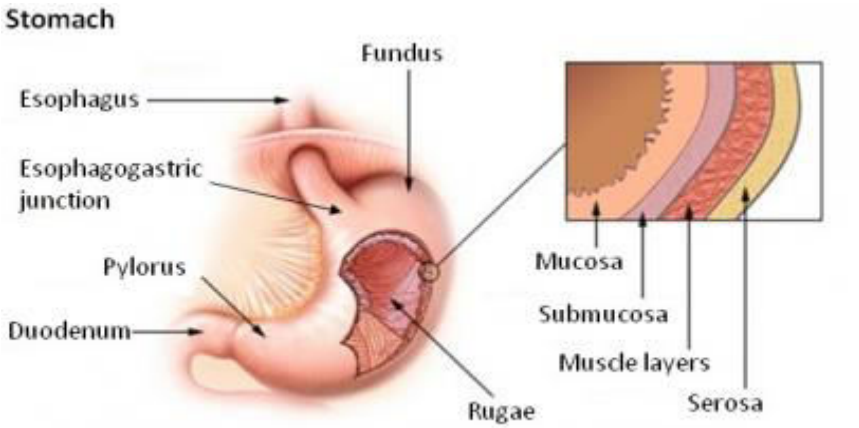
Mucosa: The mucosa is the absorptive and secretory layer. It is composed of simple epithelium cells and a thinconnective tissue. There are specialized goblet cells that secrete mucus throughout the GI tract located within themucosa. On the mucosa layer there are Villi and Micro Villi.

Submucosa: The submucosa is relatively thick, highly vascular, and serves the mucosa. The absorbed elements thatpass through the mucosa are picked up from the blood vessels of the submucosa. The submucosa also has glands andnerve plexuses.

Muscularis: The muscularis is responsible for segmental contractions and peristaltic movement in the GI tract. The Muscularis is composed of two layers of muscle: an inner circular and outer longitudinal layer of smooth muscle.These muscles cause food to move and churn with digestive enzymes down the GI tract.

Serosa: The last layer is a protective layer. It is composed of avascular connective tissue and simple squamousepithelium. It secretes lubricating serous fluid. This is the visible layer on the outside of the organs.

Fig.no. 1.2 Layers of Stomach



1.9.1.2 Physiology of gastrointestinal tract:

The stomach anatomy is mainly consists of 3 regions;fundus, body, and antrum pylorus. The proximal part ismade up of fundus and body. It serves as a reservoir forthe materials which remain undigested, whereas theantrum is the main site for mixing motions and acts as apump for gastric emptying by propelling actions. Gastricemptying occurs during both fasting as well as fed states.The pattern of motility is distinguished in 2 states. During the fasting state an interdigestive series of electricalevents takes place, which cycles through stomach and intestine every 2 to 3 hours.This is called theinterdigestive myloelectric cycle or migrating myloelectric Cycle (MMC),which is further divided into following 4phases[53].

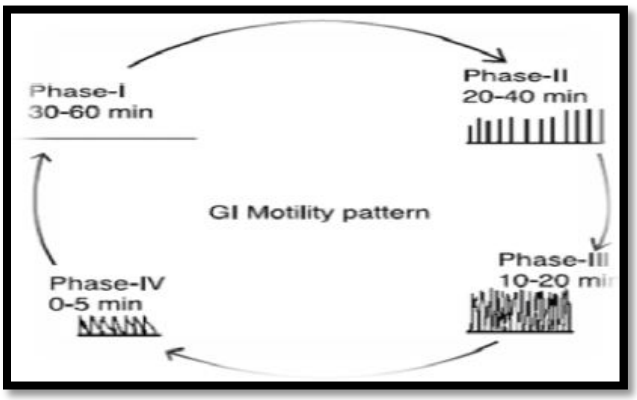


Figure no 1.3: A simplified schematic diagram of the interdigestive balanced motility pattern.

1. Phase I (basal phase) - lasts from 40 to 60 minutes with rate contractions.

2. Phase II (preburst phase) - lasts for 40 to 60 minutes with intermittent action potential

andcontractions. As the phase progresses, the intensity and frequency also increase gradually.

3. Phase III (burst phase) - lasts for 4 to 6 minutes. It includes intense and regular contraction for short period. It is due to this wave that all the undigested material is swept out the stomach down to the small intestine. It is also known as the housekeeper wave.

4. Phase IV- lasts for 0 to 5 minutes and occurs between phases III and 1 to 2 consecutive cycles.

1.9.1.3Determining Gastric Emptying Rates

γ- scintigraphy, radiology, endoscopy, ultrasonography, radio telemetry and magnetic marker monitoring studies have been applied to determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically two complications that of short gastric residence time and unpredictable gastric emptying rate[54].

Drugs that areeasily absorbed from gastrointestinal tract (GIT) and with short half-lives are eliminated quicklyfrom the systemic circulation. Repeated dosingof these drugs is required to achieve suitabletherapeutic activity. To avoid this limitation, the development of oral sustained-controlledrelease formulations is an attempt to release thedrug slowly into the gastrointestinal tract (GIT)and maintain an effective drug concentration inthe systemic circulation for a long time.

In our present researchwe have selected Gliclazide as a project drug because of its demerits when administered as a conventional dosage form. The demerits of such a dosage form are

- Frequent dosing.

- Low bioavailability of drug.

These drawbacks can be overcome by the use of gastro retentive mucoadhesive tablets. The expected advantages are like,

- Bioavailability of drug can be improved.
- It can also reduce frequent dosing.
- It can increase gastric emptying time.
- It can increase gastric retention time.

To prepare these mucoadhesive gastroretentive tablets commonly available natural polymers like chitosan, xanthan gum, gum obtained from *Moringa Oleifera*(moringa gum) were selected. The drug and the polymers are subjected to compatibility studies, evaluated for powder properties and prepared by direct compression method. The compressed tablets are evaluated for the pharmacopeia parameters and stability tests were carried out for the optimized formulations.

2. LITERATURE REVIEW

2.1. Past work done on gliclazide

- **Kumar et al (2010),** developed microsphere of gliclazide by using natural polymer. Gliclazide microspheres with a coat consisting of alginate and gum kondu gogu were prepared by orifice-ionic gelation method and emulsification gelation technique. The encapsulation efficiency was found around 86.23 % ± 0.56 to 94.46 % ± 0.86 and % drug content is in the range 55 ± 0.65 % - 68 ± 0.86 %, drug release from the microsphere was found slow, followed zero-order release kinetics with non-fickian release mechanism stating release depended on the coat: core and the method employed in preparation in microsphere[55].

- **Patil et al (2009),** developed mucoadhesive microcapsule of gliclazide. Depending upon the variability in the concentration of alginate, percentage of cross linking agent, time of curing, the factors like particle size, incorporation efficiency and release rate of microcapsules varies. The microcapsules obtained were discrete, spherical and free flowing. The microcapsules coated with mucoadhesive polymer chitosan exhibited good mucoadhesive property in the *in vitro* wash off test and also showed high percentage drug entrapment efficiency. The swelling behavior was strongly depends upon chitosan concentration. The *in vitro* release studyindicates that the swelling is the main parameter in controlling the release rate from microcapsules[56].

- **Kumar et al (2010),** developed fast dissolving tablets of gliclazide. The prepared batches of tablets were evaluated for hardness, friability, and weight variation, disintegration, wetting time, drug content and *in vitro* dissolution studies. Based on evaluating parameters, Formulation prepared by using 5% croscarmellose sodium with 3% PVP K30 was selected as optimized formulation. Finally, the optimized formulation was compared with marketed conventional formulation. Stability studies were carried out at 25ºC / 60% RH and 40ºC / 75% RH for optimized formulation for 2 months. Stability studies on the optimized formulation indicated that there was no significant change found in physical appearance, disintegration time and wetting time of the tablets[57].

➢ **Nayak et al (2010),** developed mucoadhesive beads of gliclazide. The mucoadhesive beads were characterized for entrapment efficiency, particle size, surface morphology, and swelling index. The kinetics of drug release and their mucoadhesive nature *in vitro* using goat intestinal mucosa was also investigated at various physiological pH conditions. The effective mucoadhesion property with sustained release profile was observed from optimized mucoadhesive beads consisting of alginate and ispaghula husk (1:1) and polymer (2:1) with 5–10% w/v counter ions ($CaCl_2$). These formulations showed optimum mucoadhesion behavior having more than 70% w/v of drug entrapment and particle sizes of 896.70.8 and 920.61.2 μm, respectively[58].

2.2. Past work done on mucoadhesive gastro retentivedrug delivery system:

Review of literature:

Literature review for understanding the study was done by referring the various national and international journals, published article in various official standard book and referring various websites.

➢ **Dalvadi et al (2011),** developed the mucoadhesive tablets of captopril. The matrix tablets of captopril were formulated using different mucoadhesive polymers such as the guar gum, xanthan gum, HPMC K4M and K15M in various ratios. Swelling was increased as the concentration and viscosity of HPMC increased. Tablets formulated using guar gum and xanthan gum alone were eroded faster and dissolved completely within 5-7 hr, while tablet containing HPMC remain intact and provided slow release up to 11-12 hr. The formulation containing HPMC K15M and xanthan gum (1:1) exhibited maximum bioadhesive adhesive strength and *in vitro* drug release at the end of 24 hr[59].

➢ **Sheikh et al (2011),** developed the floating-bioadhesive tablets of tramadol. Tablets of tramadol were prepared by using varying amounts of carbopol 971P and HPMC, along with other excipients. The studies indicated successful formulation of gastroretentive compressed matrices with excellent controlled release, mucoadhesion and hydrodynamic balance. Good *in vitro* dissolution profile showing formulation containing carbopol 971 P and HPMC (80:125)[60].

- **Chandira et al (2009),** developed the mucoadhesive tablets of clarithromycin. Matrix tablets of clarithromycin were formulated using different mucoadhesive polymers namely carbopol 974 P, HPMC K15M and HPMC K4M and carried out various evaluation parameter for tablet. Formulation containing carbopol 974 P and HPMC K4M (1:4) and formulation containing carbopol 974 P and HPMC K15M (1.5:3.5) showing cumulative % release were 93.16 and 96.82 respectively[61].

- **Arora et al (2011),** developed mucoadhesive tablets of domperidone. Oral controlled release mucoadhesive matrix tablets have been developed for domperidone as model drug using natural mucoadhesive material myrrh oleo gum resin. The tablets were formulated with the natural polymer in different concentration (5, 10, 15 and 20 % w/w) employing direct compression. All the evaluation parameters were done for tablets including swelling index and tensile strength. The tensile strength increase and mucoadhesive strength also increases with the increase in natural polymer concentration. This study clearly specifies the potential of myrrh oleo gum resin to be used as binder, release retardant and mucoadhesive natural material in tablet formulation[62].

- **Single et al (2010),** developed mucoadhesive tablets of ciprofloxacin. The tablets were prepared by conventional wet granulation method, using various mucoadhesive hydrophilic polymers such as HPMC, sodium CMC, sodium alginate, tragacanth and hydrophobic polymer ethyl cellulose have been used for prepared a tablets. Formulation containing HPMC and tragacanth has shown better mucoadhesive property[63].

- **Parthiban et al (2010),** developed mucoadhesive tablet of cephalexin monohydrate. The tablets were prepared by wet granulation method Carbopol 934 P as a primary polymer and HPMC K15M, HPMC K4M and HPMC K100M as secondary polymers in different proportions has been used to formulate mucoadhesive tablets. All the evaluations were carried out for tablets which are essential. Formulation containing combination of carbopol 934P and HPMC K100M shows 99.51% drug release in 24 hr. The mucoadhesive strength

was found to be 95.04 gm. So it has enough strength to adhere on the mucosa for an extended period of time[64].

- **Singh et al (2010),** developed mucoadhesive tablets of tramadol HCl by using hydrophilic polymer. Tablets were prepared by wet granulation method by using different mucoadhesive synthetic and natural polymer such as a guar gum, xanthan gum, HPMC K15M and HPMC K100M. The combination of HPMC K15M: HPMC K100M: xanthan gum (1:2:1) and HPMC K100M: xanthan gum (2:2) showed greater bioadhesive strength as compared to single gum and other hydrophilic polymer combination tablet[65].

- **Sonar et al (2007),** developed bi-layer and floating-bioadhesive tablets of rosiglitazone maleate. The sustained layer was compressed and granules of the floating layer were added to it then both layers were compressed. HPMC and sodium bicarbonate were added to the floating layer and when immersed in 0.1 N HCl. the tablet expands and rises to the surface where the drug gradually released without interference for gas bubbles. The *in vitro* drug release from the tablet was controlled by the amount of HPMC in the sustained layer. The release of rosiglitazone maleate from the tablets followed the matrix first-order release model. The concentration of HPMC significantly affects the drug release rate, buoyancy lag-time, detachment force and swelling characteristics of the tablets. The tablet was buoyant for up to 8 h the human stomach[66].

- **Deshmukh et al (2009),** developed oral controlled release theophylline anhydrous bioadhesive tablets. Tablets were prepared by direct compression method. The combination of karaya gum: guar gum (6:4) tablets showed greater bioadhesive strength as compared with a single gum and other gum combination tablets. Karaya gum: guar gum loaded tablets were not discharged from the mucus membrane and were dissolved in the gastric fluid. An increase in the gum concentration increase the drug release profile beyond 12 hr. whereas there no significant effect of gum concentration on the bioadhesive strength of the tablets[67].

- **Senthil et al (2010),** developed gastro retentive mucoadhesive tablets of theophylline by using natural gums and their combinations. Tablets were prepared by direct compression

methods and evaluation parameters were carried out. Different types of natural gums such as locust bean gum, carrageenan gum, natural polymer like chitosan, their combination and synthetic polymer carbopol were used to formulate the mucoadhesive theophylline tablets. Out of which the formulation with the combination of locust bean gum and chitosan (4.5: 3) showed greater mucoadhesive strength, good swelling and *in vitro* drug release than using single gum, other gum combinations and synthetic polymer[68].

- **Yadav et al (2011),** developed bilayer and floating-bioadhesive tablets of propranolol HCl which exhibiting a unique combination of floatation and bioadhesion to prolong residence in the stomach using propranolol hydrochloride as a model drug. The sustained layer was compressed and granules of the floating layer were added to it then both layers were compressed using a single station rotary press. The *in vitro* drug release from the tablet was controlled by the amount of HPMC in the sustained release layer. The floating ability of the tablets was studied. The release of propranolol hydrochloride from the tablets followed the matrix first order release model. The concentration of HPMC significantly affects the drug release rate, buoyancy lag-time, detachment force and swelling characteristics of the tablets. The tablet was buoyant for up to 8 hrs. This kind of tablet exhibits independent regulation of buoyancy and drug release[68].

- **Chowdary et al (2003),** developed mucoadhesive tablets ofdiltiazem. Tablets formulated employing sodium CMC and HPMC alone were slowly eroded and were dissolved completely within 4-5 hrs. When ethyl cellulose was incorporated, the tablets remained intact and provided slow release of diltiazem for over 10-12 hrs. Tablets formulated employing sodium CMC with 5% ethyl cellulose gave slow and complete release over a period of 12 hours and were found suitable for the maintenance portion of oral controlled release tablets. These tablets exhibited good mucoadhesion in the intestine for 10-12 hrs in the x-ray studies. Non-Fickian release was observed from most of the formulations[69].

- **Dias et al (2009),** developed mucoadhesive tablets for acyclovir. Tablets were prepared by direct compression and evaluated for mucoadhesive strength and *in vitro*

dissolution parameters. In all the nine formulations studied, the exponent (n) varied between 0.5266 and 0.7110 showing non-fickian release behavior corresponding to coupled diffusion or polymer relaxation, resulting in a controlled and complete drug release up to 12 hrs[70].

- **Ranga et al (2011)** developed gastro retentive floating-bioadhesive tablets of glipizide. The tablets are formulated by direct compression method. The prepared tablets exhibited satisfactory physical parameter and good *in vitro* bouncy. The modified *in vitro* assembly was used to measure the bioadhesive strength of tablets with fresh gastric mucosa of a goat as a model tissue. Bioadhesion strength was increased with increase concentration of carbopol increase. Carbopol 974 P and HPMC K15M combination could be used to design effective and stable floating and bioadhesive tablets of glipizide[71].

- **Shinde et al (2010),** developed mucoadhesive tablets of niacin using mucoadhesive polymer. The tablets were prepared using Sodium Carboxy methyl cellulose (SCMC), carbopol940P and HydroxyPropyl Methyl Cellulose (HPMC K4M) as bioadhesive polymers to impart mucoadhesion. Formulation containing sodium CMC: carbopol 940P: HPMC K4M (1:2.5:1.5) it's showing good mucoadhesive strength and *in vitro* release[72]

- **Kumar et al (2010),** developed innovative gastro retentive formulation based on mucoadhesive patches of pioglitazone. Mucoadhesive films were prepared by using the solvent casting technique, allowing a final structure with improved cohesion by mucoadhesive swelling and which releases drugs in the stomach. Ethyl cellulose used as rate controlling polymer, HPMC and Carbopol-934 were used as mucoadhesive polymers. The present work is aimed to formulate and evaluate mucoadhesive films contain Pioglitazone. The following physic-chemical studies were film thickness, Surface pH of Films, Percent Swelling, folding endurance checked and bioadhesion studies were conducted by using sheep stomach and The range was found to be between 57.33 to 80.00 gm/ cm[73].

- **D. S. Panda, et.al.,** undertaken a study to find out the potential of gum from Moringa oleifera to act as a binder and release retardant in tablet formulations. The release mechanism

was found to be Fickian. The values suggest that the nature of excipient used appeared to play a minor role in regulating the release, while the gum content was a major factor[75].

- **Dhruba Sankar Goswami (2013) et.al.,** The polymers are playing an important role in field of controlled or sustained release drug delivery system. The selected natural mucoadhesive agent from gum of Azadirachta indica and Moringa oleifera was successfully tested against their adhesive characteristic in the available physical studies like shear stress method, wihelmy's method, falling spheres method along with some synthetic polymer such as HPMC and Carbopol 934. The results were comparable to that of same synthetic polymer. The mucilage obtained from gum of Azadirachta indica and Moringa oleifera was having mucoadhesive character which may replaces the synthetic mucoadhesive polymer[76].

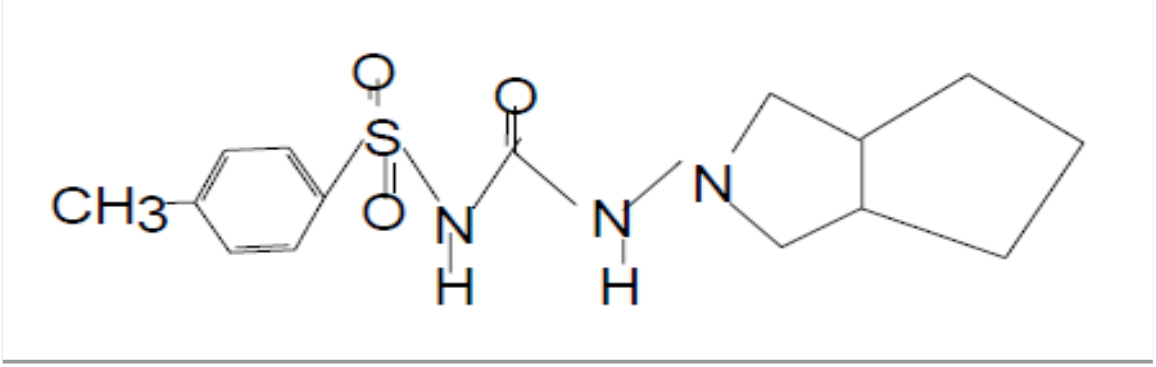
- **Dhruba Sankar Goswami (2012) et.al.,** Objective of this research was to design mucoadhesive tablets of Amoxicillin trihydrate with moringa gum as a natural mucoadhesive polymer. This drug having low biological half-life and the dosing frequency is very high. Results for in vitro drug release and wash-off studies suggest that the formulation (F1) containing Moringa gum has shown better mucoadhesive property. Other studies have shown satisfactory results in all ten formulations. Thus, the present investigation suggests that Moringa gum is suitable for preparation of mucoadhesive tablets77.

3. DRUG & EXCIPIENTS PROFILE

3.1 Drug profile:

Gliclazide[78, 79, 80]

Structure:



Empirical formula: $C_{15}H_{21}N_3O_3S$

Chemical name: N-[[(Hexahydrocyclopenta[c] pyrrol-2 (1H)-yl) amine] carbonyl]-4-methylbenzesulfonamide.

Molecular weight: 323.4

Solubility: Practically insoluble in water, slightly soluble in methanol, sparingly soluble in acetone and freely soluble in dichloromethane.

Appearance: A white or almost white powder.

Log P: 2.1

PKa: 5.8

BCS Class: II -high permeable and less soluble.

Stability: Stable under ordinary conditions.

Melting point: 179-181 ℃

Dosing: The usual initial dose is 40 to 80 mg daily, gradually increased, if necessary, up to 320 mg daily. Doses of more than 160 mg daily are given in 2 divided doses. A modified-release

Tablet is also available: the usual initial dose is 30 mg once daily, increased if necessary up to a maximum of 120 mg daily.

Storage: Itshould be stored at room temperature.

Pharmacokinetics:

Gliclazide is readily absorbed from the gastrointestinal tract. It is extensively bound to plasma proteins. The half-life is about 10 to 12 hours. Gliclazide is extensively metabolized in the liver to metabolites that have no significant hypoglycemic activity. Metabolites and a small amount of unchanged drug are excreted in the urine. Oral absorption of gliclazide is similar in patients and healthy volunteers, but there is intersubjects variation in time to reach peak plasma concentrations *(tmax). Gliclazide has low volume of distribution (13 to 24L) in both patients and healthy volunteers due to its high protein binding affinity (85 to97%). its plasma clearance is 0.78 L/h (13 ml/min).

Pharmacodynamics:

Sulfonylurea causes hypoglycemia by stimulating insulin release from pancreatic β cells. Their effects in the treatment of diabetes, however, are more complex. The acute administration of sulfonylurea to type 2 DM patients increases insulin release from the pancreas. Sulfonylurea also may further increase insulin levels by reducing hepatic clearance of the hormone. Sulfonylurea binds to the SUR1 subunits and blocks the ATP-sensitive K^+ channel. The drugs thus resemble physiological secretagogues (e.g., glucose, leucine), which also lower the conductance of this channel. Reduced K^+ conductance causes membrane depolarization and influx of Ca^{2+} through voltage-sensitive Ca^{2+} channels.

Adverse drug reaction:

Hypoglycemia: it is a commonest problem, may occasionally be severe and rarely fatal. It is more common in elderly, liver and kidney disease patients and when potentiating drug

are added.

Nonspecific side effects: nausea, vomiting, flatulence, diarrhea or constipation, headache, parentheses and weight gain.

Hypersensitivity: rashes, photosensitivity, purpura, transient's leucopenia, rarely agranulocytosis[3].

3.2 Excipient profile

3.2.1 Chitosan:

Nonproprietary Names

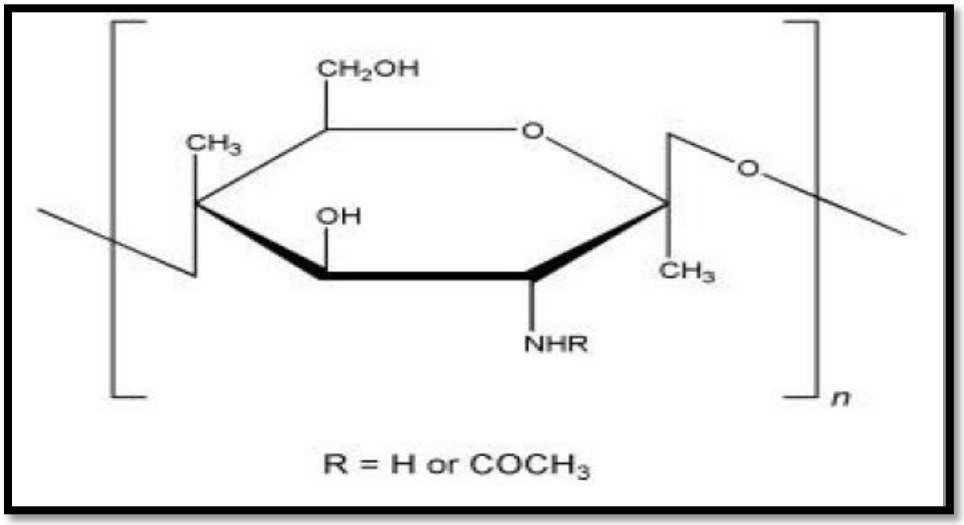
BP: Chitosan hydrochloride

PhEur: Chitosani hydrochloridum

Synonyms:

2-Amino-2-deoxy-(1,4)-ß0-D-glucopyranan; deacetylated chitin; deacetylchitin; ß0- 1,4-poly Dglucosamine; poly-D-glucosamine; poly-(1,4-ßÅ-D-glucopyranosamine).

Structural Formula:



Chemical name: Poly-b-(1,4)-2-Amino-2-deoxy-D-glucose

Molecular weight:10 000–1 000 000

Category:

Coating agent; disintegrant; film-forming agent; mucoadhesive; tablet binder; viscosity increasing agent.

Description:

Chitosan occurs as odorless, white or creamy-white powder orflakes. Fiber formation is quite common during precipitationand the chitosan may look like cotton.

Typical properties:

Acidity/alkalinity: pH = 4.0–6.0 (1% w/v aqueous solution)

Density: 1.35–1.40 g/cm^3

Glass transition temperature:203^{0}C

Moisture content: Chitosan absorbs moisture from the atmosphere.**Solubility:**

Sparingly soluble in water; practically insoluble in ethanol (95%), other organic solvents, and neutral or alkali solutions at pH above approximately 6.5. Chitosan dissolves readily in dilute and concentrated solutions of most organic acids and to some extent in mineral inorganic acids

Viscosity (dynamic):

A wide range of viscosity types is commercially available. Owing to its high molecular weight and linear, unbranched structure, chitosan is an excellent viscosity-enhancing agent in an acidic environment. It acts as a pseudo-plastic material, exhibiting a decrease in viscosity with increasing rates of shear. The viscosity of chitosan solutions increases with increasing chitosan concentration, decreasing temperature, and increasing degree of deacetylation;

Stability and Storage Conditions:

Chitosan powder is a stable material at room temperature,although it is hygroscopic after drying. Chitosan should bestored in a tightly closed container in a cool,

dry place. ThePhEur 2005 specifies that chitosan should be stored at atemperature of 2–8^{o}C.

Applications in Pharmaceutical Formulation or Technology

The suitability and performance of chitosan as a component of pharmaceutical formulations for drug delivery applications has been investigated in numerous studies. These include controlled drug delivery applications, use as a component of mucoadhesive dosage forms, rapid release dosage forms, improved peptide delivery, colonic drug delivery systems, and use for gene delivery.

3.2.2. XANTHAN GUM

Nonproprietary Names

BP: Xanthan gum

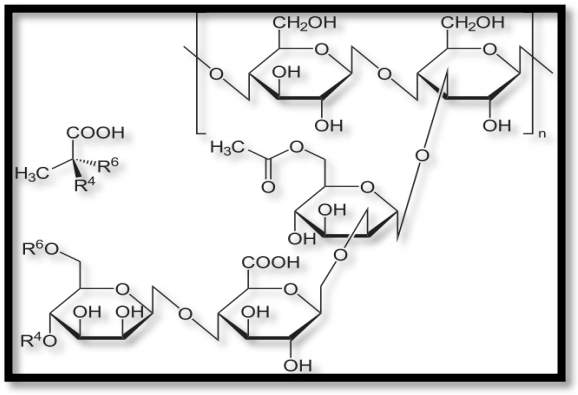
PhEur: Xanthani gummi

USPNF: Xanthan gum

Synonyms:

Corn sugar gum, Keltrol, Merezan, Polysaccharide B-1459, Rhodigel

Structure:



Empirical Formula:

It is a high molecular weight polysaccharide gum. It contains D-glucose and D-mannose as the dominant hexose unit, along with D-glucuronic acid, and is prepared as the sodium, potassium, or calcium salt.

Molecular Weight: 2×10^6

Description:

Xanthan gum occurs as a cream or white-colored, odorless, free flowing, fine powder

Functional Category:

Stabilizing agent, suspending agent, viscosity increasing agent.

Typical Properties

Acidity/alkalinity: pH = 6.0–8.0 for a 1% w/v aqueous solution.

Freezing point: 0°C for a 1% w/v aqueous solution.

Heat of combustion: 14.6 J/g (3.5 cal/g)

Melting point: chars at 270°C**.**

Solubility: Practically insoluble in ethanol and ether. Soluble in cold or warm water.

Viscosity (dynamic): 1200–1600 mPa s (1200–1600 cP) for a 1% w/v aqueous solution at 25°C.

Stability and Storage Conditions:

The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Xanthan gum is an anionic material and is not usually compatible with cationic surfactants, polymers, and preservatives since precipitation occurs. It is compatible with most synthetic and natural viscosity increasing agents.

Safety:

Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics and food products and it is generally regarded as nontoxic and nonirritant at the levels employed as pharmaceutical excipients.

Applications in Pharmaceutical Formulation:-

Xanthan gum is widely used in oral and topical formulations, cosmetics, and foods as a suspending and stabilizing agent. It has also been used to prepare sustained release matrix tablets.

Xanthan gum has been incorporated in an ophthalmic liquid dosage form, which interacts with mucin, thereby helping in the prolonged retention of the dosage form in the precorneal area.

3.2.3. MICRO CRYSTALLINE CELLULOSE

Nonproprietary Names:

BP: Microcrystalline cellulose

JP: Microcrystalline cellulose

PhEur: Cellulosum microcristallinum

USPNF: Microcrystalline cellulose

Synonyms:

Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose; Vivapur.

Chemical Name and CAS Registry Number:

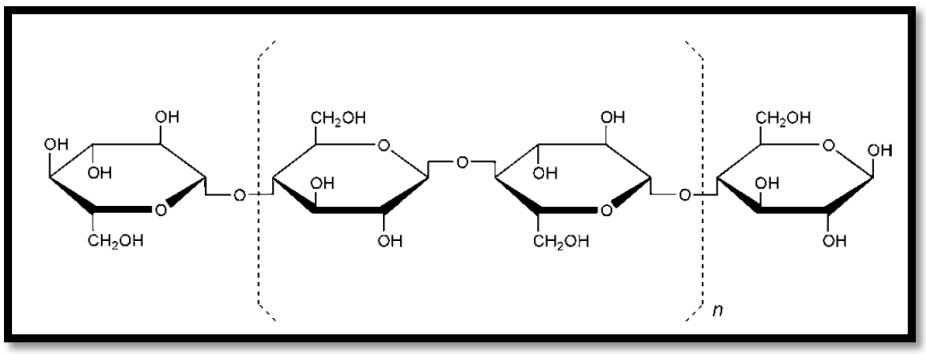
Cellulose [9004-34-6]

Empirical Formula and Molecular Weight:

$(C_6H_{10}O_5)n \approx 36\,000$

Wheren ≈ 220.

Structural Formula:



Functional Category:

Adsorbent; suspending agent; tablet and capsule diluents; tablet disintegrant.

Applications in Pharmaceutical Formulation or Technology:

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluents in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as binder/diluents, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

Uses of microcrystalline cellulose

Adsorbent 20–90%

Antiadherent 5–20%

Capsule binder/diluent 20–90%

Tablet disintegrant 5–15%

Tablet binder/diluent 20–90%

Description:

Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is

commercially available in different particle sizes and moisture grades that have different properties and applications.

Typical properties:

Density (bulk): 0.377 g/cm^3

Density (tapped): 0.478 g/cm^3

Density (true): 1.512-1.668 g/cm^3

Melting point: 260-270 ^{0}C

Moisture content:

Typically less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic.

Stability and Storage Conditions:

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Microcrystalline cellulose is incompatible with strong oxidizing agents.

3.2.4. MORINGA GUM

SOURCE : Natural gum obtained from the plant *Moringa Oleifera***.**

PH: Neutral PH 7.0±0.8

SOLUBILITY: fastly soluble in water at lower concentrations and took more time to hydrate on higher concentrations

CHEMICAL CONSTITUENTS:

L-Arabinose, D-Galactose, D-glucronic acid, L-Rhamnose,D-Mannose, D-Xylose.

USES OF MORINGA GUM:

Good binder,

Retardant,

Mucoadhesive polymer,

Disintegrant.

Stability and Storage Conditions:

Gum should store at lower humidity conditions. Protect from sun light .

Incompatibilities:

Natural moringa gum is compatible with al most all compounds. Colour change will be seen on longer duration of storage at higher temperatures.

3.2.5 TALC

Nonproprietary Names:

BP: Purified talc

JP: Talc

PhEur: Talcum

USP: Talc

Synonyms:

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc;purified French chalk; Pure talc; soapstone; steatite; Superiore.

Chemical Name: Talc

Empirical Formula and Molecular Weight:

Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si_2O_5)_4(OH)_4$. It may contain small, variable amounts of aluminum silicate and iron.

Functional Category:

Anticaking agent, glidant, tablet and capsule diluents, tablet andcapsule lubricant.

Typical Properties

Acidity/alkalinity: pH = 7–10 for a 20% w/v aqueous dispersion.

Hardness (Mohs): 1.0–1.5

Moisture content: Talc absorbs insignificant amounts of water at 258^0C and relative humidities up to about 90%.

Particle size distribution: varies with the source and grade of material. Two typical grades are 599% through a 74 mm (#200 mesh) or 599% through a 44 mm (#325 meshes).

Solubility: practically insoluble in dilute acids and alkalis, organic solvents, and water.

Specific gravity: 2.7–2.8

Specific surface area: 2.41–2.42m^2/g

Stability and Storage Conditions:

Talc is a stable material and may be sterilized by heating at 160^oC for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Incompatible with quaternary ammonium compounds.

Applications in Pharmaceutical Formulation or Technology:

Talc was once widely used in oral solid dosage formulations as a lubricant and diluents, although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled-release products. Talc is also used as a lubricant in tablet formulations in a novel powder coating for extended-release pellets and as an adsorbent.In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves.

3.2.6. MAGNESIUM STEARATE:

Nonproprietary Names:

BP: Magnesium stearate

JP: Magnesium stearate

PhEur: Magnesii stearas

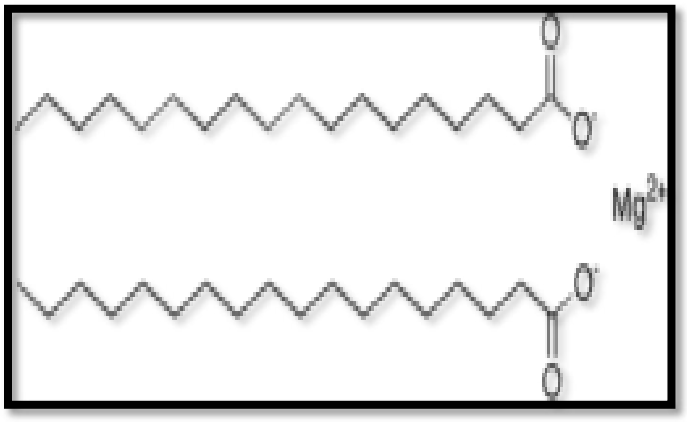
USPNF: Magnesium stearate

Synonyms:

Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.

Chemical Name: Octadecanoic acid magnesium salt

Structure:-



Empirical Formula and Molecular Weight:

$C_{36}H_{70}MgO_4$ 591.34

Structural Formula:

$[CH_3 (CH_2)_{16}COO]^2$

Functional Category: Tablet and capsule lubricant.

Typical Properties

Crystalline forms: high-purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate.

Density (bulk): 0.159 g/cm^3

Density (tapped): 0.286 g/cm^3

Density (true): 1.092 g/cm^3

Flash point: 250^{o}C

Flow ability: poorly flowing, cohesive powder.

Melting range: 117–150^{0}C (commercial samples);

126–130^{0}C (high purity magnesium stearate).

Solubility: practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Stability and Storage Conditions:

Magnesium stearate is stable and should be stored in a well closed container in a cool, dry place.

Incompatibilities:

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

4. OBJECTIVES

The main objectives of present study are as below-

1. To carryout preformulation studies for possible drug and polymer interactions by infrared studies.
2. To formulate mucoadhesive tablets by using natural polymers like Chitosan, Xanthan gum, and Moringa gum
3. To develop gastroretentive dosage form for prolong period of time for continuous release of drug in the stomach.
4. Evaluation of prepared mucoadhesive tablets for their physical and chemical characteristics.
5. To carry out Stability studies for optimized formulations as per ICH guidelines.
6. To maximize bioavailability of the drug and increased patient compliance.

EXPECTED RESULTS

1. Tablets prepared should have good satisfactory physico-chemical properties.

2. Tablet remains for 24 hours in GIT and releases the drug in controlled manner.

3. Prepared tablets should be stable throughout their shelf-life.

5. PLAN OF WORK

- To carry out literature survey.
- To carry out selection of suitable drug and polymer.
- To carry out preformulation studies of the drug and polymer for the characterization.
- To prepare mucoadhesive gastro retentive tablets by using different available natural polymers.
- To carry out pre-compression parameter of powders.
- To carry out Evaluation of mucoadhesive tablets.
    - Physical texture.
    - Thickness.
    - Hardness.
    - Weight variation.
    - % Friability.
    - % Drug content.
    - *In vitro* drug release study.
    - *in vitro* mucoadhesive strength.
    - swelling study.
- To carry out stability study for optimized formulation.

6. MATERIALS & METHODS

The following materials that were either AR/LR grade or the best possible Pharma grade available were used as supplied by the manufacture.

Table 6.1: List of chemicals with grade and suppliers

Drug:

S.No.	Drug	Grade	suppliers
1.	Gliclazide	AR	Madras Pharmaceuticals

Polymers:

S.No.	Polymers	Grade	Suppliers
1.	Chitosan	LR	Yarrow chem
2.	Xanthan gum	LR	Himedia lab. Pvt.ltd
3.	Moringa Gum	-	Prepared In Lab.

Other excipients:

S.No.	Materials	Grade	Suppliers
1	Micro crystalline cellulose	LR	yarrowchem
2	Magnesium stearate	LR	Loba Chem.
3	Talc	LR	Loba Chem.
4	Hydrochloric acid	LR	Loba chem.

Table 6.2: List of instruments used.

S.NO	Equipment	Manufacture
1	Electronic Balance	Contech, Navi Mumbai
2	Tablet compression machine	Shakti Engeenering ltd. Ahmedabad
3	UV-Vis spectrophotometer	UV-1800, Shimadzu Corporation, Japan

4	FTIR spectro photometer	Shimadzu 00518, Japan.
5	Tablet dissolution tester USP XXIII	Electrolab dissolution tester TDT- 08L, Mumbai
6	Friability test apparatus	EF-2 Friabilator, Electrolab, Mumbai.
7	Hot air Oven	Servewell Instruments and Equipments Pvt. Ltd., Bangalore.
8	Tap density tester	Electrolab ETD-1020, Bombay
9	Digital melting point apparatus	Servewell Instruments and Equipments Pvt. Ltd., Bangalore
10	Hardness tester	Monsanto
11	Digital pH meter	Servewell Instruments and Equipments Pvt. Ltd., Bangalore
12	Magnetic stirrer	Servewell instrument pvt.ltd
13	Stability chamber	Remi elektrotechnik Ltd, Vasai.
14	Screw gauze	Mitu toyo
15	Sieves	Jayant test sieves, mumbai
16	Desiccators	Tarsons vacuum desiccator, Kolkata

6. METHODOLOGY

6.1 Preformulation studies:

A comprehensive preformulation study helps in characterizing the physico-chemical properties of the drug molecule. It provides the foundation for development of a robust dosage form that can sustain the rigors of processing and shelf life. Efforts spent on preformulation provide cost savings in the long run, by reducing challenges during formulation development.

GOALS OF PREFORMULATION

1. Too establish the physico chemical parameter of new drug substances
2. To establish the kinetic rate profile
3. To establish physical characteristics
4. To establish compatibility with the common excipients.

6.1.1. DETERMINATION OF MELTING POINT

Melting point of drug sample was determined by taking small quantity of drug in a capillary tube sealed at one end and was placed in digital melting point apparatus and temperature range at which the drug melts was noted.

6.1.2. Determination of λmax:

Preparation of 1.2 pH buffer:

8.5ml of conc. HCl was taken in 1000mL of volumetric flask and final volume was made up to 1000mL with distilled water to get 0.1N HCl.

Most drugs absorbs light UV wavelength (200-400nm), since generally they aromatic contain double bond. The solution containing 20µg/mL of gliclazide was prepared and scanned over the range of 200-400nm against pH 1.2 buffer as blank using double beam UV spectrophotometer. The maximum wave length obtained in the graph was considered as λmax for the pure drug.

6.1.3. Preparation of calibration curve in 0.1N HCl:

• Standard solution:

Accurately weighed 100 mg of gliclazide was dissolved in 10 mL of methanol and the final volume was made up to100 mL with 1.2 pH buffer, to get a solution containing 1000 µg/Ml

• **Stock solution:**

From the standard solution, a stock solution was prepared to give a concentration of 20 µg/mL in 1.2 pH buffer. Aliquots of 2, 4, 6, 8 and 10 mL of stock solution were pipette out into 10 mL volumetric flasks. The volume was made up to the mark with pH 1.2 buffer. These dilutions give 4, 8, 12, 16 and 20 µg/mL concentration of gliclazide respectively. The absorbance was measured at 229 nm using UV spectrophotometer.

6.1.4. Compatibility studies of gliclazide and polymers:

- **FTIR studies:**

FTIR spectra help to confirm the identity of drug and to detect the interaction of the drug with the carriers. IR spectroscopy of pure drug and physical mixture of drug with polymers was carried out using FTIR to check the compatibility between drug and polymers. The IR spectra of drug with polymers were compared with the standard IR spectrum of the pure drug.

Dose calculation for mucoadhesive tablet of gliclazide for 24 hrs[81]

Initial dose (D.I) = 30 mg[81]

- **First order elimination rate constant = K_E**

$K_E = 0.693 / t_{1/2}$

$= 0.693/10$

$= 0.0693$

- **Zero order calculation:**

Desired release rate from maintenance dose= Ko

$Ko = D.I \times K_E$

$= 30 \times 0.0693$

$= 2.079 mg$

- **Calculation of maintenance Dose=Dm**

$Dm = Ko \times (T - t_{½})$

$= 2.079 \times (24-10)$

$= 2.079 \times 14$

$= 29.10 mg$

- **Corrected Initial dose = C.D.I**

C.D.I =D.I- (Ko ×t_{max})

=30 - (2.079×10)

=30 - 20.27

=09.21mg

- **Total dose** =Dm+ C.D.I

=29.10+09.21

=38.31mg

For ease in calculation, it is rounded off as **40 mg**

6.2. Method of formulation

In the present investigation, an accurately weighed quantity of Gliclazide and the subjected polymers, remaining excipients were added together in mortar& pestle and triturated. Tablets were prepared by Direct Compression Method.

Table 6.3: Preliminary Formulation

Ingredients	PF1	PF2	PF3
GLZ	40	40	40
Chitosan	100	-	-
Xanthan gum	-	100	-
Moringa gum	-	-	100
MCC	50	50	50
Magnesium stearate	5	5	5
Talc	5	5	5
Total (mg)	200	200	200

*All quantities in mg/tablet

- **Screening of polymers and excipients:**

  Preliminary formulations were designed by different natural polymer for screening of mucoadhesive system. Based on the results obtained, further experiments were designed using various natural polymers to develop optimized formula.

Table 6.4: formulation of mucoadhesive tablets of gliclazide

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
GLZ	40	40	40	40	40	40	40	40	40	40
Chitosan	30	-	40	-	50	-	60	-	30	40
Xanthan gum	-	30	-	40	-	50	-	60	40	30
Moringa gum	70	70	60	60	50	50	40	40	30	30
MCC	70	70	60	60	50	50	40	40	30	30
Magnesium stearate	5	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5	5
Total (mg)	200	200	200	200	200	200	200	200	200	200

*All quantities in mg/tablet

6.3. Evaluation parameters:

6.3.1 Precompressional parameters[82]:

1) Bulk density

2) Tapped density

3) Angle of repose

4) Hasusner's ratio

5) Carr's consolidation index

1) Bulk density:

It is the ratio of total mass of powder to the bulk volume of powder. Accurately weighed batch (F1 –F10) powder was placed in 10 mL graduated measuring cylinder. Initial volume was observed. The $D_b$andwas calculated in gm/ mL using following formulae,

$$D_b = M/V_b \quad \text{..... (1)}$$

Where, D_b = Bulk density

M = Mass of the powder

V_b = Bulk volume of powder

2) Tapped density:

Accurately weighed batch (F1 –F10) powder was placed in 10 mL graduated measuring cylinder.The cylinder was tapped initially 100 times from a distance of 14 $\pm$ 2 mm. The tapped volume was measured to the nearest graduated unit. Again the tap volume was measured to the nearest graduated unit. The $D_t$were calculated in g/ mL using following formulae,

$$D_t = M/V_t \quad \text{..... (2)}$$

Where, D_t = Tapped density

V_t = Tapped volume of the powder

D_t = Tapped density

M = mass of the powder

3) Angle of repose:

Good flow properties are critical for the development of any pharmaceutical tablets, capsule or powder formulations. Angle of repose is defined as the maximum angle possible between the surface of the pie of powder and horizontal plane. It is performed to determine the flow property of powder done by the funnel method. The powder mass was allowed to flow through the funnel orifice, kept vertically to a plane paper kept on horizontal surface, giving a heap angle of powder on a paper. The diameter of the powder cone was measured and angle of repose was calculated using the following equation

$\tan\theta = h/r$ ……..(3)

Where, h and r are the height and radius of the powder cone, respectively. Flow properties for different values of angle of repose were given below

Table 6.5: Comparison between Angle of Repose and Flow Property

Angle of Repose	Flow
< 25	Excellent
25 – 30	Good
30 – 40	Moderate (addition of 0.2% glidant required)
> 40	Poor

4) Hasusner's ratio:

Hasusner's ratio carried out by tapped density divided bulk density.

$$\text{Hasusner's ratio} = \frac{Tapped\ density}{Bulk\ density}$$

Table no 6.6 Hausner's ratio

Hausner's ratio	Types of Flow
Less than 1.25	Good flow
1.25- 1.5	Moderate
More than 1.5	Poor flow

5) Carr's consolidation index:

Carr developed an indirect method of measuring powder flow from bulk densities. The % compressibility of the powder was direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated using the given formula.

Carr's index (%) = $[(D_t - D_b) \times 100]/D_t$ …….. (4)

Table 6.7: flow property related to Carr's index.

CARR'S INDEX	TYPE OF FLOW
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

6.3.2. Post compression parameters[83]:

1) Appearance:

The tablets were checked for presence of cracks, pinholes etc. There should be uniformity in the color and the dimensions of the tablets.

2) Hardness:

This test is used to check the hardness of the tablet, which may undergo chipping or breakage during storage, transportation, and handling. In this, three tablets were selected randomly and the hardness of each tablet was measured with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm^2.

3) Thickness:

Thickness of tablet was important for uniformity of the tablet size. In this three tablets were selected randomly and the hardness of each tablet was measured with using screw gauze.

4) Friability test:

Friability test was carried out to evaluate the hardness and stability instantly. In roche friabilator, 10 tablets were weighed (W_0) initially and put in a tumbling and rotating apparatus drum. Then they were subjected for completion of 4 min or 100 rpm, the tablets were again weighed. The % loss in weight or friability (F) was calculated by the formula given below.

$$\% friability = \frac{weight_{initial-} weight_{final}}{weight_{initial}} \times 100 \text{.....(5)}$$

5) Weight variation:

This test was performed to maintain the uniformity of weight of each tablet, which should be in the prescribed range. This was done by weighing 10 tablets at random and average weight was calculated. Not more than two of individual weight deviates from the average weight. The weight data from the tablets were analyzed for sample mean and percent deviation.

$$PD = \frac{W_{avg} - W_{ind}}{W_{avg}} \times 100$$

Where, PD = percentage deviation

W_{avg} = average weight of tablets

W_{ind} = individual weight of tablets

Table 4.8: percentage deviation allowed under weight variation test

Average weight of tablets	Percentage deviation
130 or less	10
130-324	7.5
More than 324	5

6) Uniformity of drug content[84]:

The content uniformity was mandatory for tablets. This test was performed by taking five tablets were selected randomly, weighed and powdered. A tablet triturate equivalent to 40 mg of drug weighed accurately, dissolved in 10 mL methanol then final volume made up to 100 mL by using pH 1.2 buffer. Further dilutions were done suitably and absorbance was measured at 229nm using UV spectrophotometer.

7) Swelling index[85]:

The swelling of tablet involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle results to saturation of capillary spaces within the particles. The liquid enters the particles through pores and bind to large molecule breaking the hydrogen bond and resolution in the swelling of particle. One tablet from each batch was

weighed and placed in a Petri plate containing 25 mL of pH 1.2 buffer solution. After each 2 hrs interval the tablet was removed from plate, removes excess of buffer by using filter paper and weighed again up to 24 hrs. The swelling index was calculated using following formula.

$$\textbf{Swelling index } (\mathbf{S.I}) = \frac{\mathbf{W_t - W_o}}{\mathbf{W_o}} \times \mathbf{100}$$

Where, Wt = Weight of tablet at time t

Wo = Weight of tablet before placing in the Petri plate.

8) *In vitro*dissolution studies[85]:

Dissolution tests were performed in USP dissolution eight dissolution apparatus II (paddles) at 37±0.5°C. The baskets were rotated at a speed of50 rpm. The test was performed in 37±0.5°C with a rotation speed of 50 rpm using 900 mL of 0.1 N HCl, pH 1.2, as a dissolution medium. According to the sampling plan, samples of 5 mL were withdrawn till 24 hrs and immediately replaced with an equal volume of the respective dissolution medium maintained at 37±0.5°C. Test samples were filtered through Whatman filter paper for Gliclazide at 229 nm using a blank solution as reference with a UV-VIS double-beam spectrophotometer

9) Release kinetics:

The results of *in vitro* release profiles obtained for all the HBS formulations were fitted into four models of data treatment as follows:

1. Cumulative percent drug released versus time (zero-order kinetic model).
2. Log cumulative percent drug remaining versus time. (First-order kinetic model).
3. Cumulative percent drug released versus square root of time. (Higuchi's model).
4. Log cumulative percent drug released versus log time (Korsmeyer-Peppas equation).

1) Zero Order Kinetics: A zero-order release would be predicted by the following equation.

$$\mathbf{A_t = A_0 - K_0 t} \quad \text{..... (6)}$$

Where,

A_t = Drug release at time't'

A_0 = Initial drug concentration

K_0 = Zero-order rate constant (hr^{-1}).

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to K_0[86].

2.First Order Kinetics: A first-order release would be predicted by the following equation

$$\textbf{Log C = Log C}_0 \textbf{ – 303.2Kt} \text{……..(7)}$$

Where,

C = Amount of drug remained at time‘t’

C_0 = Initial amount of drug

K = First-order rate constant ($hr.^{-1}$).

When the data is plotted as log cumulative percent drug remaining versus time, yields a straight line, indicating that the release follows First-order kinetics. The constant ‘K’ can be obtained by multiplying 2.303 with slope values[86].

3. Higuchi’s Model:

Drug released from the matrix devices by diffusion has been described by following Higuchi’s classical diffusion equation.

$$Q = \left(\frac{D\epsilon(2A - \epsilon Cs) Cst}{\tau} \right)^{1/2} \text{…….. (8)}$$

Where,

Q = Amount of drug released at time‘t’

D = Diffusion coefficient of the drug in the matrix

A = Total amount of drug in unit volume of matrix

C_S = The solubility of the drug in the diffusion medium

ε = Porosity of the matrix

τ = Tortuosity

t = Time (hrs) at which ‘Q’ amount of drug is released.

Equation-8 may be simplified if one assumes that D, C_S and A are constant.

Then equation-8 becomes:

$$Q = Kt^{½} \text{ ..... (9)}$$

When the data is plotted according to equation-4 i.e., cumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism[87].The slope is equal to 'K'.

4. Korsmeyer and Peppas Model:

The release rates from controlled release polymeric matrices can be described by the equation (10) proposed by korsmeyer et al[88].

$$Q = K_1 t^n \text{ ..... (10)}$$

Q is the percentage of drug released at time't', K is a kinetic constant incorporating structural and geometric characteristics of the tablets and 'n' is the diffusional exponent indicative of the release mechanism.

For Fickian release, n=0.45 while for anomalous (Non-Fickian) transport, n ranges between 0.45 and 0.89 and for zero order release, n = 0.89

10) *In vitro* mucoadhesive strength[85]:

Mucoadhesion strength of the tablet was measured by using sheep stomach mucosa as model mucosal membrane. Fresh sheep stomach mucosa was obtained from a local slaughter house and was used within 2-3 h of slaughtering. The mucosal membrane was washed with distilled water and then with pH 1.2.

The mucoadhesive strength measurement apparatus was fabricated locally as shown in to the Figure no 4.1. The mucoadhesive strength of the tablets was determined using this locally fabricated apparatus. The weight at which the tablet was detached was recorded. The mean value of three trials was taken for each set of formulations. After each measurement, the tissue was gently and thoroughly washed with phosphate buffer and left for 5 minutes before placing a new tablet to get appropriate results for the formulation.

11) Stability studies:

Stability of a dosage form has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specification.

The purpose of stability studies is to provide evidence that the quality of drug substance or drug product varies with time under the influence of a verity of environmental factors such as temperature, humidity and light enables recommended storage conditions, re-testing periods and shelf-lives to be established.

Accelerated stability study was carried out as per the ICH guidelines.

Selected formulations were subjected to determine its shelf life i.e. stability study by using accelerated stability chamber, according to the WHO guidelines. The tablets were stored in the stability chamber under temperature 40 ± 2^0C and 75 ± 5 % RH (relative humidity) for 90 days. After the specified period the tablets are subjected to physical appearance, drug content and dissolution study.

7. RESULTS AND DISCUSSION

7.1. PREFORMULATION STUDIES

7.1.1. Melting point determination

Melting point of Gliclazide was obtained in the range of 177-179 ^{0}C.

The standard melting point value of gliclazide is 179 ^{0}C.

7.1.2. Drug-polymer interaction studies by FT-IR

Fourier-transform infrared (FT-IR) spectra were obtained by using an FT-IR Spectrometer-SHIMADZU. The Dug sample gliclazide alone and with the subjected polymers were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 2 min in a hydraulic press.

Table No. 7.1. IR SPECTRUM OF GLICLAZIDE

Groups	**Peaks (cm^{-1})**
N-H (amine group)	3413.15
C=O stretching	1709.15
C=C aromatic ring	1473
C-H	1432
O=S=O (sulphoxide group)	1164.08
C-H stretching	1086.92
C-S stretching	6668.36

7.1.3. Drug - polymer compatibility studies:

Under the pre formulation studies the drug was studied for the Compatibility studies. Pure drug gliclazide with selected polymers were carried out prior to the formulation of tablets. IR spectra of pure drug and polymers were taken. All the characteristic peaks of gliclazide were present in spectra at respective wavelengths. Thus, indicating compatibility

between drug and polymers. It shows that there was no significant change in the chemical integrity of the drug. The FT IR spectrum of the drug and polymers were recorded in figure no.7.1, 7.2, and 7.3.

7.1.4.Standard Plot of Gliclazide

The λ_{max} of gliclazide was determined in pH 1.2 buffer which was scanned between 200 – 400 nm in the UV spectrophotometer. It was found to be 229 nm.The absorbance reading of gliclazide standard solution containing 2-20 µg/mL (Beers range) of drug in pH 1.2 buffers at the maximum wavelength of 229 nm. The calibration curve for Gliclazide with slope, intercept, regression coefficient and molar absorptivity were determined. The calculations of drug content and *in vitro* drug release study are based on this standard calibration curve.

Fig.no. 7.4. Scanning Of Gliclazide

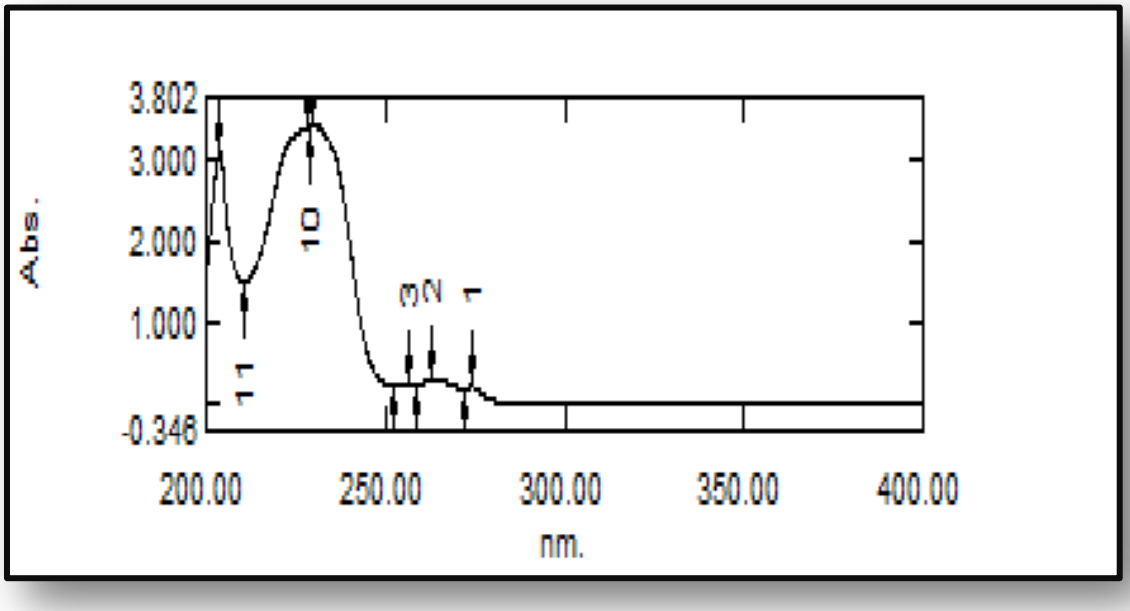
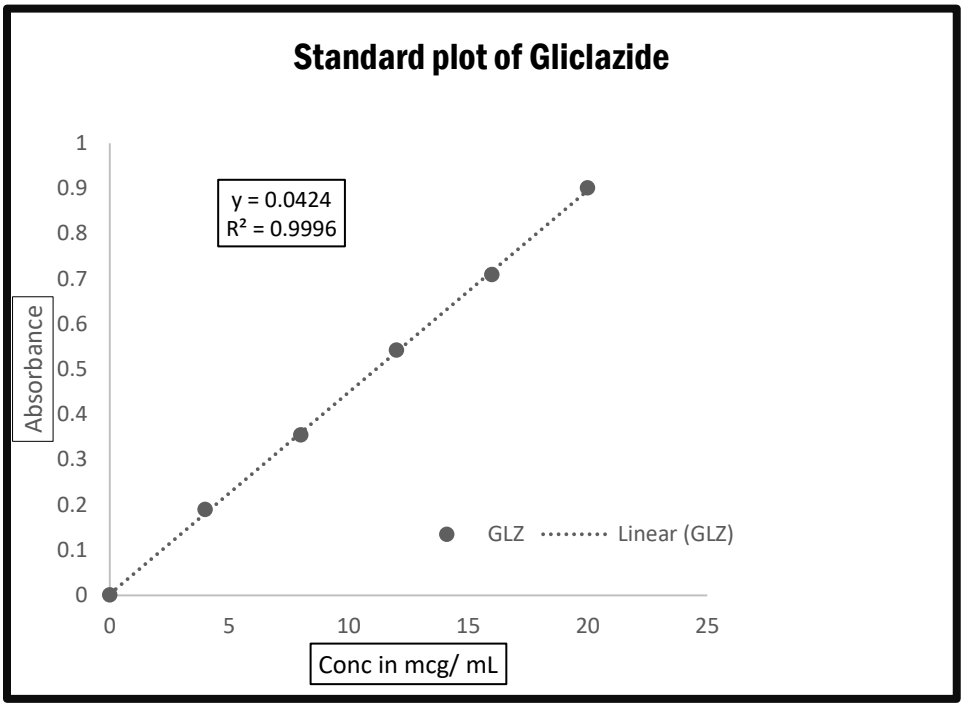


Table no. 7.2: Calibration data of gliclazide in pH 1.2 buffer

S.No	Concentration (µg/ml)	Avg. absorbance at 229 nm	Standard deviation(SD)	Molar absorptivity L/mol.cm
1	4	0.189	0.021	15280
2	8	0.354	0.191	14755
3	12	0.542	0.006	14606
4	16	0.709	0.011	14573
5	20	0.901	0.017	14569

Figure no 7.5: Calibration curve of Gliclazide in pH 1.2 buffer



7.2. Evaluation of powder properties

7.2.1. Bulk density and Tapped density:

The loose bulk density (LBD) and Tapped bulk density (TBD) of the powders of different formulations were evaluated before the compression of powders in to tablets. The bulk

density and the tapped density for all the formulations varied from 0.4284±0.005 to 0.4679±0.003 gm/cm^3 and 0.4763±0.011 to 0.5361±0.0105gm/cm^3 respectively.

The values obtained lies within the acceptable range. The difference exists between the bulk density and tapped density found to be very few. This result helps in calculating the % compressibility of the powder.

Table No.7.3.bulk density and tapped density of the powder formulation

S.No of Formulation	Bulk Density	Tapped Density
PF1	0.4432±0.049	0.5124±0.006
PF2	0.4431±0.049	0.5124±0.006
PF3	0.4679±0.003	0.5361±0.005
F1	0.4477±0.005	0.5357±0.008
F2	0.4580±0.006	0.5357±0.008
F3	0.4284±0.005	0.4918±0.007
F4	0.4511±0.005	0.5218±0.077
F5	0.4313±0.005	0.4839±0.006
F6	0.4285±0.005	0.4979±0.006
F7	0.4651±0.006	0.5313±0.007
F8	0.4285±0.005	0.4763±0.011
F9	0.4361±0.005	0.4840±0.013
F10	0.4477±0.005	0.5173±0.007

7.2.2. Angle of repose (θ):

The angle of repose data for all the formulations ranges from $18^0.92'$±0.313 to $25^0.37'$±0.171.The data were tabulated in the table no 7.4.Angle of repose of all the formulations were found to be less than 30^o, which indicates a good flow property of the powders.

Table No.7.4. Angle Repose of the Powder Formulation

S.NO OFFORMULATION	ANGLE OFREPOSE (θ)
PF1	19^0.98'±0.335
PF2	18^0.92'±0.313
PF3	25^0.37'±0.171
F1	24˚.47±0.013
F2	23˚.98±0.149
F3	22˚.83±0.396
F4	22˚.53±0.334
F5	21^0.69±0.439
F6	21^0.31±0.234
F7	20^0.43±0.135
F8	20˚.93±0.313
F9	20˚.13±0.191
F10	19˚.89±0.147

7.2.3. Hausner's ratio:

The result of Hausner's ratio of all formulations ranges from 1.1098±0.027to 1.1965±0.017. Results of Hausner's ratio of all formulations were shown in Table no 7.5 which indicates that the flow ability of all the formulation.

S.NO OF FORMULATION	HAUSNER'S RATIO
PF1	1.1561±0.003
PF2	1.1956±0.002
PF3	1.145±0.003
F1	1.1965±0.017
F2	1.1696±0.016
F3	1.1479±0.002
F4	1.1567±0.002
F5	1.1219±0.025
F6	1.1619±0.017
F7	1.1423±0.032
F8	1.1115±0.030
F9	1.1098±0.027
F10	1.1554±0.002

Table No.7.5. Hausner's Ratio of the Powder Formulation

7.2.4. Carr's consolidation index:

The results of the Carr's consolidation index of all the formulations ranges from 09.80 % to 16.42 %. Results of Carr's consolidation index of all the formulations were shown in the Table no 7.6. Results clearly showed that the flow ability of all the formulations was good and also the powder had good compressibility.

Table No.7.6. Carr's Consolidation Index of the Powder Formulation

S.NO OF FORMULATION	CARR'S CONSOLIDATION INDEX
PF1	15.39
PF2	15.41
PF3	14.95
F1	16.42
F2	14.50
F3	12.89
F4	13.54
F5	10.87
F6	13.93
F7	12.46
F8	10.03
F9	09.80
F10	13.45

7.3. Post compression parameters:

The formulated tablets were subjected for post- compressional evaluation such as

1. Shape of tablets.
2. Friability.
3. Hardness.
4. Weight variation.
5. Thickness.
6. Uniformity of drug content.
7. *In vitro* dissolution.
8. *In vitro* mucoadhesive strength.
9. *In vitro* swelling study
10. Stability Studies

7.3.1. Shape of the tablets:

Visually inspection of prepared all tablets were done. The shapes of the tablets were found to be good.

7.3.2. Friability (F)

Friability determines the strength of the tablets. The values of friability test were given in the Table no 7.7. The friability for all the formulations was below 1% indicating that the friability was within the prescribed limits. The results of friability test indicates that the tablet possesses good mechanical strength. The friability value ranges from 0.67 to 0.92

7.3.3. Hardness:

The mean hardness values were measured for all the formulation using Monsanto hardness tester. The results were tabulated in Table no 7.7. The hardness value ranges from 4.97± 0.032 to 6.93± 0.133 kg/cm^2.

7.3.4. Weight variation:

Twenty tablets were randomly selected from each formulation and evaluated. The average weight of each formulation was recorded and is shown in Table no 7.7. The obtained data were almost uniform. The values of tablets ranging from 197.9± 1.786 to 199.8± 1.259 mg. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeia's limits of ±7.5% of the weight.

Formulation Code	Friability (%)	Hardness (kg/cm2)	Weight Variation(mg) (n=20)
PF1	0.83	5.04± 0.051	198.4± 1.471
PF2	0.74	4.97± 0.032	198.7± 1.364
PF3	0.79	6.93± 0.133	199.4± 1.658
F1	0.88	6.42± 0.0421	199.5± 1.865
F2	0.83	6.23± 0.121	198.6± 1.371
F3	0.87	6.29± 0.121	198.9± 1.452
F4	0.77	5.99± 0.111	199± 2.258
F5	0.88	5.85± 0.113	198.9± 1.492
F6	0.68	5.54± 0.119	198.7± 1.531
F7	0.87	5.35± 0.046	197.9± 1.786
F8	0.92	5.23± 0.075	199.3± 1.942
F9	0.67	5.14± 0.924	198.6± 1.545
F10	0.73	5.03± 0.0421	199.8± 1.259

Table no 7.7: Postcompressional parameters of gum formulations

7.3.5. Thickness

The thickness of the tablets was reported in the micrometer (mm).The thickness of tablet indicates that, die fill was uniform. The thickness depends on the size of the punches (8 mm) and the weight of one tablet (200 mg). The average weight of each formulation was recorded in shown in Table no 7.8. The value of thickness ranges between 2.839± 0.026 to 3.129± 0.043 mm.

7.3.6. Uniformity of drug content

The % drug content of all the formulated tablets were found within the limit. % drug content value of gliclazide was within 94.89± 0.886% to 97.89± 1.009%.The results within the range indicate uniform of mixing. The Table no 7.8 shows the % drug content in each formulation.

Table no 7.8: Postcompressional parameters of gum formulations

Formulation Code	Thickness (mm) (n=3) Mean±S.D	Drug Content (%) (n=3) Mean±S.D
PF1	2.899± 0.083	94.89± 0.886
PF2	2.879± 0.046	97.78± 0.572
PF3	3.059± 0.019	96.73± 1.001
F1	2.969± 0.038	97.98± 1.154
F2	2.839± 0.026	96.27± 0.891
F3	2.929± 0.021	97.59± 0.672
F4	3.049± 0.039	97.40± 0.866
F5	2.969± 0.054	97.59± 0.865
F6	3.129± 0.043	96.82± 0.861
F7	2.919± 0.021	96.43± 0.869
F8	2.959± 0.047	96.24± 0.586
F9	2.999± 0.079	97.83 ± 0.654
F10	3.019± 0.033	97.89± 1.009

7.3.7Swelling study

Swelling index was carried out for preliminary formulation and results were shown in Table no. 7.9 .The swelling index of the tablets from each formulation (F1 to F10) was evaluated and the results are mentioned in Table no 7.10

- PF1 to PF3 were hydrated to an extent of 220.44±0.512, 312.59±0.514, 165.44±0.847,
- F1 to F5 were hydrated to an extent of 118.05, 157.31, 102.83, 132.21, and 98.28.
- F6 to F10 were hydrated to an extent of121.78, 101.91, 121.48, and 255.98.

Table no 7.9: % swelling index for preliminary formulations

FORMUL. CODE	% Swelling index Time (hrs) (n=3) Mean±S.D								
	2 Hrs	**4 Hrs**	**6 Hrs**	**8 Hrs**	**10 Hrs**	**12 Hrs**	**16 Hrs**	**20 Hrs**	**24 Hrs**
PF1	94.48 ±0.741	136.44 ±0.235	156.74 ±0.824	166.84 ±0.941	176.64 ±0.236	185.94 ±0.613	192.74 ±0.312	208.14 ±0.841	220.44 ±0.512
PF2	211.17 ±0.212	269.57 ±0.906	279.47 ±0.548	285.37 ±0.726	295.37 ±0.749	297.77 ±0.514	305.67 ±0.701	308.87 ±0.847	312.59 ±0.514
PF3	69.34 ±0.514	80.56 ±0.424	93.44 ±0.814	105.52 ±0.716	117.45 ±0.476	129.68 ±0.164	141.55 ±0.258	153.65 ±0.371	165.44 ±0.847

Table no 7.10: % swelling index for polymer gum formulations

FORM. CODE	% Swelling index Time (hrs)								
	2 Hrs	**4 Hrs**	**6 Hrs**	**8 Hrs**	**10 Hrs**	**12 Hrs**	**16 Hrs**	**20 Hrs**	**24 Hrs**
F1	41.15	50.7625	60.375	69.9875	79.6	89.2125	98.825	108.4375	118.05
F2	90.75	99.07	107.39	115.71	124.03	132.35	140.67	148.99	157.31
F3	34.98	43.46125	51.9425	60.42375	68.905	77.38625	85.8675	94.34875	102.83
F4	72.17	79.675	87.18	94.685	102.19	109.695	117.2	124.705	132.21
F5	32.61	40.81875	49.0275	57.23625	65.445	73.65375	81.8625	90.07125	98.28
F6	62.36	69.7875	77.215	84.6425	92.07	99.4975	106.925	114.3525	121.78
F7	32.94	41.56125	50.1825	58.80375	67.425	76.04625	84.6675	93.28875	101.91
F8	57.73	65.69875	73.6675	81.63625	89.605	97.57375	105.5425	113.5113	121.48
F9	114.97	132.5963	150.2225	167.8488	185.475	203.1013	220.7275	238.3538	255.98
F10	127.38	144.6788	161.9775	179.2763	196.575	213.8738	231.1725	248.4713	265.77

7.3.8. In vitro dissolution

In vitro drug release studies were performed by using USP XXIII dissolution test apparatus-II at 50rpm using 900 mL of 1.2 pH buffer maintained at 37±0.5ºC as the dissolution medium.

7.3.8.1. In vitro dissolution studies of preliminary & polymer formulations:

The in vitro drug release profiles for the preliminary formulations) were tabulated in Table no 7.11. The plot of cumulative percentage drug release V/s time (Hr) for preliminary formulations were plotted and depicted in Figure.

Table no 7.11: % Cumulative drug release of Preliminary formulations

Time (Hrs)	PF1	PF2	PF3
1	8.506 ± 1.084	9.895 ±1.377	6.631 ± 1.310
2	14.804 ± 1.316	18.631 ±1.681	13.467 ± 1.090
3	24.908 ± 1.317	25.797 ± 1.093	20.755 ± 1.316
4	32.429 ± 0.908	29.656 ± 1.680	29.123 ± 1.090
5	40.630 ± 0.800	33.150 ± 0.306	35.502 ± 1.090
6	47.967 ± 1.833	38.724 ± 0.522	41.708 ± 1.047
7	55.994 ± 0.911	42.228 ± 0.797	49.170 ± 0.907
8	65.066 ± 1.833	45.893 ± 0.304	56.124 ± 1.566
9	76.054 ± 1.202	50.253 ± 0.522	67.950 ± 0.909
10	84.969 ± 1.209	53.750 ± 0.601	74.717 ± 1.382
12	88.316 ± 1.589	60.192 ± 0.523	81.700 ± 1.979
16	-	71.166 ± 0.904	87.0694±1.516
20	-	79.039 ± 1.801	89.148±1.719
24	-	87.589 ± 1.670	-

Table no 7.12: % Cumulative drug release of polymer gum Formulations (F1-F5)

Time (Hrs)	F1	F2	F3	F4	F5
1	18.923±1.591	14.583±0.520	16.840±1.310	13.888±1.310	10.651± 1.172
2	21.806±0.299	19.872±1.565	20.753±1.588	25.424±1.681	20.190±0.306
3	25.120±1.378	23.721±0.608	24.073±0.910	29.481±1.600	22.363±0.522
4	28.611±1.091	26.867± 1.087	26.695±1.379	36.100±1.386	26.789± 0.302
5	31.408±0.907	29.662±1.208	29.835±1.385	42.039±1.598	34.817±0.527
6	34.722±0.800	32.455±1.384	33.151±1.598	50.406±1.598	37.158±0.521
7	38.212±0.906	35.042±1.511	35.773±1.600	55.139±1.315	42.682±1.565
8	41.357±0.907	38.042±1.682	38.392±1.093	66.624±0.802	43.659±0.804
9	44.673±0.800	41.529±1.512	41.531±1.316	75.368±1.566	45.974±1.283
10	47.295±1.206	45.021±1.386	44.500±0.528	81.493±1.837	48.912±1.191
12	54.775±1.316	50.943±1.091	49.898±1.594	87.082±0.801	56.778±0.801
16	66.275±1.088	64.691±0.603	62.428±0.788	-	65.226±1.594
20	78.665±1.679	82.996±1.313	74.130±1.313	-	79.369±1.836
24	82.379±1.683	87.264±1.318	84.090±0.802	-	87.020±1.317

Table no 7.13: % Cumulative drug release of polymer gum Formulations (F6-F

Time (Hrs)	F6	F7	F8	F9	F10
1	9.722± 1.084	16.145± 1.877	17.708± 1.041	10.243±0.795	11.631±0.795
2	18.109±0.304	23.527±0.510	22.841± 0.305	19.154±0.800	20.377±1.381
3	20.933±0.520	28.081±0.798	24.952± 1.379	21.981±0.902	24.071±0.528
4	24.768± 0.300	30.016±0.304	29.304± 0.542	24.774±0.305	26.174±1.563
5	29.824±0.520	34.888±0.796	32.627± 1.086	29.303±0.520	30.005±1.599
6	32.977±0.523	38.213±0.525	35.249± 0.800	32.627±0.796	34.540±0.908
7	37.682±1.565	43.266±0.798	39.430± 0.799	36.812±1.595	39.253±1.382
8	40.659±0.804	45.898±0.800	42.579± 0.799	40.828±0.908	42.751±0.608
9	43.974±1.382	50.253±0.525	45.895± 0.605	44.149±1.087	46.590±0.523
10	47.812±1.091	54.444±0.523	49.906± 0.798	47.987±0.605	50.431±0.798
12	54.778±0.801	61.932±1.086	56.525± 0.905	57.383±0.798	59.827±0.299
16	65.226±1.594	72.738±1.047	72.013±11.315	79.310±0.299	80.886±0.301
20	83.369±1.837	82.346±0.300	87.203± 0.294	90.36±1.085	91.072±0.902
24	89.002±1.387	89.691±1.085	91.107± 0.502	94.24±1.037	94.07±0.790

7.3.7. Release kinetic data

In order to describe the kinetics of the release process of drug in all formulations, various equations were used, such as zero-order rate equation, which describe the system where release rate was independent of the concentration of the dissolved species.

The first-order equation describes the release from the systems where dissolution rate was dependent on the concentration of the dissolved species.

Higuchi square root equation describes the release from system where solid drug was dispersed in insoluble matrix, and the rate of drug release is related to the rate of diffusion. The Korsmeyer-peppas equation was used to analyze the release of pharmaceutical polymeric dosage forms, when the release mechanism is not well known or when more than one type of release phenomenon could be involved**.**

The value of *n* gives an indication of the release mechanism, When *n* = 1, the release rate is independent of time (Zero order), *n* = 0.5 for Fickian diffusion and when between 0.5 and 1.0, diffusion and non-Fickian transport or anomalous diffusion are implicated. Lastly when *n* is more than 1.0 supercase II transport is apparent.

7.3.9.1.Release kinetic data for preliminary formulation:

Release kinetic data for preliminary formulations tabulated in Table no 7.14 and zero-order plot (Figure no 7.3), first-order plot (Figure no 7.4),Higuchi plot (Figure no 7.5) and Korsmeyer–Peppas plot (Figure no 7.6).

Table no 7.14: Release kinetics data of preliminary formulations

Formln. code	Mathematical models (kinetics)				
	Zero order (R)	First order (R)	Higuchi (R)	Korsmeyer-Peppas	
				n	(R)
PF1	0.9867	0.9412	0.9741	0.993	0.9957
PF2	0.9597	0.9903	0.9988	0.665	0.9812
PF3	0.8825	0.9566	0.9543	0.928	0.9724

Figure no. 7.3 %Cumulative drug release vs. time (Zero order) model for PF1-PF3

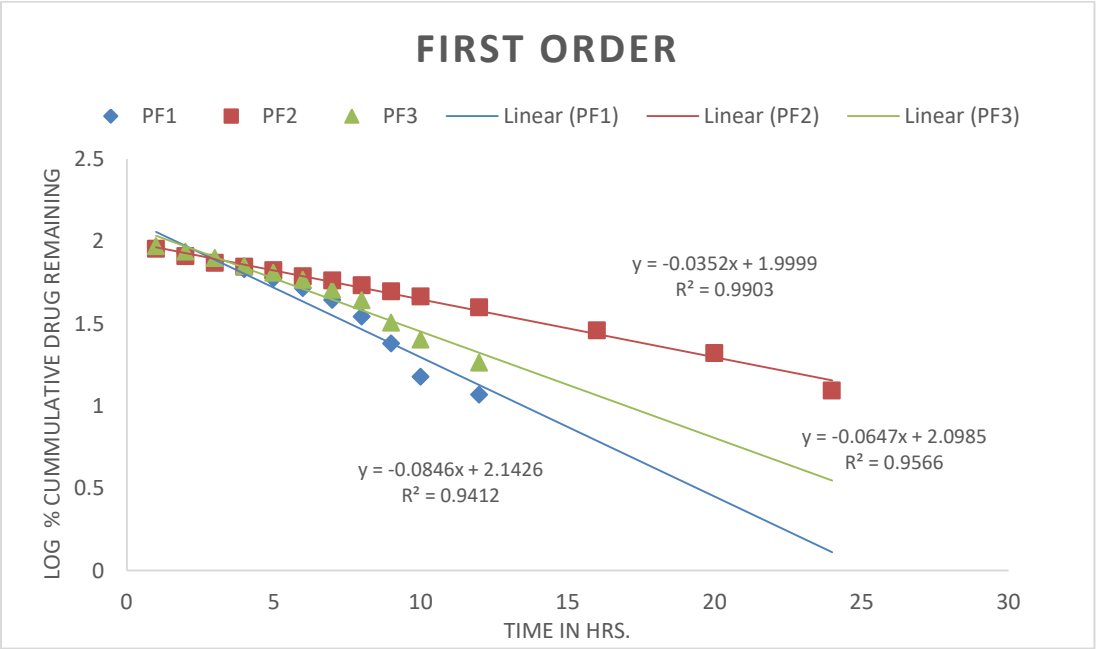


Fig.No:7.4 Average % drug remaining vs. time (First order model) for PF1-PF3

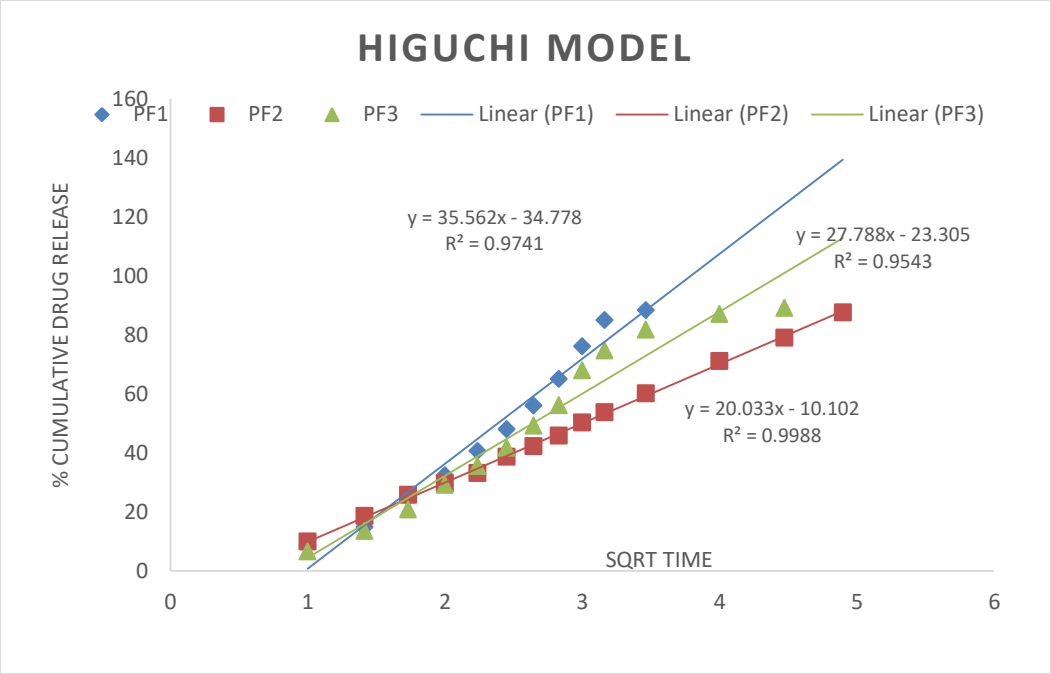


Fig.No:7.5 Average % CDR vs. SQRT time (Higuchi model) for PF1-PF3

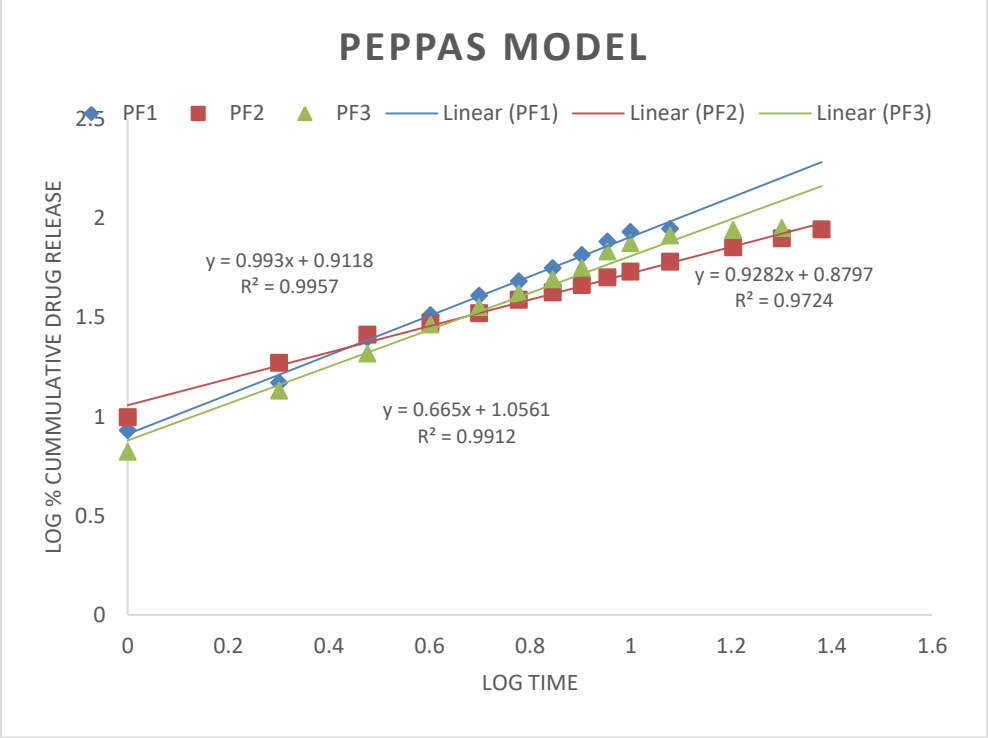


Fig.No:7.6 Average log % CDR vs. log time (Peppas model) for PF1-PF3

7.3.9.2.Release kinetic data for polymer gum formulation:

Release kinetic data for gum formulations tabulated in Table no 7.15 and zero-order plot (Figure no 7.7 and 7.8), first-order plot (Figure no 7.9 and 7.10),Higuchi plot (Figure no 7.11 and 7.12) and Korsmeyer–Peppas plot (Figure no 7.13 and 7.14). The data of various models reviewed that formulations followed Peppas model with n value more than 0.5 and thus release can be concluded as non Fickanian diffusion. All the formulations followed zero order release kinetics.

Table no 7.15: Release kinetics data of all the formulations

FORMLN. CODE	Mathematical models (kinetics)				
	Zero order (R)	First order (R)	Higuchi (R)	Korsmeyer-Peppas	
				N	(R)
F1	0.9902	0.9778	0.9919	0.5559	0.9841
F2	0.9927	0.9382	0.976	0.6024	0.971
F3	0.9992	0.9564	0.9877	0.5619	0.9773
F4	0.987	0.9465	0.981	0.7373	0.9768
F5	0.9736	0.9704	0.9911	0.5971	0.9895
F6	0.9884	0.9521	0.9832	0.6608	0.9945
F7	0.9795	0.9771	0.9913	0.5358	0.9899
F8	0.9919	0.9417	0.9659	0.5299	0.961
F9	0.983	0.9363	0.9653	0.6776	0.9832
F10	0.9794	0.9441	0.9696	0.6479	0.983

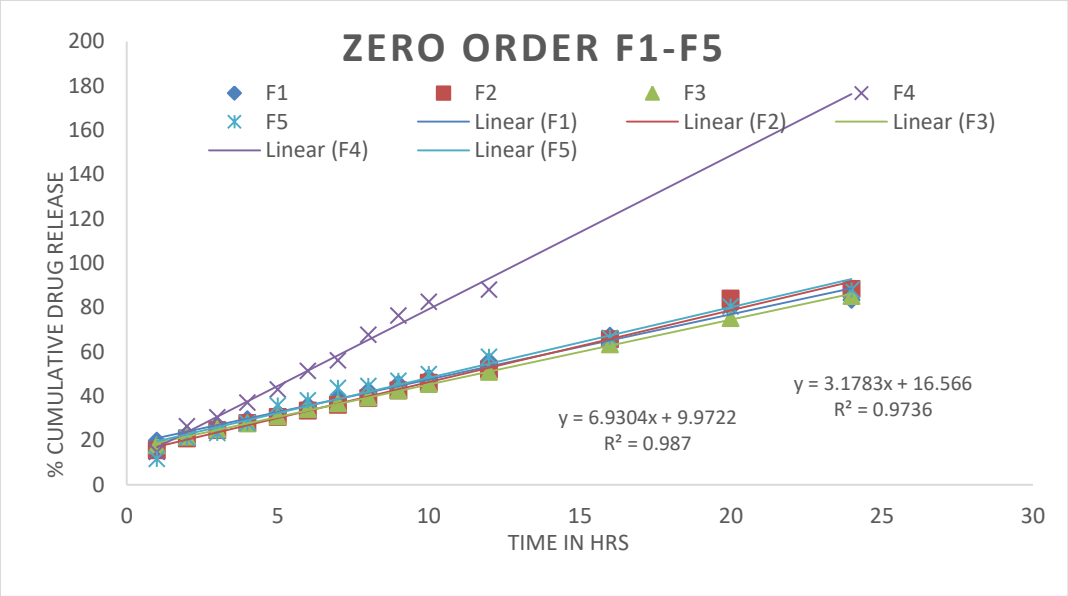


Fig.No:7.7 % cumulative drug release vs. time (Zero order model) for F1-F5

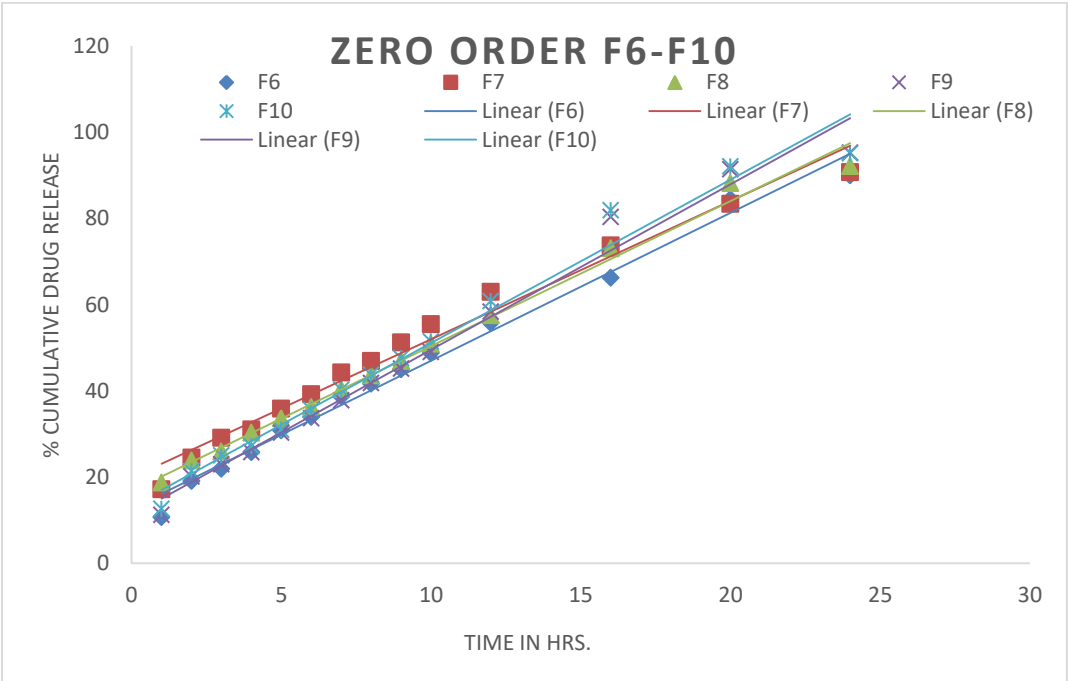


Fig.No:7.8 % cumulative drug release vs. time (Zero order model) for F6-F10

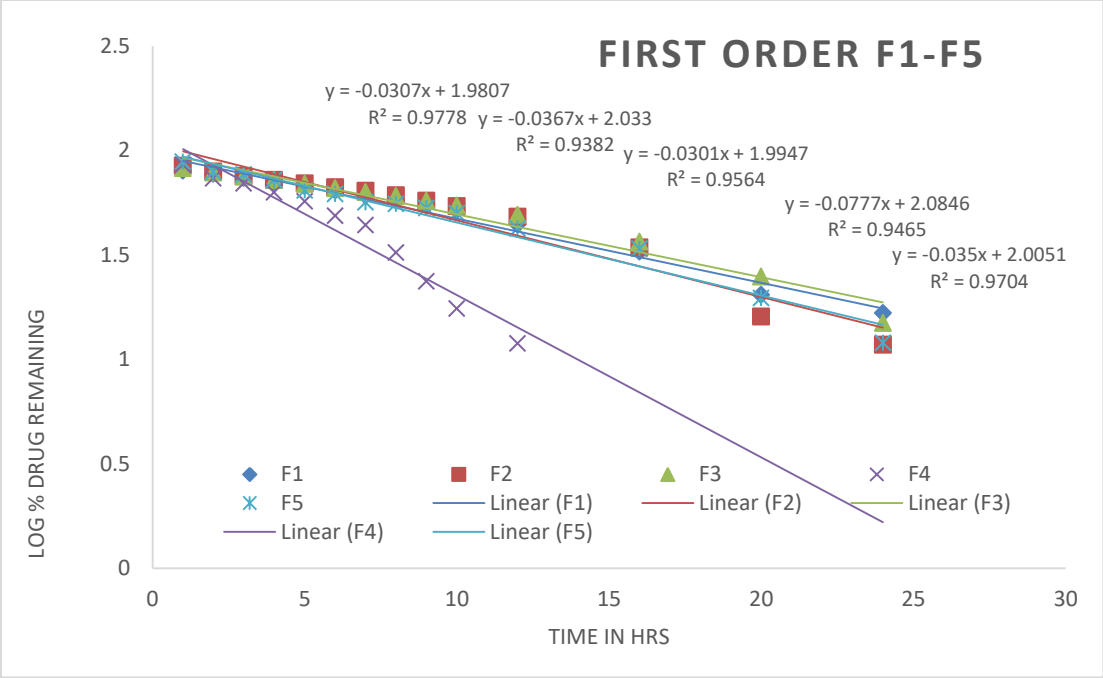


Fig.No:7.9 Average log % drug remaining versus time (First order model) for F1-F5

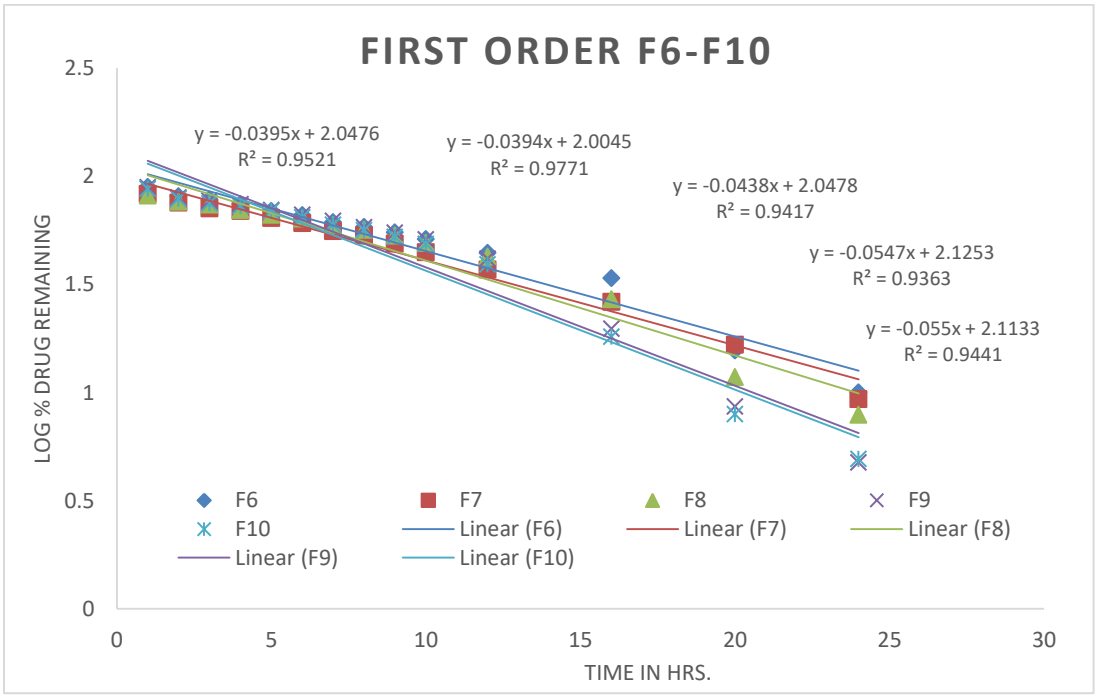


Fig.No:7.10 Average log % drug remaining versus time (First order model) for F6-F10

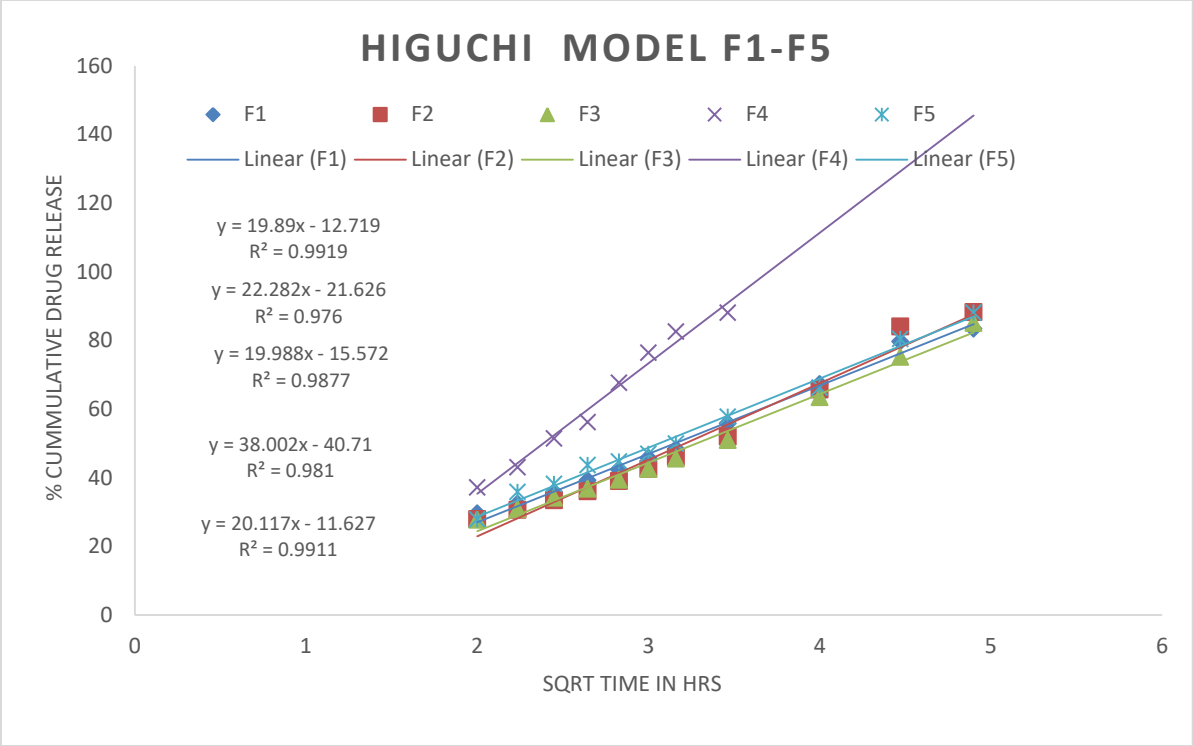


Fig.No:7.11.Average % CDR versus SQRT time (Higuchi model) for F1-F5

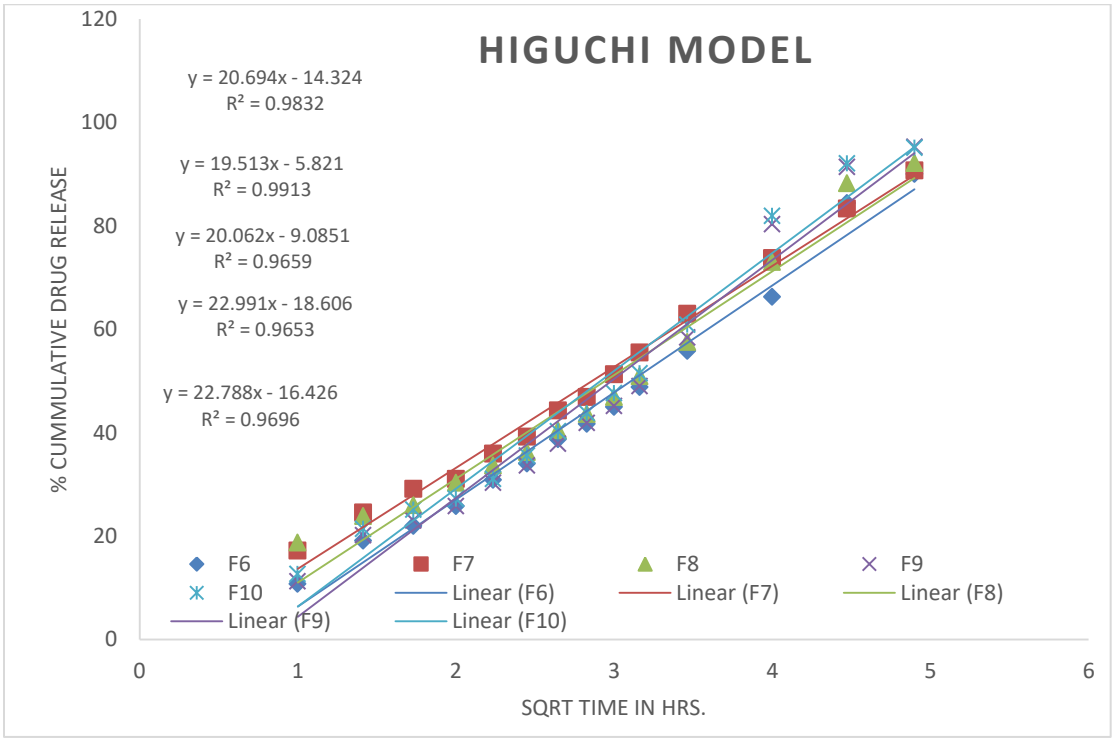


Fig.No:7.12. Average % CDR versus SQRT time (Higuchi model) for F6-F10

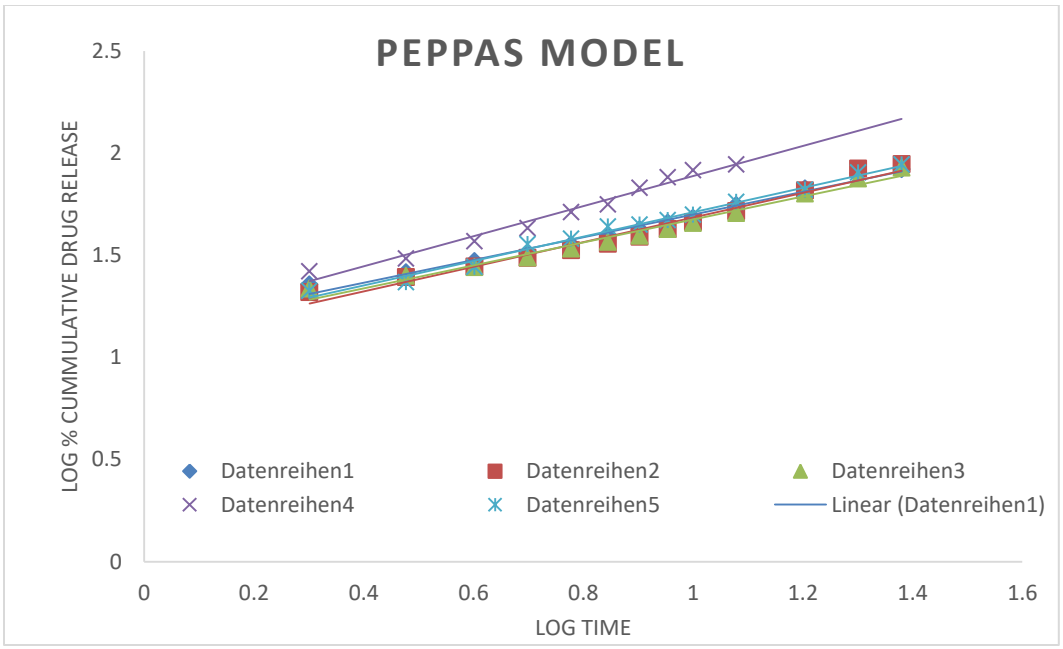


Fig.No:7.13. Average log % CDR versus log time (Peppas model) for F1-F5

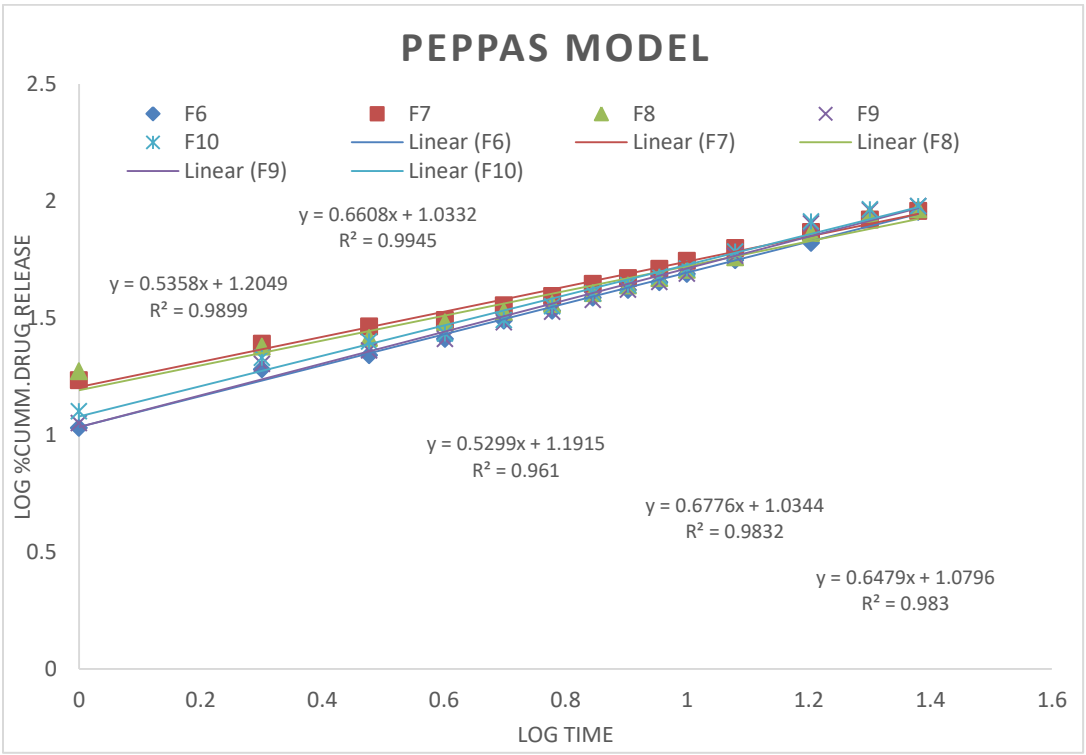


Fig.No:7.14 Average log % CDR versus log time (Peppas model) for F6-F10

7.3.10. *In vitro* mucoadhesive strength:

In vitro mucoadhesive strength was carried out by using self-fabricated instrument. Results for *in vitro* mucoadhesive strength and force of adhesion were shown in Table no.7.16

Table no: 7.16: mucoadhesive strength of preliminary formulations

Formulation code	Mucoadhesive strength (g)	Mucoadhesion force (N)
PF1	23.510	2.305861
PF2	21.443	2.103129
PF3	24.666	2.419241

Table no: 7.17: mucoadhesive strength of polymer gum formulations

Formulation code	Mucoadhesive strength (g)	Mucoadhesion force (N)
F1	23.471	2.302036
F2	22.300	2.187184
F3	22.720	2.228378
F4	21.350	2.094008
F5	20.580	2.018486
F6	23.890	2.343131
F7	22.576	2.214254
F8	22.680	2.224454
F9	24.053	2.359118
F10	24.670	2.419634

7.3.11. Stability study:

The accelerated stability studies were carried out according to ICH guidelines. Optimized formulations F6 and F9 were packed in amber color bottle and aluminum foil laminated on the upper part of the bottle and these packed formulations were stored in ICH certified stability chambers. Maintained at 40^0C ± 2^0C and 75 % RH ± 5 % (zone III conditions as per ICH Guidelines) for 3 months. The tablets were evaluated before and after one month for change in appearance, the drug content and *in vitro* release.

After a period of one month, the samples were observed for any change on appearance. It was observed that tablet was devoid of any change in color or appearance of any kind of spot on it. It was also noted that tablet was free of any kind of microbial or fungal growth or bad odor. The formulation batch showed circular shape with no cracks. The drug content of the formulation F9 was found to be 97.83 %, 97.19% and 96.92 % at interval of 30 days respectively and formulation F10 was found to be 97.89%, 96.93% and 96.69 % at internal of 30 days respectively. The %CDR of formulation F9 was found to be 94.16% , 93.98% and 93.82 % at interval of 30 days respectively and the %CDR of formulation F10 was found to be 94.06%, 93.91% and 93.76 % at interval of 30 days respectively. The % CDR of formulation F9 and F10 were found to be Result show there was slight decrease in drug content but difference is insignificant.

TablTable no 7.18: Stability study for F9

T

Time (days)	Physical appearance	Drug content	% CDR
30	No change	97.83%	94.16
60	No change	97.19%	93.98
90	No change	96.92%	93.82

a

b

l

Table no 7.19: Stability study for F10

Time (days)	Physical appearance	Drug content	% CDR
30	No change	97.89%	94.06
60	No change	96.93%	93.91
90	No change	96.69 %	93.76

8. CONCLUSION

The present study has been a satisfactory attempt to formulate mucoadhesive drug delivery system of gliclazide, an orally administrated anti-diabetic drug with a view of improving its oral bioavailability and giving sustained release of the drug for prolonged period of time.

From the experimental results it can be concluded that,

1. Mucoadhesive drug delivery systems of gliclazide can be prepared by direct compression method using various polymers like Chitosan, Xanthan gum, and Moringa gum

2. A suitable method of analysis of drug by UV spectrophotometry was developed. Gliclazide showed maximum absorption at a wavelength 229 nm in pH 1.2 buffer (0.1N HCl). The value of regression coefficient (r^2) was found to be 0.999, which showed linear relationship between concentration and absorbance.

3. IR spectroscopic studies indicated that there is no drug-polymer interaction in the prepared formulations.

4. On the basis of prepared preliminary formulations, final formulations were formulated using combinations of two or three natural polymers.

5. All the prepared tablet formulations were found to be good without capping and chipping.

6. From this study, it was concluded that as the concentration of gum increases the swelling index also increases. Xanthan gum found more swelling as compare to other polymers. The increasing order of swelling is Moringa gum>Xanthan gum > chitosan.

7. All most of the designed formulations of gliclazide Mucoadhesive Drug Delivery Systems displayed zero order release kinetics, and drug release follows non-Fickanian diffusion mechanism.

8. From this study, it was concluded that as the concentration of gum increases the *in vitro* mucoadhesive strength also increases. Chitosan showed greater mucoadhesive strength. The increasing order of mucoadhesive strength is Chitosan > Xanthan gum > Moringa gum.

9. Short-term stability studies of optimized formulations F9 and F10 indicates, that there are no significant changes in drug content and dissolution parameter values after 1 month storage at 40^0C ± 2^0C and 75 % RH ± 5 %.

SCOPE FOR FURTHER STUDY:

- The work can be extended for its *in vivo* studies for *in vitro-in vivo* correlation and gamma Scintigraphy and various *in vivo* studies.
- The formulation of mucoadhesive drug delivery system can be tried with other natural gums, synthetic gums and their combinations.

9. SUMMARY

Gliclazide is extensively used in patients with type 2 diabetes mellitus. Gliclazide is readily absorbed from the gastrointestinal tract. It is extensively bound to plasma proteins. The half-life is about 10 to 12 hours. Gliclazide is extensively metabolized in the liver to metabolites that have no significant hypoglycemic activity. Metabolites and a small amount of unchanged drug are excreted in the urine. The usual initial dose is 40 to 80 mg daily, gradually increased, if necessary, up to 320 mg daily.

In the present study, an attempt was made to design and optimize GMDDS of Gliclazide using natural polymers like Chitosan, Xanthan, and Moringa gum

Drug and polymers were subjected for the compatibility study using FTIR, which suggested that there is no interaction between the drug and polymer.

The tablets were prepared by direct compression technique. Three batches of preliminary formulations were designed and from the results of evaluation data, final formulations were selected for further study by using natural polymers.

Further development of mucoadhesive tablets of gum formulations were carried out by using combinations of various natural polymers. The prepared mucoadhesive formulations were evaluated for hardness, friability, weight variation, drug content uniformity, *in vitro* swelling study studies, *in vitro* drug release pattern, *in vitro* mucoadhesive strength, short-term stability and drug-excipients interaction.

The results are quoted in different section of the result and discussion.

Various evaluation parameters, we can summarize:

- From IR and physical observation it was observed that there was no significant Drug-Excipient interaction. Melting point of Gliclazide was found to be in range between 177-179 ^{0}C.
- The bulk density and the tapped density for all the formulations varied from 0.4284±0.005 to 0.4679±0.003 gm/cm^3 and 0.4763±0.011 to 0.5361±0.0105gm/cm^3 respectively.
- The angle of repose data for all the formulations ranges from 18^0.92'±0.313 to 25^0.37'±0.171. Hausner's ratio of all formulations ranges from 1.1098±0.027to 1.1965±0.017. The results of the Carr's consolidation index of all the formulations

ranges from 09.80 % to 16.42 %.

- Tablet thickness (n=3) were almost uniform in all the formulations and values for tablets ranged from 2.839± 0.026 to 3.129± 0.043 mm. The weight uniformity of tablets ranged from197.9± 1.786 to 199.8± 1.259 mg.
- The hardness of all formulations was in the range of 4.97± 0.032 to 6.93± 0.133 kg/cm^2.

  The values of friability of all formulations ranged from 0.67 to 0.92%.
- The % drug content of all the formulated tablets were found within the limit. % drug content value of gliclazide was within 94.89± 0.886% to 97.89± 1.009%.
- All three polymeric gums containing tablets shows good mucoadhesion strength as compare to two combinational gums containing tablets. Among all thirteen formulations F10 show maximum mucoadhesion strength of 2.4196and F5 shows lowest mucoadhesion strength of 2.0184.
- Xanthan gum shows highest swelling index and Moringa gum shows less swelling index among others.
- % cumulative drug release after 24 hrs for F9 and F10 showed 94.24±1.037, 94.07±0.790 respectively. These two optimized formulations follows zero order with non fickian diffusion on the basis of regression coefficient of the kinetic data of cumulative drug release from the dosage form.
- The results of accelerated stability study showed that there was no change in the formulation after three month.

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