DESIGN AND DEVELOPMENT OF PULSATILE DRUG DELIVERY SYSTEM FOR ANTI DIABETIC DRUG

Thesis Submitted To

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY, GUINDY, CHENNAI

As a partial fulfillment of the requirement
for the award of the degree of

DOCTOR OF PHILOSOPHY

IN

FACULTY OF PHARMACY

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DECEMBER – 2012

LIST OF ABBREVIATIONS USED

API	:	Active Pharmaceutical Ingredient
α	:	Alpha
β	:	beta
BP	:	British Pharmacopoeia
BD	:	Bulk Density
ChrDDS	:	Chronopharmaceutical drug delivery system
CPR	:	Cumulative percent release
CR	:	Controlled Release
Conc.	:	Concentration
cm	:	Centimeter
CI	:	Carr‘s index
cp	:	Centi Poise
DM	:	Diabetes mellitus
DSC	:	Differential Scanning Calorimetry
et al	:	and others
FDA	:	Food and Drug administration
Fig.	:	Figure
FTIR	:	Fourier Transform Infra-Red Spectroscopy
gm	:	gram
GI	:	Gastrointestinal
GIT	:	Gastrointestinal tract
GMP	:	Good Manufacturing Practice
Hrs	:	hours
HR	:	Hausner‘s ratio
HCl	:	Hydrochloric Acid
HPLC	:	High performamce liquid chromatography

HPMC	:	Hydroxy Propyl Methyl Cellulose
IDDM	:	Insulin Dependent Diabetes mellitus
i.e.	:	That is
IP	:	Indian pharmacopoeia
IR	:	Immediate release
ICH	:	International Conference on Harmonization
IVIVC	:	Invitro- invivo corelation
KBr	:	Potasium bromide
Kg	:	Kilogram
L-HPC	:	Low substituted Hydroxy Propyl Cellulose
L	:	Litre
mm	:	Millimeter
ml	:	Millilitre
min	:	Minute
M	:	Molar
MW	:	Molecular Weight
mg	:	Milligram
µg	:	Microgram
µl	:	Microlitre
NaOH	:	Sodium Hydroxide
NIDDM	:	Non Insulin Dependent Diabetes mellitus
pH	:	Negative logarithm of hydrogen ion concentration
Ph.Eur	:	European Pharmacopoeia
PDDS	:	Pulsatile drug delivery system
PVP	:	Poly vinyl pyrolidine
rpm	:	Revolutions Per Minute
RT	:	Real time
RSD	:	Relative Standard Deviation

RH	:	Relative Humidity
SD	:	Standard déviation
Sec.	:	Second
SSG	:	Sodium Starch Glycollate
SR	:	Sustained release
t ½	:	Time required to reduce the amount to half of its original concentration
TD	:	Tapped Density
Temp.	:	Temperature
USP	:	United States Pharmacopoeia
UV	:	Ultraviolet
V	:	Volume
V/V	:	Volume / Volume
W	:	Weight
W/V	:	Weight / Volume
W/W	:	Weight / Weight
WS	:	Working Standard

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1. INTRODUCTION

PULSATILE DRUG RELEASE SYSTEMS

Pulsatile systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed according to the circadian rhythm of the body. Circadian rhythm regulates many body functions in humans, viz., metabolism, physiology, behavior, sleep patterns, hormone production, etc. It has been reported that more shocks and heart attacks occur during morning hours. The patients suffering from diabetes are reported to have high blood sugar levels after meals compared to other timings.[1,2,3,4]

The pulsatile effect, i.e., the release of drug as a "pulse" after a lag time has to be designed in such a way that a complete and rapid drug release should follow the lag time. Such systems are also called time controlled as the drug released is independent of the environment. These systems beneficial for drugs having high first-pass effect, drugs administered for diseases that follow chronopharmacological behavior, drugs having specific absorption site in GIT, targeting to colon, and cases where night time dosing is required.[2]

In recent years considerable attention has been focused on the development of pulsatile drug delivery system. Pulsatile release pattern has gained most popular form of controlled drug delivery system because conventional systems with a continuous release are not ideal. Oral controlled drug delivery systems are generally used due to convenient dosage form & it also releases drug in constant or variable rates. In these system drug release generally occurs within therapeutic window for prolong period of time. Hence these systems show timed release of drug from dosage form.[5, 6]

Pulsatile drug release system, allows the release of active pharmaceutical material in single or successive pulses at precise and well controlled time periods. Assuming that physiological processes and biological functions display constancy over time,

much effort had been devoted in the past in developing the drug delivery systems that maintain a flatter plasma level for an extended period of time.[7]

Pulsed or pulsatile drug release is defined as the rapid and transient release of a certain amount of drug molecules within a short time-period immediately after a predetermined off-release period[2] called the lag time.

However, chronotherapy belie this concept. Along with many applications in local and systemic delivery of drugs, pulsatile release system would also be advantageous when a delay in absorption is desirable from a therapeutic point of view as for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythm, such as nocturnal asthma, angina and rheumatoid arthritis. So by developing the pulsatile device, plasma peak is obtained at an optimal time, number of doses per day can be reduced, saturable first pass metabolism and tolerance development can also be avoided.[8]

Chronotherapeutics refers to a clinical practice of synchronizing drug delivery in a manner consistent with the body's circadian rhythm including disease states to produce maximum health benefit and minimum harmful effects.[9]

Such novel drug delivery has been attempted for: (i) chronopharmacotherapy of diseases which show circadian rhythms in their pathophysiology ; (ii) avoiding degradation of active ingredients in upper GI tract, e.g. proteins and peptides (iii) for time programmed administration of hormones and many drugs such as isosorbide dinitrate, respectively to avoid suppression of normal secretion of hormones in body that can be hampered by constant release of hormone from administered dosage form and development of resistance (iv) to avoid pharmacokinetic drug–drug interactions between concomitantly administered drugs etc.[9]

However, in drug delivery in biology of living species, time is a fundamental dimension that has been long overlooked in drug design and delivery.

It is now documented that cycles of different scales/mechanical rhythms exist in biological activities ranging from,

- rhythms with a period of approximately one day (circadian)
- very short rhythms (ultradian) and
- rhythms with longer cycles, of a week, a month, a season, or even longer (infradian).[10,11]

Instead of being a passive response to external changes, these rhythms are generated by endogenous biological clocks, i.e., time-keeping structures. In mammals, the central pacemaker is the supra chiasmatic nucleus (SCN). For example, it has been reported that non-pharmacological (light therapy, sleep deprivation, and rhythm therapy) and pharmacological (lithium, antidepressants, and agomelatine) therapies of affective disorders influence circadian rhythms. Beside familial advanced sleep-phase syndrome, the importance of the biological rhythm in drug dosing, metabolic syndromes have also been demonstrated.[12]

Circadian phase dependent patterns have been well documented in conditions such as asthma, arthritis, epilepsy, migraine, allergic rhinitis, cardiovascular disease (myocardial infarction, angina, and stroke) and peptic ulcer disease. Results of several epidemiological studies demonstrate the elevated risk of different pathologies during a 24-h cycle. Specifically, symptoms of rheumatoid arthritis and osteoarthritis, dyspnoea and epilepsy appear to have a peak during the night or early in the morning. Ischemic heart diseases, such as angina pectoris and myocardial infarction, are manifested more frequently during these times. Blood pressure which arises notably just before waking up is usually responsible for these attacks. Treating these diseases with immediate release dosage forms may be impractical if the symptoms of the disease are pronounced during the night or early morning. Therapy with modified release dosage forms with zero order drug release theoretically leads to controlled and constant levels of drug in plasma throughout the day. However this does not provide extra therapeutic levels at the time of increased symptoms and unwanted plasma drug concentration at other times of day may produce adverse effects with little therapeutic benefit.[7,10.]

In order to optimize therapy in terms of safety, patient compliance and efficacy, chronopharmaceutical formulations based upon time controlled drug delivery

systems (TCDDS) are considered to be potential therapeutic options.[11] TCDDS are dosage forms that are designed to mimic the circadian rhythm of the disease by releasing the drug at the appropriate time, by means of an internal pre-programmed clock that is initiated when the dosage forms come in contact with gastrointestinal (GI) fluids.[12,13]

Diseases with established oscillatory rhythm in their pathogenesis [7,9,10,13]

The diseases currently targeted for chronopharmaceutical formulations are those for which there are enough scientific backgrounds to justify ChrDDS compared to the conventional drug administration approach. These include: asthma, arthritis, duodenal ulcer, cancer, diabetes, cardiovascular diseases. The rationales for chronotherapy for each of these diseases are briefed here.

Asthma

The role of circadian rhythms in the pathogenesis and treatment of asthma indicates that airway resistance increases progressively at night in asthmatic patients.

Arthritis

There is a circadian rhythm in the plasma concentration of C-reactive protein and interleukin of patients with rheumatoid arthritis. Patients with osteoarthritis tend to have less pain in the morning and more at night; while those with rheumatoid arthritis, have pain that usually peaks in the morning and decreases throughout the day.

Duodenal ulcer

In peptic ulcer patients, gastric acid secretion is highest during the night.

Diabetes mellitus

Increased blood glucose level immediately after meals.

Cancer

The blood flow to tumors and tumor growth rate are each up to threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase.

Cardiovascular diseases

Capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet aggregability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood.

Hypercholesterolemia

Cholesterol synthesis is generally higher during the night than during daylight and diurnal synthesis may represent up to 30–40% of daily cholesterol synthesis. Many individuals display a paradoxical synthesis, with an inverted diurnal cholesterol synthesis. It seems therefore that cholesterol is synthesized during the night as well as during daylight; however the maximal production occurs early in the morning, i.e. 12 h after the last meal. [7,9,10]

The development of Pulsatile drug delivery systems will lead for:

- Extended daytime or night time activity.
- Reduced side effects.
- Reduced dosage frequency.
- Reduction in dose size.
- Improved patient compliance.
- Lower daily cost to patient due to fewer dosage units are required by the patient in therapy.
- Drug adapts to suit circadian rhythms of body functions or diseases.
- Drug targeting to specific site like colon.
- Protection of mucosa from irritating drugs.
- Drug loss is prevented by extensive first pass metabolism.

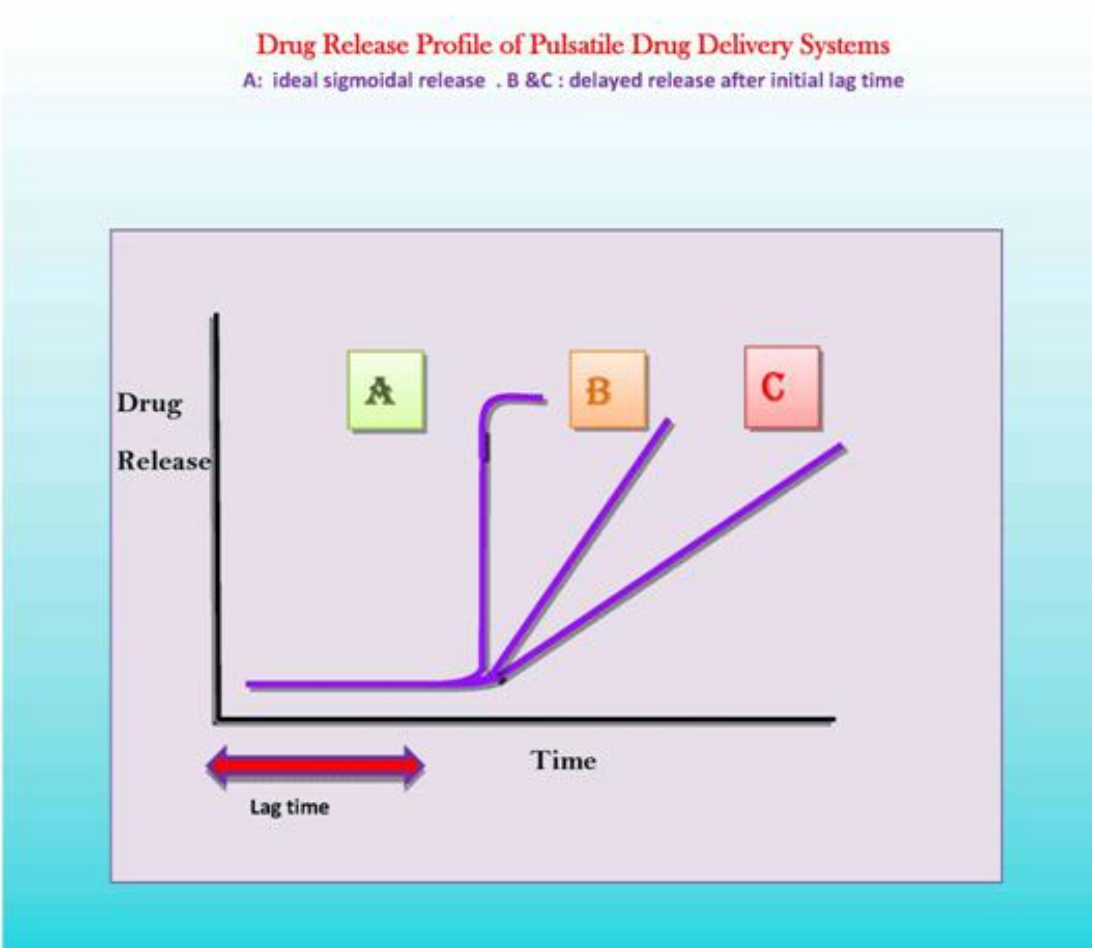


Fig.1.1.Drug release profile of pulsatile drug delivery systems[14]

Table 1.1. Diseases that requires pulsatile delivery

Chronological behavior	Drugs used	Diseases
Acid secretion is high in the afternoon and at night	H_2 blockers	Peptic ulcer
Precipitation of attacks during night or at early morning	β_2 agonist, Antihistamines	Asthma
BP is at its lowest during the sleep cycle and rises steeply during the early morning	Nitroglycerin,Calcium channel blocker, ACE inhibitors	Cardiovascular diseases
Pain in the morning and more pain at night	NSAIDs, Glucocorticoids	Arthritis
Increase in the blood sugar level after meal	Sulfonylureas, Insulin, Pioglitazone	Diabetes mellitus
Cholesterol synthesis is generally higher during night than day time	HMG CoA reductase inhibitors	Hypercholesterolemia[5]

Table 1.2. Marketed technologies of pulsatile delivery [5,6,9,14]

Technology	Mechanism	Proprietary name and dosage form	API	Disease
OROS	Osmotic Mechanism	Covera-H5; XLtablet	Verapamil HCL	Hypertension
Three dimentional printing	Externally regulated system	Their Form	Diclofenac Sodium	Inflammation
DIFFUCAPS	Multiparticulate System	Innopran; XL Tablets	Verapamil HCL, Propranolol HCL	Hypertension
PulsincapTM	Rupturable system	Pulsincap	Dofetilide	Hypertension

Classification of Pulsatile Drug Delivery Systems [14]

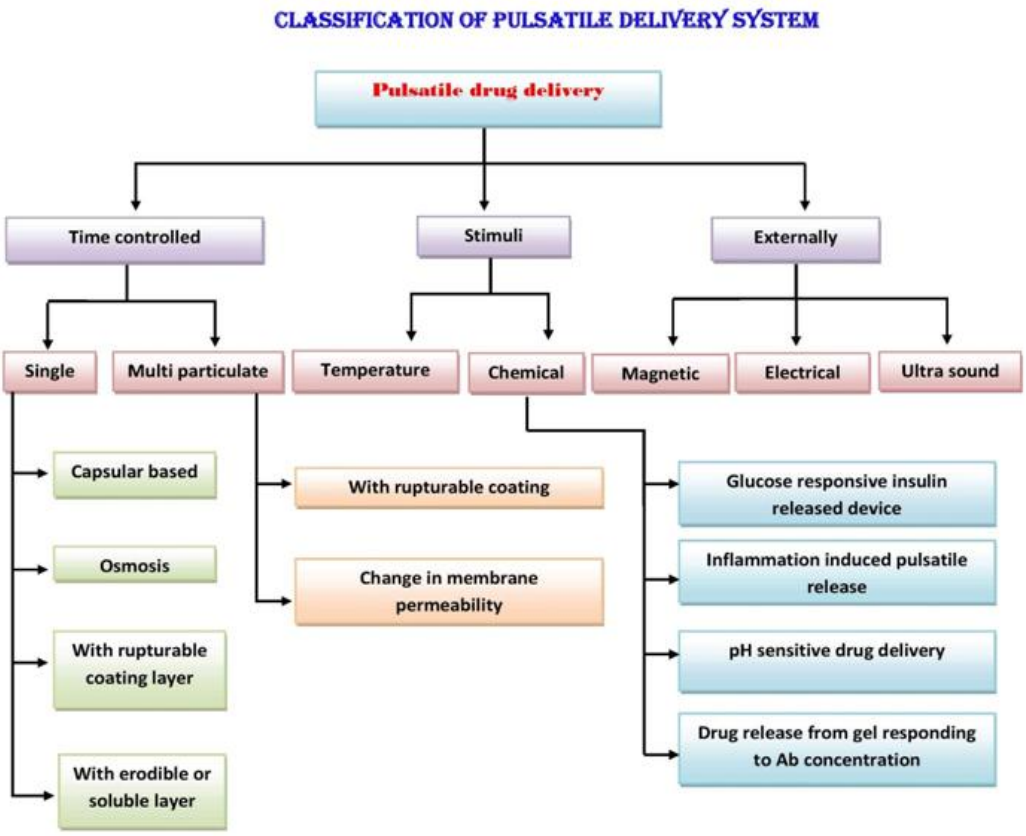


Fig 1.2. Classification of Pulsatile drug delivery systems

TIME CONTROLLED EXPLOSION SYSTEM[5,6]

This is a multiparticulate system in which drug is coated on non-pareil sugar seeds followed by a swellable layer and an insoluble top layer. The swelling agents include superdisintegrants like sodium carboxy methyl cellulose, sodium starch glycolate, l-hydroxyl propyl cellulose, polymers like poly vinyl acetate, polyacrylic acid, poly ethylene glycol, an effervescent system comprising a mixture of tartaric acid and sodium bicarbonate may also be used. The release is independent of environmental factors like pH and drug solubility.

A. SINGLE SYSTEMS

(i) Pulsincap system with swellable plug (Capsular based systems)[15,16]

Single-unit systems are mostly developed in capsule form. The lag time is controlled by a plug, which gets pushed away by swelling or erosion and the drug is released as a "Pulse" from the insoluble capsule body. It comprises of a water-insoluble capsule enclosing the drug reservoir. The length of the plug and its point of insertion into the capsule controlled the lag time. Plug material is generally made up of following-

1. Swellable materials coated with insoluble but permeable polymer (polymethacrylates)
2. Erodible compressed polymer (HPMC, polyvinyl alcohol, polyethylene oxide)
3. Congealed melted polymer (glyceryl monooleate)
4. Enzymatically controlled erodible polymer (pectin)

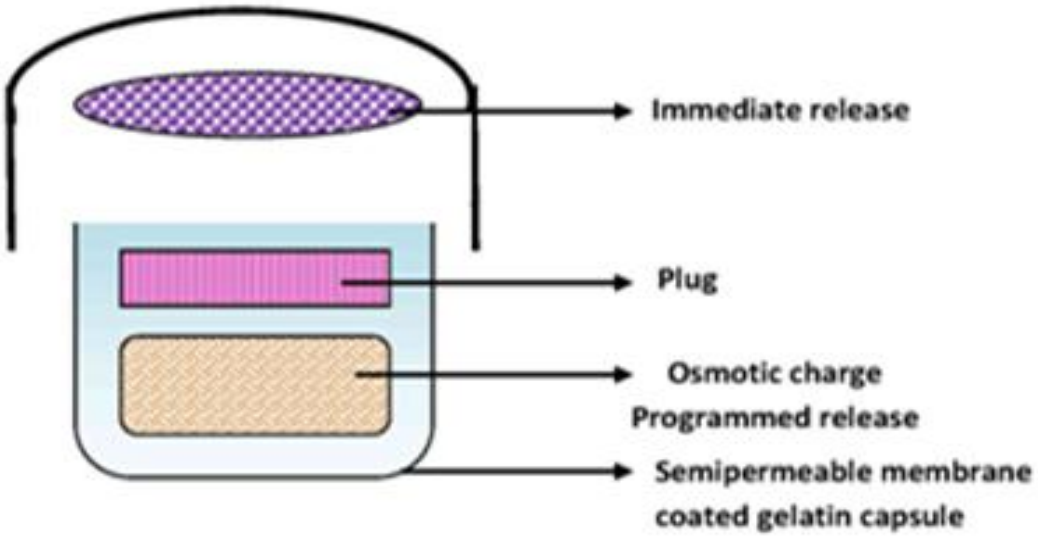


Fig1.3. Plan of port system

(ii) System based on expandable orifice (Osmosis)[7]

To deliver the drug in liquid form, an osmotically driven capsular system was developed in which the liquid drug is absorbed into highly porous particles, which release the drug through an orifice of a semipermeable capsule supported by an expanding osmotic layer after the barrier layer is dissolved. The capsular system delivers drug by capsule osmotic infusion of moisture from the body. The capsule wall is made up of an elastic material and possesses an orifice. Pulsatile release was achieved after lag time of 1 to 10 hours, depending on the thickness of the barrier layer and that of semipermeable membranes.

(iii) Drug delivery system with rupturable layers/membranes [10, 15]

These systems are based upon a reservoir system coated with a rupturable membrane. The outer membrane ruptures due to the pressure developed by effervescent agents or swelling agents. The time clock system is a delivery device based on solid dosage form that is coated by an aqueous dispersion. The coating is made of a hydrophobic–surfactant layer to which a water-soluble polymer is added to improve adhesion to the core. Once in contact with the dissolution fluid, the dispersion rehydrates and redisperses. The lag time could be controlled by varying the thickness of the film. After the lag time, i.e., the time required for rehydration, the core immediately releases the drug.

In contrast to the swellable or erodible coating systems, these systems depend on the disintegration of the coating for the release of drug. The pressure necessary for the rupture of coating can be achieved by the effervescent excipients, swelling agents or osmotic pressure.

(iv) Pulsincap system with erodible matrix [16]

These are erodible compressed tablets. As the swelling hydrogel polymer plug replaced the erodible tablet, the dependence of the dimensional accuracy between the plug and the capsule for the pulling mechanism of the plug from the capsule was also overcome. The erodible tablets made of low substituted

hydroxypropylcellulose (HPC) for the expulsion system for the release of drug over a time period of 2-10 h.

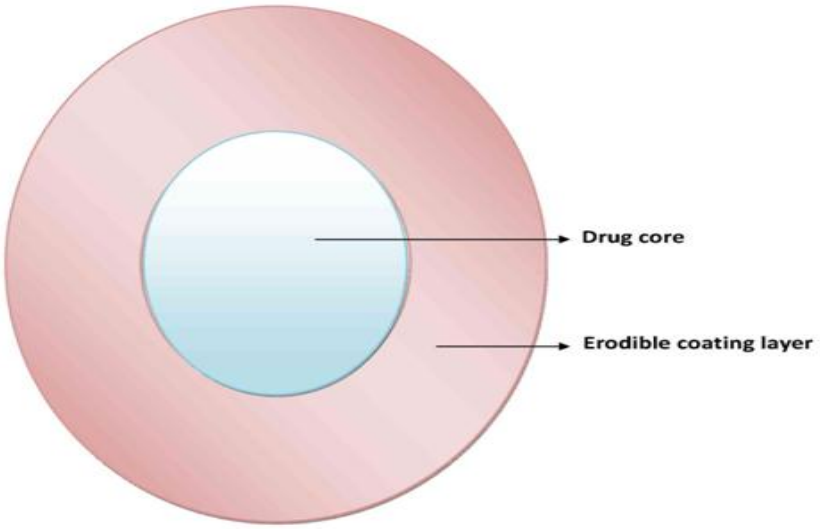


Fig 1.4. Schematic diagram of Delivery systems with erodible coating layer

B. MULTIPARTICULATE SYSTEM [5,6,16,17,18]

Multiparticulate systems are reservoir type of devices with a coating, which either ruptures or changes its permeability. Drug is coated over sugar seeds these granules may then be packaged in a capsule or compressed with additional excipients to form a tablet. These systems are sub classified as

1. **Pulsatile system based on change in membrane permeability.**
2. **Pulsatile system with rupturable coating.**
3. **Low density floating pulsatile systems**

Advantages

- Short gastric residence time
- Reproducible gastric residence time
- No risk of dose dumping
- Flexible to blend pellets with different composition or release pattern

- Lowest transit time variability
- Unique profiles
- Amenable to capsule & tablets
- Capable of pulsatile release

Disadvantages

- Multiple manufacturing steps
- Low drug load
- Incomplete release

(i) Pulsatile system based on change in membrane permeability:

A sigmoidal release system (SRS) is reported which is based upon the interaction of acrylic polymers with quaternary ammonium groups in the presence of different counter ions. SRS system consists of pellet cores having drug and succinic acid coated with ammonio-methacrylate copolymer USP/NF type (B). The water in the medium dissolves succinic acid. The drug inside and the acid solution increase the permeability of the polymer film.

(ii) Pulsatile system with rupturable coating

Pulsatile drug delivery system comprising of a plurality of particles that are divided into several individual delivery units, each having its own distinct composition. Drug delivery was controlled by the rupture of the membrane.

iii) Time controlled, low density floating pulsatile systems[9,10,18,19]

As the name suggests these systems are comprised of low density floating pulsatile dosage forms, reside in stomach only and not affected by variation in gastric pH, local environment or gastric emptying rate. These dosage forms may be either single unit (floating tablets) or multiparticulates (beads, pellets, granules, microspheres) with capability of gastro-retention. These are specifically advantageous for drugs either absorbed from the stomach or requiring local delivery in stomach.

Polysaccharides are widely used in oral delivery systems because of simplicity to obtain the desired drug delivery system and drug release profile, by the control of cross linking, insolubility of cross linked beads in gastric environment and broad regulatory acceptance.

STIMULI INDUCED SYSTEMS[9,19, 20]

This system releases drug only after stimulation by any biological factor like the temperature or any other chemical stimuli.

i) Temperature induced systems

In thermo-responsive hydrogel systems polymer undergoes swelling or deswelling phase in response to temperature which modulate drug release in swollen state. Indomethacin pulsatile pattern in the temperature ranges between 20^0C and 30^0C by using reversible swelling properties of co-polymers of N-isopropylacrylamide and butyrylacrylamide.

ii) Chemical stimuli induced pulsatile systems

It includes

- Glucose-responsive insulin release devices.
- Inflammation induced pulsatile release.
- Drug release from intelligent gels responding to antibody concentration.

EXTERNALLY REGULATED SYSTEMS

In this system the drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. The oral controlled drug delivery system with continuous release does not show suitability in various conditions of the body which require pulsatile release of drug defined as “a pulsatile release profile” and is characterized by a time period of no release (lag time) followed by a rapid & complete drug release of drug from dosage form. A condition requiring pulsatile release included a number of hormones like rennin, aldosterone & cartisole which

shows daily fluctuation in their blood levels. These changes are generally known as circadian rhythm which is responsible for changes in many functions of the body like activity of liver enzyme, blood pressure, intra-ocular pressure etc.,

TYPES OF DOSAGE FORMS THAT CAN BE DESIGNED FOR PULSATILE DRUG DELIVERY

1. Compression coated / press coated tablets[19,20,21]

These are timed release formulations, simple to manufacture, comprised of an inner core that contains an active pharmaceutical ingredient and excipients surrounded by an outer layer that dissolves or disintegrates slowly to produce the lag time. The core is placed between two layers of polymer and directly compressed by flat punches of tablet machine.

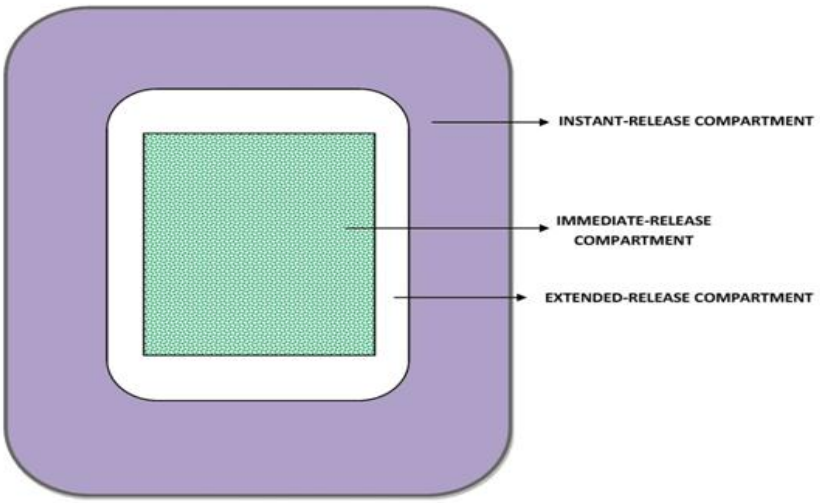


Fig 1.5. Press coated pulsatile tablet system with two pulses of drug.

2. Core in cup tablets

It is a novel oral pulsatile release drug delivery system based on a core-in-cup dry coated tablet, where the core tablet surrounded on the bottom and circumference wall with inactive material. The system consists of three different parts, a core tablet, containing active ingredient, an impermeable outer shell and a top cover layer-barrier of a soluble polymer. The impermeable coating cup consisted of cellulose acetate propionate and the top cover layer of hydrophilic swellable materials such as polyethylene oxide, sodium alginate or sodium carboxy methyl cellulose. The system releases the drug after a certain lag time generally due to the erosion of top cover layer. The quantity of material, its characteristics (viscosity, swelling, gel layer thickness) and the drug solubility was found to modify lag time and drug release.

3. Pulsincap systems [17,18,21,22,23]

As discussed previously that these are the well designed pulsatile release drug delivery systems capable of releasing drug at a pre determined time. Drug formulation is contained within the insoluble capsule body which is sealed by means of a hydrogel plug. On oral administration the water soluble capsule cap dissolves in the gastric juices and hydrogel plug swells. At a controlled and predetermined time point after the ingestion, the swollen plug is ejected from the pulsincap dosage form after which the encapsulated dosage formulation is then released[21].

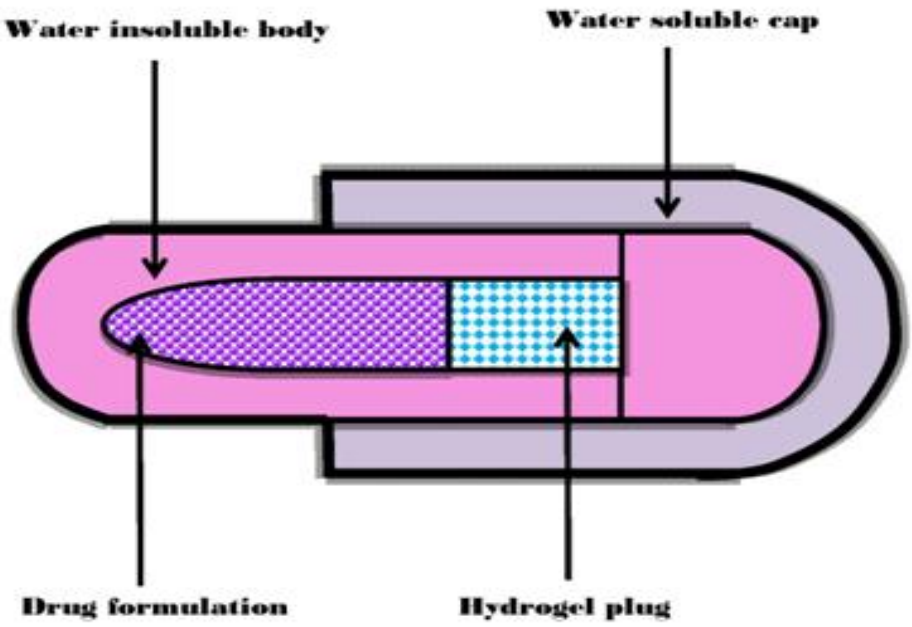


Fig1.6. Pulsincap system

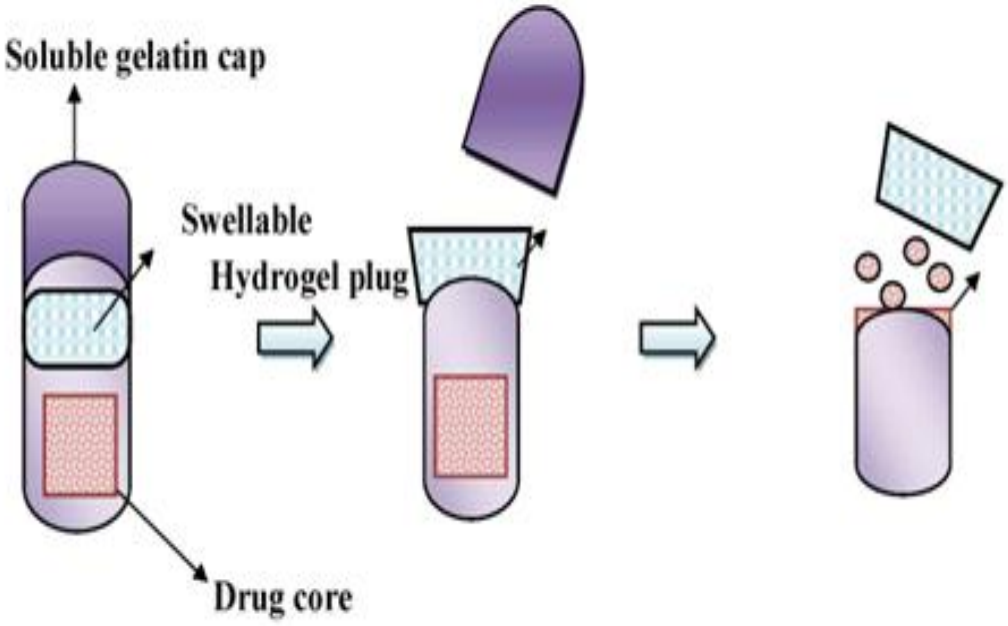


Fig.1.7. Mechanism of drug release from pulsincap

4. Chronomodulating infusion pumps[6,21,22]

Chronomodulating infusion pumps are externally or internally controlled systems across a range of technologies including pre-programmed systems, as well as systems that are sensitive to modulated enzymatic or hydrolytic degradation, pH, magnetic fields, ultrasound, electric fields, temperature, light and mechanical stimulation. These pumps have been effectively used in the chronotherapy of several disease conditions such as cancer and diabetes. Chronomodulating infusion pumps that are available in the market are Melodie, Programmable Synchromed, Panomat V5 infusion, and the Rhythmic pumps.

Examples of chronopharmaceutical technologies[4,5,6,9,20]

Currently key technologies in chronopharmaceutics includes: CONTIN, Physico-chemical modification of the active pharmaceutical ingredient, OROS, CODAS, CEFORM, DIFFUCAPS, chronomodulating infusion pumps, TIMERx, three dimensional printing, controlled-release erodible polymer and CR microchip strategies.

CONTIN technology

In this technology, molecular coordination complexes are formed between a cellulose polymer and a non-polar solid aliphatic alcohol optionally substituted with an aliphatic group by solvating the polymer with a volatile polar solvent and reacting the solvated cellulose polymer directly with the aliphatic alcohol, preferably as a melt. This constitutes the complex having uniform porosity which is utilized as a matrix in controlled release formulations. This technology has enabled the development of sustained-release aminophylline, theophylline, morphine and other drugs in the form of tablets. It also provides for closer control over the quantity of drug released to the bloodstream and reducing the frequency of dosing and unwanted side effects.

OROS technology

This technology utilizes an osmotic mechanism to provide pre-programmed, controlled drug delivery to the gastrointestinal tract. In this active drug is housed in a reservoir, surrounded by a semi-permeable membrane or wall (e.g. cellulose esters, cellulose ethers and cellulose ester–ethers) and formulated into a tablet. The tablet consists of two layers, an active drug layer and a layer of osmotically active agent .When the water from the gastrointestinal tract diffuses through the membrane at a controlled rate into the tablet core, causing the drug to be released in solution or suspension at a predetermined rate. This creates a 'pump' effect that pushes the active drug through a hole in the tablet. It actually enabled delayed, overnight release of verapamil to prevent the potentially dangerous surge in BP that can occur in the early morning.

CODAS technology

The Chronotherapeutic Oral Drug Absorption System (CODASR) is a multiparticular system which releases the drug at bed time after a lag time of 4-5 hrs. This delay is achieved by the level of non-enteric release-controlling polymer applied to drug loaded beads. The release rate is controlled by combination of water soluble and water insoluble polymers. As water from the GIT comes into contact with the polymer coated beads, the water soluble polymer slowly dissolves and the drug diffuses through the resulting pores in the coating. The water insoluble polymer continues to act as a barrier, maintaining the controlled release of Verapamil. The CODASR-Verapamil extended release capsules as chronopharmaceutical drug delivery system actually provided enhanced BP reduction during the morning period when compared with other time intervals of the 24 hrs dosing period.

CEFORM technology

The CEFORM technology allows the formulation of uniformly sized and shaped microspheres of pharmaceutical compounds. The microspheres obtained are almost perfectly spherical, having a diameter that is typically 150–180 A_m and allow for high drug content. The microspheres can be used in a various dosage forms,

including tablets, capsules, suspensions, effervescent tablets, and sachets. The microspheres may be coated to achieve controlled release either with an enteric coating or combined into a fast/ slow release combination. This technology has been actually used to develop once a day Diltiazem formulation as chronopharmaceutical drug delivery system .

DIFFUCAPS technology

In the DIFFUCAPS technology, drug in the form of beads or pellets or granules are filled in to a capsule for delivering drugs into the body in a circadian release fashion. Each bead population exhibits a pre-designed rapid or sustained release profile with or without a predetermined lag time of 3–5 h. This technology has been used to formulate the first and recently FDA approved propranolol-containing chronopharmaceutical drug delivery system for the management of hypertension.

DIABETES MELLITUS

Diabetes is the main cause of death in most developed countries, and there is evidence that it will reach epidemic proportions in many developing nations. Around 246 million people are estimated to have diabetes worldwide.

As the diabetic people multiply worldwide, the disease takes a higher proportion of worldwide healthcare budgets. It is proposed to become one of the world's disables within the next 25 years. Diabetes is popularly known as "silent killer" in medical history. Regions like Asia and Africa, which are greatly potential, the diabetes mellitus rates are bound to rise to two to three –folds more than the present rates.

Diabetes mellitus is a group of disorders characterized by deficient insulin secretion or peripheral insulin resistance, resulting in hyperglycemia and impaired metabolism.

Normal of blood glucose level before a meal is between 70 and 110 mg/dl. After food, level rises to be in between 100 to 140 mg/dl. Above 140 mg/dl is considered to be symptoms of diabetics[24,25]

Classification [26,27]

Diabetes mellitus fall into three broad categories: Type 1, Type 2 and gestational diabetes.

Type 1: Insulin dependent diabetes mellitus

Type 1 diabetes is caused by a lack of insulin due to the destruction of insulin-producing beta cells in the pancreas. In Type 1 diabetes—an autoimmune disease—the body's immune system attacks and destroys the beta cells. Normally, the immune system protects the body from infection by identifying and destroying bacteria, viruses, and other potentially harmful foreign substances. But in autoimmune diseases, the immune system attacks the body's own cells. In Type 1 diabetes, beta cell destruction may take place over several years, but symptoms of

the disease usually develop over a short period of time. Type 1 diabetes typically occurs in children and young adults, though it can appear at any age. In the past, Type 1 diabetes was called juvenile diabetes or insulin-dependent diabetes mellitus.

Latent autoimmune diabetes in adults (LADA) may be a slowly developing kind of Type 1 diabetes. Diagnosis usually occurs after age 30. In LADA, as in Type 1 diabetes, the body's immune system destroys the beta cells. At the time of diagnosis, people with LADA may still produce their own insulin, but eventually most will need insulin shots or an insulin pump to control blood glucose levels

Type 2: Non insulin dependent diabetes mellitus

Type 2 diabetes—the most common form of diabetes—is caused by a combination of factors, including insulin resistance, a condition in which the body's muscle, fat, and liver cells do not use insulin effectively. Type 2 diabetes develops when the body can no longer produce enough insulin to compensate for the impaired ability to use insulin. Symptoms of Type 2 diabetes may develop gradually and can be subtle; some people with Type 2 diabetes remain undiagnosed for years. Type 2 diabetes develops most often in middle-aged and older people who are also overweight or obese. The disease, once rare in youth, is becoming more common in overweight and obese children and adolescents. Scientists think genetic susceptibility and environmental factors are the most likely triggers of Type 2 diabetes.

Gestational diabetes

Gestational diabetes mellitus (GDM) affects pregnant women who have never had diabetes before but who have high blood sugar (glucose) levels during pregnancy are said to have gestational diabetes. It relates Type 2 diabetes in several aspects, which involve a combination of inadequate insulin secretion and responsiveness. It is seen in about 2%–5% of all pregnancies and may improve or disappear after parturition. Gestational diabetes is treatable but requires alert medical supervision throughout the pregnancy. About 20%–50% of the affected women develop Type 2 diabetes later.

Even though it is transient, untreated gestational diabetes may damage the health of the foetus or the mother. Risks of the baby may include macrosomia, congenital central nervous system anomalies and skeletal muscle malformations. Increase in foetal insulin may inhibit foetal surfactant production and cause respiratory distress syndrome. Hyperbilirubinemia results from RBC destruction. Rarely, perinatal death occurs, as a result of poor placental perfusion because of vascular impairment.[27,28]

Other Types of Diabetes

Latent autoimmune diabetes in adults (LADA), also called Type 1.5 diabetes or double diabetes, people have signs of both Type 1 and Type 2 diabetes. Diagnosis usually occurs after age thirty. Many of the people with LADA still produce their own insulin when first diagnosed, like those with Type 2 diabetes, but within a few years, they should be taken insulin to control blood glucose levels. In LADA, as in Type 1 diabetes, the beta cells of the pancreas stop to secrete insulin because the body's immune system attacks and destroys them.

It also includes

- ✓ Genetic defects of the β cell, such as maturity-onset diabetes of the young (MODY) and neonatal diabetes.
- ✓ Genetic defects in insulin action, resulting in the body's unable to control blood glucose levels,e.g. Leprechaunism and Rabson-mendenhall syndrome.
- ✓ Diseases of the pancreas or conditions that damage the pancreas,e.g. Pancreatitis and cystic fibrosis.
- ✓ Excess amounts of some hormones resulting from some disease conditions.e.g. Cortisol in Cushing's syndrome that act against the insulin action.
- ✓ Medications that reduce insulin activities. e.g. Glucocorticoids, or Some chemicals that destroy β cells of pancreas.

- ✓ Infections due to Congenital rubella and Cytomegalovirus.
- ✓ Rare autoimmune disorders.e.g. Stiff-man syndrome, an autoimmune disease of the CNS.
- ✓ Genetic syndromes associated with diabetes.e.g. Down and Prader-Willi syndromes.

Pathopyhsiology[25,26]:

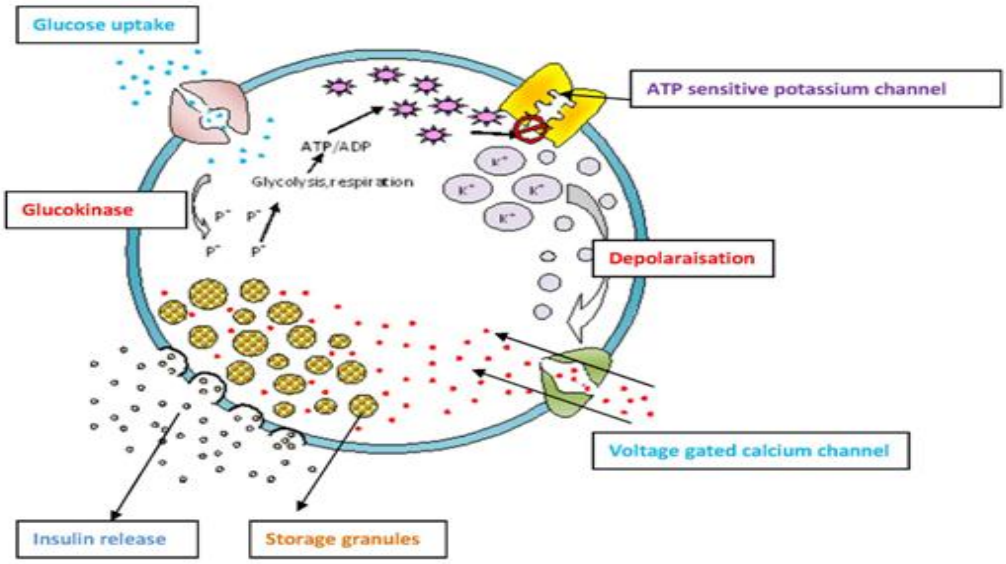


Fig.1.8. Mechanism of insulin release in normal pancreatic beta cells

Insulin is the major hormone that regulates uptake of glucose from the blood into most cells . Therefore, deficiency of insulin or the insensitivity of its receptors plays a key role in all forms of diabetes. Humans beings are capable of digesting some carbohydrates in to simpler forms, most notably the monosaccharide glucose, the principal carbohydrate energy source used by the body. The remaining are passed on for processing by gut flora largely in the colon. Insulin is released into the blood by β-cells, found in the islets of langerhans in the pancreas, in response to rising levels of blood glucose, typically after taking food. Insulin is used by about two-thirds of

the body's cells to absorb glucose from the blood for use as energy, for conversion to other essential molecules, or for storage.

Insulin is also plays a major role in conversion of glucose to glycogen for internal storage in liver and muscle cells. When there is less blood glucose level , release of insulin from the β-cells are reduced and the reverse conversion of glycogen to glucose are taking place to maintain the normal blood glucose level which is controlled by the hormone glucagon that acts in opposite way to insulin. Glucose thus forcibly created from internal liver cell stores as glycogen re-enters the bloodstream; muscle cells lack the mandatory export mechanism. Normally, liver cells do this when the insulin level is less.

Increased insulin levels increase some anabolic processes, like cell growth and duplication, protein synthesis and fat storage. Insulin or its lack is the principal signal in conversion of the duplex processes of metabolism from a catabolic to an anabolic direction, and vice versa. In particular, a low insulin level is the trigger for coming in to or effort ketosis (as the fat-burning metabolic phase).

When the amount of insulin available is insufficient, or cells respond poorly to the consequences of insulin (insulin insensitivity or resistance), or the insulin itself is flawed, then glucose will not have its usual impact, so it will not be absorbed properly by body cells those who need it, nor will it be stored appropriately in the liver and muscles. The net effect is persistent high levels of blood glucose, poor protein synthesis and other metabolic derangements like acidosis.

When the glucose concentration in the blood is raised to about 9-10 mmol/L (except certain conditions,like pregnancy), beyond its renal threshold (i.e. when glucose level surpasses the transport most of glucose reabsorption), reabsorption of glucose wthin the proximal renal tubuli is incomplete and part of the glucose remains within the urine (glycosuria). This increases the osmotic pressure level of the urine and inhibits reabsorption of water by the kidney, resulting in increased urine production (polyuria) and increased fluid loss. Lost blood volumes are replaced osmotically

from water control in body cells and different body compartments, inflicting dehydration and increased thirst[27].

Diagnosis[24,28]:

A urine analysis is used to check the presence glucose and ketones from the breakdown of fat. However, a urine test alone does not diagnose presence of diabetes. Blood tests are used in the diagnosis of diabetes.

Fasting blood glucose level-diabetes is diagnosed if higher than 126 mg/dL on two occasions. Levels between 100 and 126 mg/dL are referred to as impaired fasting glucose or prediabetes. These levels are considered to be risk factors for Type 2 diabetes and its complications.

Hemoglobin A1c test has been used in the past to help patients monitor how well they are controlling their blood glucose levels. In 2010, the American Diabetes Association recommended that the test be used as another option for diagnosing diabetes and identifying pre-diabetes. Levels indicate:Normal: Less than 5.7%, Pre-diabetes: Between 5.7% - 6.4%, Diabetes: 6.5% or higher

Oral glucose tolerance test -diabetes is diagnosed if glucose level is higher than 200 mg/dL after 2 hours. (This test is used more for Type 2 diabetes.)

Random (non-fasting) blood glucose level- diabetes is suspected if higher than 200 mg/dL and accompanied by the classic diabetes symptoms of increased thirst, urination, and fatigue. (This test must be confirmed with a fasting blood glucose test.)

Persons with diabetes need to have their **hemoglobin A1c (HbA1c) level** checked every 3 - 6 months. The HbA1c is a measure of average blood glucose during the previous 2 - 3 months. It is a very helpful way to determine how well treatment is working.

Management

Diabetes mellitus is very difficult to cure. Management concentrates on keeping sugar levels as close to normal (euglycemia) as attainable without presenting patient danger. This can be through with dietary management and use of appropriate medications (insulin is effective only in the case of Type 1 diabetes mellitus. Oral medications may be used in the case of Type 2 diabetes, further as insulin).

Patient education, understanding, and participation is important because the complications of diabetes are less common and severe in people that have well-managed blood sugar levels. Wider unhealthiness accelerates the harmful effects of diabetes. Smoking, elevated cholesterol levels, obesity, high blood pressure, and lack of standard exercise also worsen the deleterious effects of diabetes.

Treatment

Anti-diabetic drugs act by lowering increased blood glucose levels in the blood to normal. The selection of anti-diabetic drugs depends on the nature of the diabetes, age and situation of the person and other factors.

Type 1diabetes- Insulin must be used, which must be injected or inhaled. They include

1. Insulin Syringes
2. Insulin Infusion Pumps
3. Insulin Jet Injectors
4. Insulin Pens

Type 2 diabetes-Treatments include (1) agents that increase the amount of insulin secreted by the pancreas (2) agents that increase the sensitivity of target organs to insulin (3) agents that decrease the rate at which glucose is absorbed from the gastrointestinal tract.

Insulins[29]

Rapid-acting insulin analogues-it mimics the normal physiologic insulin response and have a rapid onset of action, peak activity and a short duration of action.

Biphasic insulins- are combinations of a rapid-acting insulin analogue with intermediate-acting insulin that mimic the normal physiological insulin response and reduce the postmeal hyperglycemia. There are several rapid-acting biphasic insulin formulations commercially available.

Inhaled insulin- consists of human insulin inhalation powder administered using an inhaler. It has an onset of action similar to rapid-acting insulin analogues and a duration of glucose-lowering activity comparable to subcutaneously administered normal human insulin.

Development of Insulin Injections

Insulin syringes

In 1973 insulin syringes were introduced. Initially it was large and heavy with reusable glass plungers and barrels with a long, large bore needle. These syringes underwent significant changes over the years. Today, many insulin injection syringes are available in the markets that are derived from plastics being light in weight, disposable and versatile in use of variety of micro fine needles. These syringes increase patient comfort and offer convenience, thus better patient compliance.[30]

Insulin Infusion Pumps

In 1974 the first insulin infusion pump was introduced in the market. Continuous subcutaneous insulin infusion (CSII) is an approach to simulate the physiology of daily insulin secretion. It consists of a reservoir filled with insulin, a small battery operated pump and a computer chip which allows the patient to control the insulin delivery. It delivers the required amounts of insulin into the body by the pump

through a thin plastic tube known as an infusion set. In these pumps, the insulin reservoir is connected to a subcutaneous catheter, which needs to be changed every two to three days. It is convenient for people who do not like injections as it is only necessary to insert a needle once every three to four days. [31]

Insulin Jet Injectors

In 1980 Jet injectors were introduced to deliver a fine stream of insulin transcutaneously at high speed and pressure to penetrate the skin without need of needle. The use of force on a fluid under pressure through a very small orifice allows such systems to deliver insulin. The dose is controlled by a dial-a-dose operation through a single component design in comparison to the conventional multicomponent syringe and vial method. The available jet injectors allow a dose range of two to 50 units of insulin and can deliver insulin in half-unit increments. Insulin that is administered by the jet injector method is absorbed rapidly. In gestational diabetes, jet injection therapy is associated with less antiinsulin antibody (AIA) production and better postprandial glycemia.[32]

Insulin Pens

In 1987 insulin pens were introduced which eliminate the inconvenience of carrying insulin and syringes. They combine the insulin container and the syringe into a single modular unit. The first insulin pen was introduced by Novo Nordisk. There are two main types of insulin pens, one that is reusable and the other a prefilled device, both pens hold cartridges containing from 1.5 ml to 3 ml of U100/ml insulin. Prefilled devices are well suitable in a bedtime insulin regimen for Type 2 patients.[32]

CLASSIFICATION OF ORAL ANTI DIABETIC DRUGS[27,28,33,34]

1. **Sulfonylureas**

- **First-generation agents**
  Tolbutamide (Orinase)**,** Cetohexamide (Dymelor)

- **Second-generation agents**

  Glipizide (Glucotrol)**,** Glyburide (Diabeta, Micronase, Glynase)

2. **Meglitinides**

   Repaglinide (Prandin), Nateglinide (Starlix)

3. **Biguanides**

   Metformin, Phenformin

4. **Thiazolidinediones**

   Rosiglitazone (Avandia), Pioglitazone (Actos)

5. **Alpha-glucosidase inhibitors**

   Miglitol (Glyset), Acarbose (Precose/Glucobay)

6. **Dipeptidyl peptidase-4 inhibitors**

   Vildagliptin (Galvus), Sitagliptin (Januvia), Saxagliptin (Onglyza)

7. **Newly approved agents for diabetes**

   Pramlintide, Exenatide

1. Sulfonylureas (Glipizide, Glyburide, Glimepiride)[27,28]

The mechanism of action of the sulfonylurea agents is enhancement of insulin secretion by binding to a specific sulfonylurea receptor on pancreatic beta cells. This closes a potassium-dependent adenosine triphosphate channel, leading to decreased potassium influx and depolarization of the beta-cell membrane. This results in increased calcium flux into the beta cell, activating a cytoskeletal system that causes translocation of secretory granules to the cell surface and extrusion of insulin through exocytosis . These medications must be started with the lowest effective dose and titrated upward every 1–2 weeks until the desired control is achieved. In patients with Type 2 diabetes the fasting plasma glucose level will generally decrease by 60–70 mg/dl (3.3–3.9 mmol/l) and the hemoglobin A1c value will usually decrease by 1.5–2.0%. About 75% of patients treated with a sulfonylurea will not be at goal and will require the addition of a second oral agent or bedtime insulin. All the sulfonylureas have comparable glucose lowering potency. They differ in their pharmacodynamics and pharmacokinetics, with each having its own onset, peak, and duration of action. As the drug reaches peak activity, stimulation of pancreatic insulin secretion is at its highest. These drugs can cause hypoglycemia if

there is insufficient glucose in the bloodstream at the time of peak activity. Weight gain is another potential side-effect of the sulfonylureas.

2. Meglitinides (Repaglinide, Nateglinide)

The meglitinides are non-sulfonylurea insulin secretagogues which act by closing an adenosine triphosphatase-dependent potassium channel in the presence of glucose. They have a rapid onset but short duration of action, stimulating the release of insulin. Thus, these meglitinides are usually given before meals. With the rapid rise of glucose level in blood, insulin secretion rises rapidly. These medications generally decrease the hemoglobin A1c value by 1.7–1.8% from baseline. Some of the side-effects include weight gain and occasional hypoglycemia.

3. Biguanides (Metformin)

Metformin belongs to the second-generation biguanide which decreases blood glucose levels by inhibition of gluconeogenesis and decreasing peripheral insulin resistance. The site of action is mainly at the hepatocyte mitochondria, where metformin interferes with intracellular handling of calcium, inhibiting gluconeogenesis and increasing expression of glucose transporters. Metformin induces increase in adenosine monophosphate which is an activated protein kinase activity that is associated with higher rates of glucose disposal and muscle glycogen concentrations. The diabetes prevention program showed that people with impaired glucose tolerance, metformin reduced the incidence of Type 2 diabetes by 31%. When used as a monotherapy, metformin decreases the fasting plasma glucose level by 60–70 mg/dl (3.3–3.9 mmol/l) and the hemoglobin A1c by 1.5– 2.0%. Metformin decreases plasma triglyceride and low-density lipoprotein cholesterol levels by 10–15% and high-density lipoprotein cholesterol levels either do not change or increase slightly after metformin therapy. Serum plasminogen activator inhibitor-1 levels, which are often, elevated in Type 2 diabetes, but these are decreased by metformin. It does not promote weight gain as it does not alter insulin secretion and has a very low risk of hypoglycemia. Metformin is usually started at a dosage of 500 mg twice daily, taken with the two largest meals to minimize gastrointestinal intolerance. The

dose is increased by 500 mg/day every week to achieve the target glycemic control. The maximum dosage is 2000 mg/day. Its adverse effects include abdominal discomfort and diarrhea. Lactic acidosis has been reported in some cases. Drug Contraindications include hepatic dysfunction, hypoxemic conditions, renal dysfunction and severe infection with alcohol abuse.[34]

4. Thiazolidinediones (rosiglitazone, pioglitazone)

Thiazolidinediones are useful in people with Type 2 diabetes as it improves insulin sensitivity. The peroxisome-proliferator-activated receptors are a subfamily of the 48-member nuclearreceptor superfamily and they regulate gene expression in response to ligand binding. Peroxisome-proliferator activated receptor-c is a transcription factor activated by thiazolidinediones. In transactivation, DNA-dependent peroxisome-proliferator-activated receptor-c forms a heterodimer with the retinoid X receptor and recognizes specific DNA response elements in the promoter region of target genes which results in transcription of peroxisome proliferator- activated receptor-c target genes which is expressed mainly in adipose tissue, where it regulates genes involved in adipocyte differentiation, fatty acid , glucose uptake

and storage. They are also found in pancreatic beta cells, vascular endothelium and macrophages. These act as insulin sensitizers in the muscle and decrease hepatic fat content. Decrease in triglyceride levels has been observed more commonly with pioglitazone than with rosiglitazone. .Adverse effects include fluid retention, increased body weight, and expansion of plasma volume, and slight decrease in the hemoglobin level. They can cause hepatotoxicity, and measurements of transaminases must be performed periodically. These are rarely associated with hypoglycemia.

5.α-Glucosidase inhibitors (acarbose, miglitol) [34,35,36,37,45,48,49]

These medications competitively inhibit the ability of enzyme in the small intestine and break down oligosaccharides and disaccharides into monosaccharides, and by delaying the digestion of carbohydrates, these inhibitors shift carbohydrate

absorption to more distal parts of the small intestine. This allows the β- cell more time to increase insulin secretion. α-glucosidase inhibitors decrease the fasting plasma glucose level by 25–30 mg/dl (1.4–1.7 mmol/l) and the hemoglobin A1c value by 0.7–1.0%. Side effects include abdominal discomfort, bloating, diarrhea and flatulence. These agents do not induce hypoglycemia. However, they slow down the absorption of carbohydrates from the intestine and can alter the required timing or dose of other medications such as insulin or meglitinides.

Combination oral agents[34,38,39]

Combination oral agents are combinations which have been recently introduced in the market. These drugs combine either a sulfonylurea (glipizide or glyburide) or a thiazolidinedione (rosiglitazone) with metformin. Because sulfonylureas are associated with potential hypoglycemia, combination agents containing sulfonylureas carry some risk. The combination agent containing rosiglitazone has a minimal risk for hypoglycemia.

6. Dipeptidyl peptidase-4 inhibitors[40,44] (Vildagliptin, Sitagliptin, Saxagliptin)

Dipeptidyl peptidase-4 inhibitors (DPP-4s), also commonly called gliptins, are a relatively new class of drugs for the treatment of Type 2 diabetes. These agents work in a unique way to improve insulin secretion from the β-cells of the pancreas in response to an increase in blood sugar and simultaneously decrease glucagon output from the α-cells of the pancreas, which results in decreased hepatic glucose output. Specifically, gliptins decrease the breakdown of glucagon-like peptide-1 (GLP-1) such that the circulating levels reach the high normal physiologic GLP-1 range. This results in more prompt and appropriate secretion of insulin and suppression of glucagon in response to a carbohydrate-containing meal or snack. The change in glucagon correlates linearly with improvement in glucose tolerance. Since these drugs improve insulin secretion in response to an increase in blood glucose, it seems appropriate to pair them with drugs that have a different mechanism of action, such as insulin sensitizers or metformin. In fact, improvements in fasting and postprandial glucose levels, improved β-cell function, and improvement in HbA1c levels have

been demonstrated in numerous clinical trials using different gliptins as monotherapy and in combination with various Type 2 diabetes medications, including insulin.

7. Newly approved agents for diabetes (Pramlintide, Exenatide)[34,49]

In the few years, newer agents have come on the market for diabetes management such as Pramlintide, which was approved by the Food and Drug Administration in 2005; it is an antihyperglycemic drug for use in diabetic patients who are also treated with insulin.

Pramlintide is a synthetic analog of the hormone amylin. It modulates gastric emptying and prevents the post-prandial rise in plasma glucagon, leading to decreased caloric intake and weight loss. In Type 1 diabetes, destruction of pancreatic beta cells eliminates the production of both insulin and amylin.

Pramlintide injection decreases post-prandial glucose and also decreases cellular oxidative stress, which is a major cause of diabetic complications[41]. Meal time pramlintide treatment as an adjunct to insulin-improved long term glycemic control without inducing weight gain in Type 1 diabetic patients. This can also be used alongside insulin therapy in patients with Type 2 diabetes, improving long term glycemic and weight control. It was found to provide an average reduction in hemoglobin A1c of 0.7% from baseline. It is given by subcutaneous injection twice a day (before large meals). It cannot be mixed with insulin, and should be injected separately. The major side-effect includes hypoglycemia, which can be severe. The Food and Drug Administration requires that the package insert for pramlintide carry a black box warning, clearly identifying the high risk for hypoglycemia.

Exenatide (Byetta)- Exendin-4 is an incretin hormone which is isolated from the salivary secretions of the lizard Heloderma suspectum (Gila monster). The drug exenatide (a synthetic form of exendin-4), approved for use in the U.S. in 2005, it is a 39-amino-acid peptide incretin mimetic which exhibits glucoregulatory activities similar to the mammalian incretin hormone glucagon-like peptide 1. Its actions include glucose- dependent enhancement of insulin secretion, suppression of

inappropriately high glucagon secretion, and reduction of gastric emptying. Exenatide stimulates insulin production in the pancreas in response to post-meal elevations in blood glucose. As insulin is released and blood glucose levels subsequently fall, exenatide allows reduced pancreatic insulin secretion, mimicking the insulin dynamics in patients without diabetes. It is usually injected subcutaneously in a dose of 5 or 10 mcg twice daily, given within 1 h before meals. It can be added to metformin or sulfonylurea or both for patients with less than optimal glycemic control. Side-effects include hypoglycemia when added along sulfonylureas. The most common adverse event is nausea.[34]

POSTMEAL HYPERGLYCEMIA[50,51,52]

Postmeal hyperglycaemia is a very frequent phenomenon in people with Type 1 and Type 2 diabetes and can occur even when overall metabolic control appears to be adequate as assessed by HbA1c.

Poorly controlled diabetes is associated with the development of postmeal hyperglycemia complications as neuropathy, renal failure, vision loss, macrovascular diseases and amputations. Macrovascular complications are the major cause of death in people with diabetes. Furthermore, a strong association between poorly controlled diabetes and depression has been reported, which in turn can create significant obstacles to effective diabetes management.

The progressive relationship between plasma glucose levels and cardiovascular risk extends well below the diabetic threshold. Furthermore, a recent study demonstrated that improvement in glycaemic control significantly reduced the incidence of macrovascular events in people with Type 1 or Type 2 diabetes.

Complications of postmeal hyperglycemia [52,53]

Postmeal and postchallenge hyperglycaemia are independent major risk factors for macrovascular disease. It also causes

- Increased risk of retinopathy.

- Increased carotid intima-media thickness (IMT)
- Oxidative stress, inflammation and endothelial dysfunction.
- Decreased myocardial blood volume and myocardial blood flow
- Increased risk of cancer
- Impaired cognitive function in elderly people with Type 2 diabetes.

Therapies effective in controlling postmeal hyperglycemia[34,36,35]

Diets with a low glycaemic load are beneficial in controlling postmeal plasma glucose. Traditional therapies include the α-glucosidase inhibitors, glinides (rapid-acting insulin secretagogues) and insulin (rapid-acting insulin analogues, biphasic insulins, inhaled insulin, human regular insulin).

In addition, new classes of therapies for managing postmeal plasma glucose in people with diabetes (amylin analogs, glucagon-like peptide-1 [GLP-1] derivatives, dipeptidyl peptidase-4 [DPP-4] inhibitors) have shown significant benefits in reducing postmeal plasma glucose excursions and lowering HbA1c[50].

2. AIM AND OBJECTIVE

The main aim of the present work is

- To design, develop and evaluate the pulsatile drug delivery system for miglitol, an anti-diabetic drug.

- As the chronological behavior of diabetes mellitus confirms increased blood glucose level after meal it is preferable to opt a dosage form which will provide desired concentration of the drug at pre-determined time points. These dosage forms are designed to mimic the circadian rhythm by releasing the drug at the appropriate time, by means of an internal pre programmed design that is initiated when the dosage form comes in contact with gastrointestinal fluids.

- As the postmeal hyperglycaemia is associated with increased risk of retinopathy, increased carotid intima-media thickness (IMT), oxidative stress, inflammation and endothelial dysfunction, decreased myocardial blood volume and myocardial blood flow, increased risk of cancer, impaired cognitive function in elderly people with type 2 diabetes. These pulsatile drug delivery systems are designed to prevent the above mentioned complications caused by postmeal hyperglycemia by delivering the drug immediately after a meal.

- So, the objective of the present study is to formulate and evaluate the pulsatile drug delivery systems for anti diabetic drug (Miglitol) to control the increased blood sugar level by releasing the drug with predetermined lag time (after meals).

3. REVIEW OF LITERATURE

Ishino *et al.*, (1992) [54] studied the absorption of diltiazem in beagle dogs from pulsatile release tablets prepared from diltiazem and a polyvinyl chloride-hydrogenated castor oil-polyethylene glycol mixture as the outer shell of the tablet. The *in vitro* dissolution studies of the prepared tablets exhibited a typical pulsatile pattern with a 7 h lag phase. The results of *in vivo* study in non-fasting beagle dogs suggested that the drug could be released in the gastro intestinal tract as in the *in vitro* test and in fating condition results suggested that the disintegration time of the tablet tended to be influenced by the feeding condition of the subject.

Ishino *et al.*, (1992) [55] prepared a new oral drug delivery system which contains less water permeable outer shell made off with hydrogenated castor oil and PEG 6000 and a swellable core tablet to achieve time controlled or site specific delivery of drug in the gastro intestinal tract. The *in vitro* dissolution study results confirmed that the pulsatile release was obtained with all the tablets and a good correlation was found between the observed lag time and the estimated lag time calculated from an empirical equation deduced from the thickness and PEG 6000 content of the outer shell.

Maggi *et al.*, (1993) [56] discussed the common risk with NSAIDs on GIT. The active substances were formulated in a press-coated tablet in which the inner core contains sodium diclofenac and the outer shell sucralfate. The shell composition includes rapidly disintegrating agents for the prompt release of the mucosal protective agent. Diclofenac release from the core starts only when the outer layer has completely disintegrated. Preliminary *in vivo* studies confirm that the presence of sucralfate does not prevent diclofenac absorption from the GI tract.

Brand *et al.*, (1995) [57] studied the anodal delivery of nicotine from a solution at pH 7.4 using reasonable current densities resulted in considerable enhancement of nicotine transport *in vitro* across hairless mouse skin and extrapolation of this results to 30 cm^2 patch implies that a cigarette worth's(1mg) of drug could be delivered within 30 minutes. In this study, they concluded that the total charge

delivered determined the amount of nicotine crossing across the skin whereas the amplitude of current controlled the initial rate of drug delivery and decreasing the competitor sodium ions improves the amount of nicotine delivered whereas substituting the less mobile calcium ions did not.

Magi *et al.*, (1996) [58] studied the evaluation of stereoselective dissolution of verapamil hydrochloride from matrix tablets press coated with chiral excipients. In this study, HPMC,β-cyclodextrin, hydroxylpropyl β-cyclodextrin and cross linked amylase did not show any stereoselective dissolution properties while with pectin, galactomannan and scleraglucan seemed to give a slightly higher dissolution rate of the R, compared with the S enantiomer. Based on the *in vitro* dissolution study they concluded that the differences in the stereoselective dissolution of the two enantiomers are very little and it is thus fundamental to investigate whether this small variation may lead to effective differences in pharmacokinetics and or drug effect.

Fukui *et al.*, (1996) [59] studied the dissolution profiles of diltiazem hydrochloride release from press coated tablets with hydroxyl propylmethylcellulosee acetate succinate and plasticizers in the outer shell. The evaluation results concluded that press coated tablets with hydroxyl propylmethylcellulosee acetate succinate and water soluble plasticizers-adsorbent in the outer shell would be useful as colon targeting formulations.

Schall *et al.*, (1996) [60] studied the effect of miglitol on the pharmacokinetics and pharmacodynamics of warfarin in healthy males and measured the prothrombin time and clotting factor VII activity. The study results indicated that the concomitant administration of miglitol and warfarin does not affect the pharmacokinetics of R- and S-warfarin, or the pharmacodynamics of warfarin.

Beckert *et al.*, (1996) [61] studied enteric-coated sucrose pellets containing a layer of bisacodyl were compressed into tablets by direct compression using four different filler-binders. Different copolymers based on polymethacrylates were applied as coatings. The quality of the films before and after tableting was evaluated. Results

indicated that the most important parameters were the coating agent and the amount of coating applied to the pellets. Higher coating weights and coatings with better elastic properties lead to formulations, which liberate less bisacodyl after compression. The formulations met all the official requirements for enteric coated preparations.

Ahr *et al.*, (1997) [62] studied Pharmacokinetics of miglitol. Absorption, distribution, metabolism and excretion following administration to rats, dogs and man through different routes and at various doses. They found that on intravenous administration, miglitol was excreted rapidly and completely via the renal route (elimination half-lives of 0.4-1.8 h), no indication was found for a metabolization and it was not bound to plasma proteins. On oral administration miglitol was rapidly and at low doses also completely absorbed, distributed predominantly in the extracellular space and the volumes of distribution were low (0.3-0.8 l/ kg).

Alberti KG and Zimmet PZ (1998) [63] reviewed definition, diagnosis and classification of diabetes mellitus and its complications based on both process and stage of the disease. The processes include Type 1, autoimmune and non-autoimmune, with beta-cell destruction; Type 2 with varying degrees of insulin resistance and insulin hyposecretion.

Ishibashi *et al.*, (1998) [64] developed a new capsule-type dosage form for colon-targeted delivery of drugs by imparting a timed-release function and a pH-sensing function to a hard gelatin capsule. The developed pulsincap consisted of an organic acid together with an active ingredient coated with a three-layered film of an acid-soluble polymer, a water-soluble polymer and an enteric polymer. Based on the results they found that (1) various organic acids could be used for this system; (2) a predictable timed-release mechanism of a drug could be attained by adjusting the thickness of the eudragit layer; and (3) the outer enteric coating with HPMC provided acceptable acid-resistibility.

Krogel *et al.*, (1998) [65] developed and evaluated pulsatile drug delivery system base on an impermeable capsule body filled with drug and an erodible plug placed in the

opening of the capsule body. Based on the evaluation results they concluded that the pulsatile drug release was controlled by the erosion properties of a compressed or congealed plug placed within the opening of capsule body.

Bodmeier *et al.*, (1999) [66] designed and evaluated floating /pulsatile drug delivery systems based on a reservoir system consisting of a drug-containing effervescent core and a polymeric coating. The results of the developed floating system showed that, the polymeric coating did not retard the drug release and the polymer (cellulose acetate or HPMC) was added to the core to control the drug release. The time to floatation could be controlled by the composition and hardness of the tablet core and the composition (type of polymer and plasticizer) and thickness of the coating.

Adler et al., (2000) [67] determined the relation between systolic blood pressure over time and the risk of macrovascular or microvascular complications in patients with Type 2 diabetes. They concluded that in patients with Type 2 diabetes the risk of diabetic complications was strongly associated with raised blood pressure and any reduction in blood pressure was likely to reduce the risk of complications, with the lowest risk being in those with systolic blood pressure less than 120 mm Hg.

Reddy *et al.*, (2000) [68] made a review on newer oral antidiabetic drugs. In this article they discussed about the limitations of currently available pharmacological agents for control of blood glucose and the newer drugs, already developed or in the process of development for management of Type 2 diabetes.

Gin H and Rigalleau V (2000) [69] studied the relationship between post-prandial hyperglycemia and diabetes. In this review they concluded that the postprandial blood glycemia excursion is a complex phenomena that depends on a variety of factors including the composition of food, gut hormones, digestive enzymes, hepatic glucose production and its inhibition and peripheral glucose uptake.

Makino *et al.*, (2000) [70] developed a pulsatile release delivery system of estradiol microspheres using poly (lactide-co-glycolide), of which the monomer composition was 75% lactide and 25% glycolide. They observed that when estradiol was loaded in microspheres consisting of poly (lactide-co-glycolide) of average molecular

weight of 74 000 before degradation, the pulse of estradiol release was observed almost 50 days after the initial burst. On the other hand, if poly (lactide-co-glycolide) of MW 44 000 before degradation was used as a material to prepare the microspheres, then estradiol was released in a pulsatile manner almost 20 days after the initial burst effect. The results of evaluation revealed that that the time interval between the initial burst and the pulsatile release can be regulated by mixing the above two types of poly (lactide-co-glycolide) with different MW to prepare microspheres.

Fukui *et al*., (2000) [71] developed a enteric coated timed-release press-coated tablets using an outer shell of HPC and core tablet containing diltiazem HCL. The results of *in vitro* dissolution tests in pH 1.2 and pH 6.8 buffers indicated that these tablets showed both acid resistance and timed release.

Thomas *et al*., (2000) [72] studied the effect of miglitol on metformin-induced fall in serum folate and vitamin B_{12} in subjects with Type 2 diabetes. The evaluation data supported the hypothesis that increased carbohydrate delivery to the colon increases intestinal biosynthesis of folate. The results concluded that the combination of miglitol with metformin may prevent the metformin-induced fall in serum folate and vitamin B_{12}.

Alistair *et al*., (2000) [73] formulated a pulsatile capsule for chronopharmaceutical drug delivery based on programmable erosion mechanism. In this study the drug propranolol HCl formulation was sealed inside the insoluble capsule body by an erodible tablet (ET). The results of this study concluded that both composition and weight of ET influence the time of drug release. The drug release of the developed formulation was controlled by the quantity of HPMC, irrespective of lactose content within the tablet.

Makino *et al*., (2000) [74] developed pulsatile release of estradiol from poly (lactide-co glycolide) microspheres, of which the monomer composition was 75% lactide and 25% glycolide. When estradiol was loaded in microspheres consisting of poly

(lactide-co-glycolide) of average molecular weight of 74000 before degradation, the pulse of estradiol release was observed almost 50 days after the initial burst.

Sarasija *et al.*, (2000) [75] studied the colon specific delivery of drugs for the treatment of colonic diseases, so as to maximize the effectiveness of these drugs. Oral delivery of peptides and proteins are possible because colon provides a friendlier environment than the upper GI tract. This review deals with the anatomy and physiology of colon and various aspects of formulations by which colon targeting of drugs can be achieved.

Fukui *et al.*, (2000) [76] developed a new oral drug delivery system for colon targeting, enteric coated timed-release press-coated tablets by coating enteric polymer on timed-release press-coated tablets composed of an outer shell of hydroxypropylcellulose and core tablet containing diltiazem hydrochloride as a model drug. The results of the *in vitro* dissolution tests in JP 1st fluid (pH 1.2) and JP 2nd fluid (pH 6.8) indicated that the tablets showed both acid resistance and timed-release. The results seemed to be in accordance with the time at which the tablets reached the colon after gastric emptying.

Fukui *et al.*, (2000) [77] prepared various types of press-coated tablets, containing diltiazem hydrochloride coated with HPC. The results indicated that tablets with the timed-release function could be prepared, and that the lag times were prolonged as the viscosity of HPC and the amount of the outer shell were increased. Two different kinds of timed-release press-coated tablets showed lag times of 3 and 6 h in the *in vitro* test were administered to beagle dogs. This suggested that the effects of gastrointestinal peristalsis and contraction should also be taken into consideration for the further development of drug delivery systems.

Sangalli *et al.*, (2001) [78] carried out the *in vitro* and *in vivo* evaluation of an oral system for time and or site specific drug delivery system. The in vitro dissolution release profile of tablets prepared with methocel E50 as retarding polymer suggested that the predetermined lag phase, the duration of which depends upon the thickness

of polymeric layer applied over the core tablet and the *in vivo* results confirmed that the the release of drug in the gastro intestinal tract after a predetermined lag time.

Fan *et al*., (2001) [79] designed a pulsatile release system of diltiazem hydrochloride containing ethylcellulose and eudragit L as film coating materials and cross linked polyvinylpyrrolidone in the core tablets. The *in vitro* dissolution results concluded that the lag time was prolonged with an increase of coating level, whereas the drug release rate was almost constant, irrespective of the coating level. The water uptake study and electron microscope photographs suggested the mechanism of pulsatile drug release of drug.

Fukui *et al*., (2001) [80] developed a new colon targeting formulation, which suppresses drug release completely during 12 h in the stomach and release the drug rapidly after a lag time of 3±1h in the small intestine, the use of press-coated tablets with HPMCAS in the outer shell was investigated. The release of diltiazem hydrochloride as a model drug contained in the core tablets in the 1st fluid (pH 1.2) was suppressed with higher compression force, but the lag time in the 2nd fluid (pH 6.8) could not exceed 1.5 h. The results indicated that HMC tablets with a mixing ratio of 80% HPMCAS, 5-15% MgSt and 15-5% CaSt in the outer shell met the desired criteria and the lag time in 2nd fluid could also be controlled from 2 to 9 h. At a mixing ratio of 80% HPMCAS, 10% MgSt and 10% CaSt, the dissolution profiles of DIL in 1st fluid and 2nd fluid were not remarkably affected by agitation intensity, and addition of bile salts, pretreatment time or anticipated higher pH except for pH 6.0, respectively.

Lin *et al*., (2001) [81] investigated the influence of compression forces to inner core tablet or to outer coating layer of the compression-coated tablet on the function of time-controlled disintegration also investigated. The inner core tablet was directly compacted by sodium diclofenac (model drug) and ethylcellulose (EC) with 4.6-microm particle size ware used as an outer coating layer. The effect of the amount of the outer coating layer used on the drug release was examined. The study demonstrates that the time-controlled disintegration of the compression-coated tablet

was effectively controlled by the compression force applied and the amount of outer coating layer added.

Lin *et al.*, (2001) [82] formulated novel dry coated tablet with time controlled drug release using ethylcellulose of varying particle sizes. This dry-coated tablet, containing a core tablet of sodium diclofenac and an outer coating layer of EC, was prepared by direct compression. The drug release from dry-coated tablet exhibited an initial lag period that was dependent on the particle size of the EC powder, The results suggested that these dry-coated tablets prepared with different particle sizes of EC powder as an outer coating layer might offer a desirable release profile for drug delivery at the predetermined times and/or sites.

Stevens *et al.*, (2002) [83] prepared pulsincap formulations containing dofetilide to deliver a dose of drug following a 5-hrs delay and evaluated the capability of the formulation to deliver dofetilide to the lower gastro intestinal tract. The results showed that the preparations were well dispersed and the release was delayed up to 5 hrs.

Kikuchi *et al.*, (2002) [84] reviewed several types of drug delivery systems using hydrogels are discussed that showed pulsed and/or pulsatile drug delivery characteristics and the importance to develop new drug delivery devices to achieve pulsed delivery of a certain amount of drugs in order to mimic the function of the living systems, while minimizing undesired side effects. Development of modified alginate gel beads with pulsed drug delivery characteristics and thermal stimuli-regulated pulsed drug release were also described in this article.

Krishnaiah *et al.*, (2002) [85] developed a colon targeted oral compression coated tablets of 5-fluorouracil using 60%, 70% and 80% of guar gum as carrier and were subjected to *in vitro* drug release studies. The results showed that compression-coated tablets containing 80% of guar gum were most likely to provide targeting of 5-fluorouracil for local action in the colon, since they released only 2.38% of the drug in the physiological environment of the stomach and small intestine.

Pignatello *et al.*, (2002) [86] formulated and evaluated polymeric nanoparticle suspensions from Eudragit S100 and L100 polymer resins and loaded with flurbiprofen (FLU), with the aim at improving the availability of the drug at an intra-ocular level for the prevention of the myosis induced during extracapsular cataract surgery.

Lin *et al.*, (2002) [87] examined the effect of excipient, drug, and osmotic agent loaded in the inner core tablet on the time-controlled disintegration of compression-coated tablet prepared by direct compression with micronized ethylcellulose. The excipients [spray-dried lactose, hydroxypropyl methyl cellulose, sodium starch glycolate, microcrystalline cellulose, different drugs (sodium diclofenac: model drug, salbutamol sulfate, and theophylline anhydrate) and osmotic agent (sodium chloride)] were used to formulate the composition of the inner core tablet. The result implies that osmotic function is more suitable than superdisintegration function in designing a compression-coated tablet with time-controlled disintegration.

Turkoglu M and Ugurlu T (2002) [88] reported the pectin-HPMC compression coated core tablets of 5-aminosalicylic acid (5-ASA) for colonic delivery. Each 100 mg core tablet contained 5-ASA and was compression coated at 20 kN or 30 kN using 100% pectin, 80% pectin-20% HPMC, or 60% pectin-40% HPMC, at two different coat weights as 400 or 500 mg. The system was designed based on the gastrointestinal transit time concept, under the assumption of colon arrival times of 6 h. It was found that pectin alone was not sufficient to protect the core tablets and HPMC addition was required to control the solubility of pectin. The optimum HPMC concentration was 20% and such system would protect the cores up to 6 h that corresponded to 25-35% erosion and after that under the influence of pectinase the system would degrade faster and delivering 5-ASA to the colon. The pectin-HPMC envelope was found to be a promising drug delivery system for those drugs to be delivered to the colon.

Bussermer *et al.*, (2002) [89] evaluated the swelling, hydration and rupturing properties of the swelling layer of a rupturable pulsatile drug delivery system. The results concluded that a linear correlation existed between the swelling energy and

water uptake. They identified Ac-Di-Sol as the best choice for a rupturing release system.

Bussemer T and Bodmeier T (2003) [90] developed a rupturable pulsatile drug delivery system based on soft gelatin capsules with or without a swelling layer and an external water-insoluble but permeable polymer coating, which released the drug after a lag time (rupturing of the external polymer coating). They studied that Croscarmellose sodium (Ac-Di-Sol) was more effective as a swelling agent than low and high molecular weight hydroxypropylmethyl cellulose (HPMC; E5 or K100M). Ethyl cellulose (EC) and cellulose acetate propionate (CAPr) showed better rupturing and more complete drug release than Eudragit RS. They also concluded that the lag time of the release system increased with higher polymer coating levels and decreased with the addition of a hydrophilic pore-former, HPMC E5 and also with an increasing amount of the intermediate swelling layer. The water uptake of the capsules was linear until rupture and was higher with CAPr than with EC.

Sinha *et al.*,(2003) [91] performed a comparative study of various polymers such as eudragit, cellulose acetate phathalate, shellac and ethyl cellulose based on its *in vitro* drug release characteristics to achieve the drug release in the colon. The results revealed that, of all the polymers and coat thicknesses used, a 3% coat of shellac was most suitable for colonic drug delivery. It retarded drug release by 3-4 h (the usual small intestinal transit time) in simulated small intestinal fluid, whereafter a rapid drug release was observed

Krishnaiah *et al.*,(2003) [92] performed a study on the development of colon targeted oral drug delivery systems for Ornidazole in the treatment of amoebiasis by using guar gum as carrier. In this study they observed that the compression-coated formulations with 85%, 75%, and 65% of guar gum coat released about 21%, 38%, and 73% of ornidazole respectively in simulated colonic fluids and less than 8% of ornidazole in the physiological environment of stomach and small intestine. The results of the study showed that compression-coated ornidazole tablets with either 65% or 75% of guar gum coat were found to be suitable for targeting colon.

Mura *et al.*, (2003) [93] developed a new colonic drug delivery system which takes advantage of the combined approaches of a specifically enteric coated colon-biodegradable pectin matrix of theophylline with pH sensitive Eudragit S 100 polymeric coating. They found that the developed system was able to suitably retard the onset of drug release and provided a colon targeting which overcome the problems of pectin solubility in the upper GI tract and low site-specificity of simple pH-dependent systems.

Bussemer *et al.*, (2003) [94] developed a pulsatile delivery system based on drug-containing hard gelatin capsules, which is coated with a swelling layer and an outer insoluble, water-permeable polymeric coating. An inner pressure developed by the swelling layer resulted in the rupture of the outer coating. Preliminary studies with a simulated rupture test demonstrated the dependence of the lag time prior to rupture on the properties of the coating, such as its water permeability and mechanical strength. The lag time increased with a higher coating level, but decreased with the addition of the hydrophilic pore former, hydroxypropyl methylcellulose. Increasing the amount of the swelling layer decreased the lag time. A hydrophobic particulate material, magnesium stearate, was added to the coating layer to reduce the mechanical strength and therefore the lag time.

Sawada *et al.*, (2003) [95] improved the bioavailability of drug in tablets, the effect of their core composition of compression-coated tablet on *in vivo* pharmacokinetics, although compression-coated tablets are a commonly used timed-release drug delivery technology, their utility is often limited by poor bioavailability. These results suggested that a formulation with a large core erosion ratio can significantly increase in vivo drug release from compression-coated tablets, leading to increased drug absorption from the lower GI tract.

Shimizu *et al.*, (2003) [96] developed enteric-coated microgranules for the lansoprazole fast-disintegrating tablet (LFDT), which is a rapidly disintegrating tablet containing enteric-coated microgranules comprising seven layers: 1) core, 2) active compound layer, 3) intermediate layer, 4) first enteric layer, 5) second enteric layer, 6) third enteric layer, and 7) over coating layer. The enteric-coated

microgranules have the multiple functions of reducing the damage to the enteric layer during the compression process, improving the stability of lansoprazole, and masking the unpleasant bitter taste.

Samantha *et al.*, (2004) [97] developed salbutamol sulphate pulsincap to target the drug release in the colon and evaluated for its in vitro drug release. The results indicated that the onset of drug release was started after 7 to 8 hrs lag time.

Li *et al.*, (2004) [98] studied modulation of combined release behaviors from a novel tablet in capsule system. They developed a multiple unit system containing versatile mini tablets in a hard gelatin capsules. The evaluation results of prepared multi functional and multiple unit system concluded that programmed DDS can be modified by adding the v-t equations of various minitablets to calculate the theoretical equations and implement them.

McConvillea *et al.*, (2004) [99] investigated the effect of wet granulation on the erosion behavior of an HPMC–lactose tablet, used as a rate-controlling component in a pulsatile drug delivery capsule formulation for propranolol. They concluded that at low HPMC concentrations water mobility was at its greatest during the granulation process, such formulations were therefore more sensitive to processing techniques. Microwave dielectric analysis wer used to predict the degree of polymer spreading in an aqueous system, by determination of the water-dipole relaxation time.

Sungthongjeen *et al.*, (2004) [100] developed and evaluated pulsatile release tablets consisting of core coated with two layers of swellable and rupturable polymers such as croscarmellose sodium and ethylcellulose. The effect of core composition, level of swelling layer and rupturable coating and magnesium stearate in rupturable layer were investigated. They concluded that the lag time of the pulsatile release tablets decreased with increasing amount of microcrystalline cellulose in the core and increased with increasing levels of both swellable layer and rupturable ethylcellulose coating. Increasing levels of the ethylcellulose coating retarded the water uptake and thus prolonged the lag time.

Freiberg *et al.*, (2004) [101] studied the effect of polymer microspheres in a rate-controlled and sometimes targeted manner. Medication is released from a microsphere by drug leaching from the polymer or by degradation of the polymer matrix. In this method the preparation of microspheres from monomers or from linear polymers and discusses the physico-chemical properties that affect the formation, structure, and morphology of the spheres.

Lin *et al.*, (2004) [102] prepared oral press-coated tablet by direct compression to achieve the time-controlled disintegrating with predetermined lag time. This press-coated tablet containing sodium diclofenac in the inner core was formulated with an outer shell by different weight ratios of hydrophobic polymer of micronized ethylcellulose (EC) powder and hydrophilic excipients such as spray-dried lactose (SDL) or hydroxypropyl methylcellulose (HPMC). The effect of that formulation of an outer shell comprising both hydrophobic polymer and hydrophilic excipients on the time lag of drug release was investigated. The predetermined time lag prior to the drug release from a press-coated tablet prepared by using a micronized EC as a retarding coating shell can be adequately scheduled with the addition of hydrophilic excipients according to the time or site requirements.

Peerapattana *et al.*, (2004) [103] prepared a colon drug delivery system using dry-coated time-controlled disintegration wax matrix tablets. Indomethacin is used as a model drug. Behenic acid and lactose were used as coating materials. The effects of lactose content and pH of the dissolution medium on drug release were investigated. Four formulations of wax matrices containing different percentages of lactose in the surface layer, i.e. 70, 65, 60 and 55, were prepared. The lag times of indomethacin release from the matrices in 0.05 M phosphate buffer pH 7.4 were 50, 162, 294 and 539 minutes for formulations containing 70, 65, 60 and 55% lactose, respectively.

Ouyang *et al.*, (2005) [104] developed metformin/glipizide elementary osmotic pump tablets using sodium bicarbonate as osmogen and reported that the EOP was found to deliver both drugs at a rate of approximately zero order for up to 10 h in pH 6.8 and produced a good sustained effect in comparison with the conventional product

Saydah et al., (2006) [105] *invesigated on Postchallenge hyperglycemia and mortality in a national sample of U.S. adults* to assess the independent association of fasting and 2-h glucose levels with all-cause and cardiovascular disease (CVD) mortality. The results suggested that postchallenge hyperglycemia is associated with increased risk of all-cause and CVD mortality independently of other CVD risk factors.

Mohamad *et al.*, (2006) [106] formulated and evaluated multiparticulate drug delivery systems for propranolol HCL, coated with aqueous dispersion aquacoat ECD. A sustained release was achieved after a lag time, when low substituted hydroxy propyl cellulose and sodium starch glycolate were used as swelling agents. The results concluded that the addition of talc is very advantageous due to reduced sensitivity of lag time to the variations in the coating level and completeness of rupturing.

Sharma S and Pawar A (2006) [107] prepared the low density multiparticulate systems for pulsatile drug release of meloxicam using calcium silicate and sodium alginate for time and site specific drug delivery. The developed formulations showed instantaneous floating with very less drug release in acidic medium followed by a pulse release in simulated intestinal fluid. Quantity of porous carrier and concentrations of sodium alginate solution significantly affected the performance of beads. The developed systems offeres a simple and novel technique for pulse release of meloxicam in upper part of small intestine.

Efentakis M *et al.*, (2006) [108] designed a novel core in cup pulsatile drug delivery system and evaluated. The formulation consisted of a core tablet containing the active ingredient, an impermeable outer shell and a top cover layer barrier of a soluble polymer. They have investigated the effect of the core, the polymer characteristics and quantity of the top cover layer on the lag time and drug release. The results confirmed that these systems might offer a desired release profile for drug delivery at predetermined times.

Dashevsky *et al.*, (2006) [109] prepared and evaluated a pulsatile multiparticulate drug delivery system of theophylline, coated with aqueous dispersion Aquacoat® ECD.

They prepared the rupturable pulsatile drug delivery system of theophylline which consists of swellable layer, comprising a superdisintegrant and an an insoluble, water-permeable layer (ethyl cellulose). They concluded that the crosscarmellose sodium as preferable superdisintegrant because of its pH dependant swelling characteristics and controlled lag time followed by a quick and complete drug release. The pH independant swelling of crosscarmellose sodium and thus pH independant lagtimes of rupturable pulsatile capsule system could be achieved by adding fumaric acid to the swelling layer allowing control over the micro-environmental pH.

Shivakumar *et al.*, (2006) [110] formulated a pH sensitive multi-particulate pulsatile drug delivery system of diltiazem hydrochloride. In this the drug loaded core pellets were produced by aqueous extrusion spheronization technique using microcrystalline cellulose as a spheronizing aid and PVP K 30 as a binder. Different coat weights of Eudragit S-100 were applied to the drug loaded pellets.The *in vitro* dissolution studies of the coated pellets showed that the drug release from the coated pellets depended on the coat weights applied and pH of the dissolution media. The evaluation results revealed that the developed formulations effectively releases the drug at colonic pH only with higher coat loads (15-20% weight gain).

Karavas *et al.*, (2006) [111] prepared pulsatile release formulations consisting of two-layered tablets consists of active core constituted by a FELO/PVP 10/90 w/w solid dispersion coated with PVP/HPMC blends at different compositions, acted as a stimulus responsible layer. The evaluation results concluded that the coating layer disintegrates first, followed by the immediate release of FELO from the active core and the delaying time is based on combination of swelling and erosion of the PVP/HPMC polymer blends.

Orlu *et al.*, (2006) [112] formulated novel colon specific drug delivery system of microsponges containing flurbiprofen and Eudragit RS 100 by quasi-emulsion diffusion method. The colon specific formulations were prepared by compression coating and also pore plugging of microsponges with pectin: hydroxypropylmethyl cellulose (HPMC) mixture followed by tableting and then in vitro dissolution studies

were done on all formulations and the results were kinetically and statistically evaluated.

Akhgari *et al.*, (2006) [113] studied the combination of pH-dependent and time-dependent polymers as a single coating for colon delivery of indomethacin pellets. In that Eudragit S100 and Eudragit L100 were used as pH-dependent polymers and Eudragit RS was used as a time-dependent polymer. Factorial design was used to optimize the formulations. Dissolution studies of the pellets in the media with different pH showed the drug release in colon could be controlled by addition of Eudragit RS to the pH-dependent polymers. The lag time prior to drug release was highly affected by coating level. With combination of two factors, i.e. the percent of Eudragit RS and coating level, the optimum formulation was found to be the one containing 20% Eudragit RS, 64% Eudragit S and 16% Eudragit L, and a coating level of 10%. The results of *in vitro* experiments indicated that the proposed polymer coating may provide a colonic delivery system for indomethacin.

Efentakis M and Politis S (2006) [114] designed and evaluated controlled release systems with various structures using hydropolymers as drug carriers. The findings indicated that all systems exhibit controlled release characteristics. Furthermore, the structure of the device appears to significantly affect its release rate. The hybrid systems exhibited pulsatile release. The materials used in their study considerably influenced the behavior and function of the system. These effects may be attributed to the nature and the properties of the materials employed.

Mealey BL and Ocampo GL (2007) [115] made a review on diabetes mellitus and periodontal disease. In this article they focused on several etiologies for diabetes, type of diabetes, pathophysiology of the various forms of the disease, current classification of diabetes and various approaches in the treatment of diabetes mellitus etc.

Li *et al.*, (2007) [116] developed a novel system for the three pulse drug release based on tablet in capsule device using sodium alginate and hydroxy-propyl methyl cellulose (HPMC E5) as barrier material to achieve desired lag time. Based on the

evaluation study they concluded that the types of materials used and its concentration can significantly affect the lag time. The results of the study revealed that developed system can be used for daily programmed drug delivery for three pulses

Mastiholimath *et al.*, (2007) [117] designed and evaluated the pulsatile drug delivery system using pulsincap technology. The developed formulations releses the drug over a period of 2–24 h, consistent with the requirements for chronopharmaceutical drug delivery from insoluble gelatin capsules, in which microencapsulated theophylline was sealed by means of a suitable hydrogel plug. The gamma scintigraphic study pointed out the capability of the system to release drug in lower parts of GIT after a programmed lag time for nocturnal asthma.

Pawar *et al.*, (2007) [118] developed hollow calcium pectinate beads for floating-pulsatile release of diclofenac sodium intended for chronopharmacotherapy.In this study floating pulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release. The results concluded that the developed formulation released the drug continuosly after a lag time that would be beneficial for chronotherapy of rheumatoid arthritis and osteoarthritis.

Ghimire *et al.*, (2007) [119] investigated the *in vitro* and *in vivo* performance of a press-coated tablet (PCT) of theophylline core tablet, with barrier granules containing glyceryl behenate (GB) and low-substituted hydroxypropylcellulose (L-HPC). The PCTs showed pulsatile release with a lag time dependent upon the composition of the barrier layer. *In vivo* gamma-scintigraphic studies were carried out in beagle dogs, in either the fed or fasted state. The *in vivo* lag time in both the fed and fasted states did not differ significantly ($p > 0.05$) from the in-vitro lag time and no significant difference ($p < 0.05$) between in vivo fed and fasted disintegration times was observed, demonstrating that *in vivo* performance of the PCT was not influenced by the presence or absence of food.

Liua *et al.*, (2007) [120] developed a pulsatile release of parathyroid hormone from an implantable delivery system with a biodegradable polymer, poly(Llactic acid)

(PLLA) and an isolation layer composed of sebacic acid, 1,3-bis(p carboxyphenoxy) propane and poly(ethylene glycol). The polyanhydride isolation layers and PTH-loaded alginate layers were then stacked alternately within the delivery device. The results concluded that multi-pulse PTH release was achieved using the developed implantable device and the lag time between two adjacent pulses were modulated by the composition and the film thickness of the polyanhydride. The released PTH was demonstrated to be biologically active using an in vitro assay.

Sindhu *et al.*,(2007) [121] developed a modified pulsincap dosage form of metronidazole to achieve drug release in the colon. The results indicated that significant drug release was achieved after a lag time of 5 hours. Thus, metronidazole could be successfully targeted to colon by using modified pulsincap, thereby reducing systemic side effect.

Lanjhiyana *et al.*, (2007) [122] prepared a piroxicam modified pulsincap to achieve time dependent site specific delivery of Piroxicam into colon which is used in inflammatory bowel diseases. Dissolution studies demonstrated that polymeric coated capsule were gastro-resistant for an average time of 5 to 6 h post dose was found to be dependent on the polymeric coating layers of HPMC and Eudragit l-100 and on the concentration of guar gum, which is highly susceptible to colonic microfloras. The capsules having optimized 30% of guar gum and polymeric coating ratios with and without 4% rat caecal in PBS pH 7.4 suggested the susceptibility of polymers to the colonic microfloras.

Abraham *et al.*, (2007) [123] formulated modified pulsincap drug delivery system of diclofenac sodium, to develop time dependent colon specific drug delivery system called modified pulsincap by using hydro gel polymers, HPMC, HPC, Sodium alginate and cellulose acetate phthalate. The colon specific drug delivery was assessed by in vitro drug release studies in simulated gastric fluid for 2 hrs, simulated intestinal fluid for 3 hrs & simulated colonic fluid for 7 hours. The enteric coating and cap of the capsule dissolved in simulated intestinal fluid, exposing the hydrogel plug and facilitated slow and controlled release of the drug from the pellets in the colonic medium. The accelerated stability studies carried out for three months

as per ICH guidelines and proved that the developed pulsincap formulations were stable.

Abraham S and Srinath MS (2007) [124] developed a modified Pulsincap dosage form of metronidazole to target drug release in the colon. The formaldehyde treated bodies of the capsule were incoroporated with metronidazole pellets and plugged with polymers guar gum, HPMC 10K, carboxymethylcellulose sodium and sodium alginate separately at concentrations 20 mg, 30 mg and 40 mg. The filled capsules were completely coated with 5% cellulose acetate phthalate to prevent variable gastric emptying. The *in vitro* drug release results confirmed that significant drug release occurred only after 5 h from the start of experiment.

Abbaspour *et al.*, (2007) [125] prepared pellets by using extrusion-spheronization technique with ibuprofen (40, 60 and 80%) and Eudragit RS PO/RL PO (0%, 50% and 100%). The pellets were cued in oven at 60ºC for 24h. The cured pellets were compressed at 15kN compaction force. It was shown that the cured pellets containing 40% or 60% drug exhibited a plastic deformation without any fracture under mechanical tests. The curing process resulted in significant decrease in the elastic modulus of the pellets. The SEM of the compressed pellets were also confirmed the plastic behavior of these pellets. Increasing the ratio of Eudragit RS in the pellets decreased the yield point and elastic modulus of cured pellets containing 40% or 60% drug, indicating more plastic behavior of these pellets. This was attributed to lower Tg of Eudragit RS than Eudragit RL. Overall the results of the study revealed that thermal treating is a proper tool to produce plastic ibuprofen pellets based on Eudragit RS PO and Eudragit RL PO.

Ibrahim *et al.*, (2007) [126] developed a simple and sensitive kinetic spectrophotometric method was established for the determination of acarbose and miglitol in bulk and in their pharmaceutical preparations using alkaline potassium permanganate as an oxidizing agent.The developed method was successfully applied for the determination of these drugs in their dosage forms. The results obtained were in good agreement with those obtained with the reference methods.

Frode TS and Medeiros YS (**2008)** [127] reviewed the available animal models of diabetes and some in vitro models which have been used as tools to investigate the mechanism of action of drugs with potential antidiabetic properties. This review contributed to the researcher in the ethnopharmacology field to design new strategies for the development of novel drugs to treat this serious condition that constitutes a global public health.

Schellekens *et al.*, (2008) [128] developed Pulsatile drug delivery to ileo-colonic segments by structured incorporation of disintegrants in pH-responsive polymer Eudragit S coatings .The in vitro drug release results concluded that the structured incorporation of swelling agents in pH-responsive polymers improves the delayed, pulsatile release kinetics of coated capsules. The in vivo study results confirmed that the newly developed coating enables pulsatile delivery of the content to the lower parts of the intestines.

Maeda *et al.*, (2008) [129] designed and developed nicorandil pulsatile release tablets by fumaric acid dry coating around the core tablet including nicorandil. The results showed that the the washburn equation could be used to design the lag time of pulsatile release tablet in this study. The *in vitro* dissolution results concluded that the novel release technology using fumaric acid was appropriate to obtain nicorandil pulsatile release tablets that has well regulated lag time.

Intra *et al.*, (2008) [130] demonstrated, a robust novel polydimethylsiloxane (PDMS) chip that can provide controlled pulsatile release of DNA based molecules, proteins and oligonucleotides without external stimuli or triggers. Poly(lactic acid-co-glycolic acid) (PLGA) polymer films of varying composition and thickness were used as seals to the wells. The composition, molecular weight and thickness of the PLGA films were all parameters used to control the degradation rate of the seals and therefore the release profiles. Finally they concluded that the PDMS chip was shown to provide repeated sequential release of CpG oligonucleotides and a model antigen, Ovalbumin (OVA), indicating significant potential for this device for vaccinations or applications that require defined complex release patterns of a variety of chemicals, drugs and biomolecules.

Lin *et al.*, (2008) [131] characterized the influence of core and coat formulations on the release profiles to establish *in vitro/in vivo* correlations of a pulsatile drug delivery system activated by membrane rupture based on three core tablet formulations coated with various thicknesses of a semipermeable ethylcellulose membrane plasticized with HPMC 606 (Pharmacoat 606). Based on the *in vitro/in vivo* correlation they concluded that the desired lag time can be adjusted by the thickness and the hydrophilicity of the coated membrane and the release rate after the lag time can be adjusted as a pulsatile release pattern.

Law D and Zhang Z (2008) [132] developed a new formulation in order to stabilize NKCP in powders and to control its release rate when it passes through the gastrointestinal tract of human. NKCP powders were first compacted into a tablet, which was then coated with a mixture of an enteric material Eudragit L100-55 (EL100-55) and HPC by direct compression. The activities and release of the enzyme were determined using amidolytic and bicinchoninic acid assay. Results have shown that the activity of NKCP was pressure independent and the coated tablets protected NKCP from being denatured in the gastric juice, and realized its controlled release to the intestine based on in vitro experiments.

Kangarlou *et al.*, (2008) [133] investigated the physico-mechanical characteristics of the EC-based coating membranes plasticized with cholecalciferol and alpha-tocopherol, with respect to the commercial plasticizer DBS. The results implied the great compatibility of the oil soluble vitamins in EC networks projecting higher factors of safety and greater ultimate strength, toughness.

Wakode *et al.*, (2008) [134] developed osmotic drug delivery system for drug pramipexole with varying concentration of pore forming agents to get controlled release of pramipexole. Osmotic pressure generated was determined using osmometer and was found to be linear with drug release. The osmotic pressure developed was found to be linearly proportional to time and concentration of osmotic agent.

Deshpande *et al*., (2009) [135] desisigned the contolled release, bio adhesive formulations of miglitol using ethyl cellulose as release retardant and HPMC as bioadhesive polymer. The formulations successfully regulated the post prandial glucose level after two consecutive meals and also during the time interval between the consecutive meals.

Deshpande *et al*.,(2009) [136] designed and evaluated the oral bio adhesive controlled release formulations of miglitol, intended for prolonged inhibition of intestinal α-glucosidases and enhancement of plasma glucagon like peptide-1 levels. The results concluded that the prepared multi layered tablets of miglitol, displayed a significantly better control of post prandial glucose in comparison to placebo or immediate release formulations.

Abhinav *et al*., (2009) [137] investigated the dissolution and bioavailability characteristics of an anti-diabetic drug, glimepiride. The tablets containing solid dispersion products were formulated and compared with the commercial product. The results of this study revealed that there was significant improvement in the dissolution of glimepiride in solid dispersion products and exhibited better dissolution profile than commercial tablets.

Singh *et al*., (2009) [138] developed mucoadhesive microcapsules of pioglitazone HCL using sodium alginate as a shell forming polymer and carbopol 974, HPMC, sodium CMC, as a mucoadhesive polymer for the potential use of treating acute and chronic diabetes mellitus. From the results, it was concluded that the drug release from these mucoadhesive microcapsules was slow and extended over longer periods of time, depending on the compositions of the coat.

Gayatri CP and Madhabhai MP (2009) [139] developed modified pulsincap system of diclofenac sodium and reported that it could be beneficial to the chronotherapy of rheumatoid arthritis as it has demonstrated programmable, time and pH dependent, site specific drug release and offered effective controlled release alternative to traditional dosage forms.

Shiohira *et al.*, (2009) [140] developed a new chronotherapeutic pharmaceutical preparation as a sustained release suppository for prevention and therapeutic use against bronchial asthma in the early morning using sodium alginate (Alg-Na), sodium polyacrylate (PANa) or polyacrylate-PANa co-polymer (PA-PANa) as gelling polymers (gel agent) and investigated. The evaluation results concluded that developed sustained-release suppository for chronotherapy of theophylline using oily base material in combination with polymer such as PAPANa was found to be suitable. .

Shahiwala A and Roy P (2009) [141] developed ranitidine HCl floating pulsatile delivery system. In this study, investigated the functionality of the outer polymer coating to predict lag time and drug release statistically using the response surface methodology (RSM). The optimum ratios of ethyl cellulose to hydroxypropyl methyl cellulose in the coating formulation and coating level (% weight gain) were optimized with a 3^2 full factorial design. The results revealed that both, the coating composition and coating level, are significant factors affecting drug release profile.

Janugade *et al.*, (2009) [142] developed press-coated montelukast sodium tablets for pulsatile drug delivery systems using hydrophilic and hydrophobic polymers. They investigated the effect of hydrophobic and hydrophilic polymer on the lag time of drug release and it was observed that lag time decreases with increasing concentration of hydrophilic polymer.

Praveen *et al.*, (2009) [143] studied the modulation and optimization of drug release from uncoated low density porous carrier based delivery system. The study was carried out to explore an application of uncoated porous drug carrier prepared by single step drug absorption for a delivery system based on integration of floating and pulsatile principles intended for chronotherapy.

Nayak *et al.*, (2009) [144] developed pulsatile capsule dosage form of valsartan for controlled delivery. The prepared system contained swellable polymer (L HPC, xanthan gum, polyethylene oxide or sodium alginate) together with drug tablet and erodible tablet (L-HPC or guar gum) in a pre-coated capsule. The results concluded

that the formulation containing 200 mg sodium alginate and erodible tablet (150 mg) containing 50% guar gum and 46% lactose were found to be suitable.

Yao *et al.*, (2009) [145] designed and evaluated a three-layered, pH-independent pulsatile release pellets system containing isosorbide-5-mononitrate.In this study, pellets containing ISMN were firstly prepared as the core formulated with microcrystalline cellulose (MCC) and lactose by extrusion-spheronization and then layered with a swelling layer followed by an water insoluble control layer. The experimental results demonstrated that swelling layer and control layer plays a major role on the lag time and the drug release. Based on the *in vivo* pharmacokinetics study results they concluded that the developed pellets achieved a lag time of 4.1 h which had a good consistency with the *in vitro* results, and the relative bioavailability was nearly 100% compared to the normal tablets.

Yokoyama *et al.*, (2009) [146] studied the effect of insulin-unstimulated diabetic therapy with miglitol on serum cystatin C level and its clinical significance in diabetic patients. The results suggested that postprandial insulin secretion might increase cystatin C and that insulin-unstimulated miglitol therapy might suppress an increase in cystatin C accompanied by an anti-inflammatory effect in diabetic patients.

Kazuki *et al.*, (2009) [147] examined the effect of dietary supplementation with the α-glucosidase inhibitor miglitol on OLETF rats to check the glycemic control and gene expression of inflammatory cytokines in peripheral leukocytes. Their results suggested that dietary supplementation with miglitol from the pre onset stage in OLETF rats improves glycemic control and reduces gene expression of cytokines related to inflammation in peripheral leukocytes.

Rane *et al.*,(2009) [148] formulated a press coated tablet for pulsatile drug delivery of ketoprofen using hydrophilic and hydrophobic polymers. The press coated tablets containing ketoprofen in the inner core was formulated with an outer shell by different weight ratio of hydrophobic polymer (micronized ethyl cellulose powder) and hydrophilic polymers (glycinemax husk or sodium alginate). The release profile

of press coated tablet exhibited a lag time followed by burst release, in which outer shell ruptured into two halves.

Aswar *et al.*,(2009) [149] developed a colon targeted drug delivery system for diclofenac sodium by using gaur gum as a carrier and sodium-CMC, sucrose 70% and ethyl cellulose as binders. This study results concluded that it was possible to control the release rate of diclofenac sodium over a wide time scale using gaur gum as a carrier and ethyl cellulose as a binder.

Rao *et al.*, (2009) [150] developed swellable controlled porosity osmotic pump tablet of theophylline and defined the formulation and process variables responsible for drug release by applying statistical optimization technique. Formulations were prepared based on Taguchi Orthogonal Array design and Fraction Factorial design for core and coating; respectively. This study also revealed that optimization of semipermeable membrane thickness is very important for approaching zero order kinetics.

Nunthanid *et al.*, (2009) [151] utilized CSA and EC as new compression coats for 5-aminosalicylic acid tablets. Factors affecting in vitro drug release, i.e., % weight ratios of coating polymers, dip speeds of dissolution apparatus or pH of medium or colonic enzyme (beta-glucosidase) in stage III, and use of a super disintegrant in core tablets, was evaluated. Swollen CSA gel dissolved at lower pH and became less soluble at higher pH. The mechanism of swelling was Fickian diffusion fitting well into both Higuchi's and Korsmeyer-Peppas models. EC: CSA, at 87.5:12.5% weight ratio, provided lag time rendering the tablets to reach stage III (simulated colonic fluid of patients), and the drug was released over 90% within 12 h. The lower dip speed and higher pH medium delayed the drug release, while a super disintegrant in the cores enhanced the drug release and no enzyme effect was observed.

Prasanthi1 *et al.*, (2010) [152] developed modified pulsincap preparations for the controlled release of diclofenac using different proportions of hydrophilic carriers such as PVP, PEG, PVA and mannitol. In this research, good linear relationship was observed in between the release rate and the concentration of hydrophilic carriers

and the values of n were in between 0.605 to 0.93, indicated that release was controlled by both diffusion and erosion. Based on the evaluation results they concluded that diclofenac pulsincap containing PVA showed better sustaining capacity at 1:1 drug: carrier ratio which was found to be more suitable to prepare the better controlled release formulations.

Rujivipat S and Bodmeier R (2010) [153] developed pH-erosion-controlled compression-coated tablets and pulsatile release based on compression-coatings of enteric polymer Eudragit L100-55 and the extended release polymer ethylcellulose. Tablet cores containing model drugs of varying solubilities (acetaminophen, carbamazepine and chlorpheniramine maleate) were compression-coated with different ratios of Eudragit_ L100-55: ethylcellulose at different compression forces and tablet core: compression-coat ratios and characterized by drug release, media uptake, erosion behaviour and wettability. The evaluation results concluded that all drugs were released in a pulsatile fashion in higher pH-media after a lag time, which was controlled by the erosion properties of the Eudragit L: ethylcellulose compression-coating and the addition of ethylcellulose avoided premature drug release in lower pH-media and significantly increased the lag time in higher pH media because of a reduction in wettability, media uptake and erosion of the compression-coatings.

Jagdale *et al.*, (2010) [154] developed a novel colon targeted tablet formulation by press coating rapidly disintegrating tablet of atenolol with guar gum and Eudragit L-100 as barrier layer in different ratios and enteric coated. *In vitro* release studies for prepared tablets were carried out for 2 h in 0.1 N HCl, 3 h in pH 7.4 phosphate buffer and 6 h in simulated colonic fluid. In vitro studies revealed that the tablet coated with guar gum and Eudragit L-100 have limited drug release in stomach and small intestinal environment and released maximum amount of drug in the colonic environment.

Jagdale *et al.*, (2010) [155] developed pulsatile release tablets of atenolol consisting of cores coated with two layers of swellable and rupturable polymers in different ratio. The effect of level of swelling layer and rupturable coating was investigated.

Rupture and dissolution tests were performed using the USP Type II paddle method at 50 rpm in 0.1 N HCl. The results of dissolution studies revealed that the lag time of the pulsatile release tablets decreased with increasing amount of MCC in the core, increased with increasing levels of both swelling layer and rupturable ethyl cellulose coating. Increasing levels of the ethyl cellulose coating retarded the water uptake and thus prolonged the lag time.

Pankaj *et al.*, (2011) [156] developed oral press-coated tablets of diltiazem hydrochloride by direct compression method with an outer shell by different weight ratios of low viscosity grade hydrophilic polymer of HPMC. The release profile of the press-coated tablet exhibited a time period without drug release (time lag) in pH 1.2 followed by a rapid and complete release phase, the lag phase was markedly dependent on the weight ratios of core. *In vitro* dissolution test results of press coated tablets in pH 6.8 showed sustained drug release to avoid gastrointestinal disturbances.

Anuradha *et al.*, (2011) [157] prepared and evaluated a floating pulsatile drug delivery system of metoprolol tartrate. The prepared floating pulsatile delivery system consisted of three different parts: a core tablet, containing the active ingredient, an erodible outer shell and a top cover buoyant layer. The rapid release core tablet (RRCT) was prepared by using superdisintegrants along with active ingredient. Dry coating of optimized RRCT was done by using different grades of HPMC E5, E15, and E50 and upper most buoyant layer was prepared with HPMC K15M and sodium bicarbonate. On the basis of these evaluation parameters it was found that the optimized floating pulsatile release formulation showed floating lag time of 4 min, floating time of 12 hrs and release lag time of 6 hrs.

Basavaraj *et al.*, (2011) [158] prepared the biphasic release tablet formulation containing Metformin HCl in extended release matrix form and Pioglitazone HCl in immediate release form for the treatment of diabetes mellitus and the Influence of hydrophobic carrier, hydrophilic polymer on drug release was studied. Immediate release layer of Pioglitazone was optimized using different disintegrants. The results

of dissolution study indicated that release of pioglitazone was dependent on the level and type of disintegrant used in the formulation.

Shosaku *et al.*, (2011) [159] investigated the effect of miglitol on circulating levels of PDMP, sokuble CD40 ligand, selectins, and adiponectin in patients with Type 2 diabetes. The study results concluded that miglitol has an adiponectin-dependent anti atherothrombotic effect that may bebeneficial for primary prevention of atherothrombosis in patients with Type 2 diabetes.

Sumit *et al.*, (2011) [160] developed a press-coated pulsatile drug delivery system intended for treatment of early morning stiffness and symptomatic relief from pain in patients with rheumatoid arthritis and investigated the influence of amount of glyceryl behenate, amount of sodium chloride in the coating composition, and the coating level on the responses, i.e., lag time to release and amount of aceclofenac released in 450 minutes. The results concluded that glyceryl behenate and the coating level had a significant influence on lag time, while sodium chloride helped in the rupture of the coat by acting as a channeling agent.

Abhijit *et al.*, (2011) [161] developed oral press-coated tablets by means of direct compression and wet granulation. This press-coated tablet containing indomethacin in the inner core was formulated with an outer shell by different weight ratios of hydrophobic polymer of ethylcellulose powder and hydrophilic polymer hydroxy propyl methyl cellulose. The release profile of the press-coated tablet exhibited a time period without drug release (time lag) followed by a rapid and complete release phase.

Natarajan *et al.*, (2011) [162] prepared paraxetine hydrochloride immediate release tablets using sodium starch glycollate, croscarmellose sodium, crospovidone as superdisintegrants. The results of *in vitro* dissolution release of the prepared formulation showed their drug release in the order of Sodium Starch Glycolate > Croscarmellose > Crospovidone. They optimized the ideal concentration of Sodium Starch Glycolate which was 4%.

Kishmoto M and Noda M (2011) [163] studied the efficacy of miglitol and sitagliptin for Type 2 diabetes with a continuous glucose monitoring system and increytin related markers. The results of this study revealed that a combination of the α-GI miglitol and the DPP-4 inhibitor sitagliptin effectively reduced postprandial glucose fluctuation and stabilized blood glucose levels. Completely different response patterns of insulin, glucagon, GLP-1, and GIP were observed among the study subjects with either medication alone or in combination, suggested that individual hormone-dependent glycemic responses to the α-GI and DPP-4 inhibitors are complicated and multifactorial.

Maye *et al.*, (2012) [164] designed and evaluated press coated tablets aceclofenac by using rupturable material(EC) combined with erodible material Klucel EXF. The evaluation results of this study showed that the combinations of rupturable material ethylcellulose combined with erodible material Klucel EXF were found to be suitable to achieve pulsatile release of aceclofenac after a lag time of 6 h.

Ismail TES and Anantrao DS (2012) [165] carried out a comparative of alpha glucosidase inhibitors – miglitol, acarbose and voglibose on postprandial hyperglycemia and glycosylated hemoglobin in Type 2 diabetes mellitus. On the basis of the results they found that the adverse effect profile was better with Voglibose (6.66%) than miglitol (16.66%) and Acarbose(33.33%). Their study recommended use of voglibose based on its efficacy and safety profile as preferential choice in the management of postprandial hyperglycaemia in treatment of Type 2 diabetes mellitus.

Aparajita M and Bishwajit B (2012) [166] formulated allylestrenol immediate release tablets by direct compression method and optimized various process parameters. On the basis of *in vitro* dissolution study, disintegration time and drug content results they selected sodium starch glycollate as best superdisintegrant.

The literature review reveals the following:

- The diseases commonly affecting human body, such as asthma, rheumatoid arthritis, angina pectoris, myocardial infarction, allergy, inflammation, diabetes mellitus, cancer and other such diseases follow a circadian rhythmic pattern. The severity of such diseases peaks at only certain times of day. Thus, drug release pattern if designed in a time-controlled manner, maximum drug can be made available at peak hours and optimization of therapy can be achieved.

- The chronological behavior of diabetes mellitus confirms increased blood glucose level after meal (Postmeal hyperglycemia) which is associated with increased risk of retinopathy, increased carotid intima-media thickness (IMT), oxidative stress, inflammation and endothelial dysfunction, decreased myocardial blood volume and myocardial blood flow, increased risk of cancer, impaired cognitive function in elderly people with Type 2 diabetes. These complications will demand the development of pulsatile drug delivery for the management of complications caused by postmeal hyperglycemia by delivering the drug immediately after a meal.

- Pulsatile capsules, pulsatile microspheres, pulsatile implants, pulsatile press coated tablets and bio adhesive controlled release formulations have been successfully studied**.** However the most of the studies focused only on single pulse drug delivery system with limited number of hydrophilic or hydrophobic polymers. Drugs are encapsulated in insoluble body of the capsule which consists of swellable hydrogel plug or encapsulated using barrier layer which consists of erodible or bio degradable polymeric material. Depending upon the nature of hydrogel plug or barrier layer, thickness of hydrogel plug or barrier layer different release lag time can be achieved. After hydrogel plug or barrier layer is dissolved, swelled, eroded or degraded, drugs are rapidly released from the inner reservoir core.

- Miglitol is a drug commonly used in the management of Type 2 diabetes mellitus which belongs to the category of alpha-glucosidase enzyme inhibitor. It acts by delay the absorption of carbohydrates from the gastrointestinal tract, thereby limiting postmeal plasma glucose excursions. The biological half life of Miglitol is 2 hrs. Hence, by conventional dosage form it needs to be administered three times a day. The development of pulsatile drug delivery systems will help to reduce the frequency of drug administration, as the novel dosage form encompasses three pulses of drug in an unit dosage forms.

- Miglitol is well absorbed from intestine. Hence the delivery of Miglitol in the intestine helps to improve absorption and improve the efficacy.

- Miglitol is available in the market as film coated tablets and there is no such a pulsatile drug delivery formulations are available in the market.

Based on the above facts, the concept of once a time daily dosage forms for Miglitol, an anti-diabetic drug in a three pulse drug release system such as pulsincaps and press coated tablets for oral administration was designed.

4. PLAN OF WORK

I. Preformulation Studies

1. Characterization of Miglitol
2. Drug- Excipient compatibility studies using IR and DSC

II. Formulation and evaluation of Miglitol pulsincaps

1. Preparation of insoluble body of the capsule

2. Preparation of Miglitol immediate release tablets using various concentrations of superdisintegrant and its optimization based on its hardness, disintegration and *in vitro* drug release studies.

3. Preparation of hydrgel plug using different and various concentration of hydrophilic polymers

4. Preparation of Miglitol pulsincaps and optimization of hydrogel plug based on its *in vitro* drug release profile and lag time.

5. Evaluation of Miglitol pulsincaps

III. Formulation and evaluation of Miglitol press coated tablets

1. Preparation of Miglitol immediate release core tablets for the third pulse using various concentrations of superdisintegrant and its optimization based on its hardness, disintegration and *in vitro* drug release studies.

2. Press coating of Miglitol immediate release core tablets with barrier layer using different concentrations of hydrophobic and hydrophilic polymers

3. Press coating of barrier layer with Miglitol immediate release layer for the second pulse

4. Press coating of immediate release layer for the second pulse with second barrier layer using different concentrations of hydrophobic and hydrophilic polymers

5. Coating of second barrier layer with immediate release layer of Miglitol for first pulse

6. Evaluation of Miglitol press coated tablets and optimization of barrier layer based on *in vitro* drug release profile and lag time.

IV. Performance evaluation of optimized Miglitol pulsincaps and Miglitol press coated tablets

Pharmacokinetic studies of selected formulations of Miglitol pulsincaps and press coated tablets using male albino rabbits.

V. Stability evaluation of optimized Miglitol pulsincaps and Miglitol press coated tablets

Stability studies of the selected formulations of Miglitol pulsincaps and press coated tablets as per the ICH guidelines.

VI. Comparison of *In vitro* drug release profile of optimized Miglitol pulsincaps and Miglitol press coated tablets with marketed Miglitol tablets

Comparison of selected Miglitol pulsincaps and press coated tablets with marketed Miglitol tablets for its *in vitro* drug release profile

5. DRUG PROFILE

MIGLITOL[34, 45, 46, 48, 167, 170, 171]

Stucture:

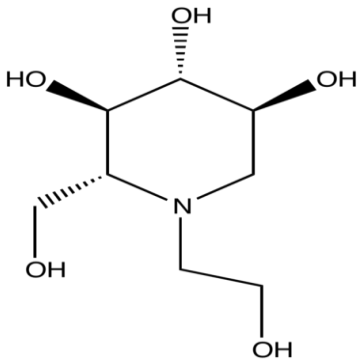


Fig. 5.1. Structure of Miglitol

IUPAC name : (2*R*,3*R*,4*R*,5*S*)-1-(2-hydroxyethyl)-2-(hydroxymethyl)piperidine-3,4,5-triol

Molecular formula : $C_8H_{17}NO_5$

Molecular weight : 207.224 g/mol

Physical appearance : White to pale yellow powder**.**

Melting point : 144-146°C

Solubility : Soluble in water

Loss on drying : Not more than 2%

Biological half life : 2hrs

Protein Binding : less than 4%

Indication

Used in the management of non-insulin-dependent diabetes mellitus (NIDDM).

Mechanism of action

By reversibly inhibiting α-glucoside hydrolase enzymes which are located in the brush border of the small intestine, Miglitol delays the hydrolysis of ingested complex sugars. By slowing the breakdown of oligosaccharides and disaccharides into monosaccharides, this action slows the absorption of glucose into the bloodstream and thus reduces postprandial hyperglycemia.

Pharmacodynamics

Miglitol, an oral alpha-glucosidase inhibitor, is a desoxynojirimycin derivative that delays the digestion of ingested carbohydrates, thereby resulting in a smaller rise in blood glucose concentration following meals. As a consequence of plasma glucose reduction, Miglitol reduce levels of glycosylated hemoglobin in patients with Type II (non-insulin-dependent) diabetes mellitus. Systemic nonenzymatic protein glycosylation, as reflected by levels of glycosylated hemoglobin, is a function of average blood glucose concentration over time. Because its mechanism of action is different, the effect of Miglitol to enhance glycemic control is additive to that of sulfonylureas when used in combination. In addition, Miglitol diminishes the insulinotropic and weight-increasing effects of sulfonylureas. Miglitol has minor inhibitory activity against lactase and consequently, at the recommended doses, would not be expected to induce lactose intolerance.

Pharmacokinetics

Absorption

Absorption of Miglitol is saturable at high doses: a dose of 25 mg is completely absorbed, whereas a dose of 100 mg is 50% – 70% absorbed. For all doses, peak concentrations are reached in 2 to 3 hours.

Distribution

The protein binding of Miglitol is negligible (<4.0%). Miglitol has a volume of distribution of 0.18 L/kg, consistent with distribution primarily into the extracellular fluid.

Metabolism

Miglitol is not metabolized in humans or in any animal species studied. No metabolites have been detected in plasma, urine or feces, indicating a lack of either systemic or pre-systemic metabolism.

Excretion

Miglitol is eliminated by renal excretion as unchanged drug. Following a 25 mg dose, over 95% of the dose is recovered in the urine within 24 hours. At higher doses, the cumulative recovery of drug from urine is somewhat lower due to the incomplete bioavailability. The elimination half-life of Miglitol from plasma is approximately 2 hours.

Toxicity

Unlike sulfonylureas or insulin, an overdose will not result in hypoglycemia. An overdose may result in transient increases in flatulence, diarrhea, and abdominal discomfort. Because of the lack of extra-intestinal effects seen with Miglitol, no serious systemic reactions are expected in the event of an overdose.

Contraindications

- Miglitol is contraindicated in patients with diabetic ketoacidosis, Inflammatory bowel disease, colonic ulceration, or partial intestinal obstruction, and in patients predisposed to intestinal obstruction, chronic intestinal diseases associated with marked disorders of digestion or absorption, or with conditions that may deteriorate as a result of increased gas formation in the intestine

- Hypersensitivity to the drug.

Precautions

Hypoglycemia

- Because of its mechanism of action, Miglitol, when administered alone, should not cause hypoglycemia in the fasted or postprandial state. When it is given in combination with a sulfonylurea or insulin will cause a further lowering of blood glucose, it may increase the hypoglycemic potential of the sulfonylurea or insulin.

- Consider reducing the dose of sulfonylureas or insulin when Miglitol is used in combination with these medications.

- Oral glucose (dextrose), whose absorption is not delayed by Miglitol, should be used instead of sucrose (cane sugar) in the treatment of mild-to-moderate hypoglycemia. Sucrose, whose hydrolysis to glucose and fructose is inhibited by Miglitol, is unsuitable for the rapid correction of hypoglycemia. Severe hypoglycemia may require the use of either intravenous glucose infusion or glucagon injection.

Adverse Reactions

- Gastrointestinal symptoms such as abdominal pain, diarrhea, and flatulence are the most common reactions.
- Dermatologic rections such as skin rashes
- Abnormal laboratory findings such as low serum iron
- Gastrointestinal Disorders: ileus (including paralytic ileus), subileus, gastrointestinal pain, nausea, abdominal distention.
- Pneumatosis cystoides intestinalis: diarrhea, mucus discharge, rectal bleeding, and constipation. Complications may include pneumoperitoneum, volvulus, intestinal obstruction, intussusception, intestinal hemorrhage, and intestinal perforation. If pneumatosis cystoides intestinalis is suspected, Miglitol is discontinued.

Overdosage

Unlike sulfonylureas or insulin, an overdose of Miglitol will not result in hypoglycemia. An overdose may result in transient increases in flatulence, diarrhea and abdominal discomfort. Because of the lack of extra-intestinal effects seen with Miglitol, no serious systemic reactions are expected in the event of an overdose.

Storage

It should be stored at 25°C.

Preparations

Miglitol is available as 25 mg, 50 mg, and 100 mg tablets.

Dose

25 -100 mg three times a day.

EXCIPIENTS PROFILE

1. POLYVINYLPYRROLIDINE K – 30[167,168]

Synonyms: Plasdone K-30, Plasdone, Povidone, PVPP, PVP-K 30; PVP; Polyvinylpyrrolidone; Poly [1-(2-oxo-1-pyrrolidinyl) ethylene); Povidone K-30; 1-Ethenyl-2-pyrrolidinone polymers; 2-Pyrrolidinone, 1-ethenyl, homopolymer; 2-Pyrrolidinone, NVinylpyrrolidinonepolymer;

Chemical name: 1-ethenyl-2-pyrrolidone homopolymer.
Empirical formula: $(C_6H_9NO)_n$
Molecular weight: 2500-300000

Functional category: Tablet binder and in tablet coating, glidant; tablet and capsule diluent; tablet and capsule disintegrant; emulsifying agent; solubilizing agent.

Description: Polyvinyl pyrrolidine k30 occurs as fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Soluble in cold water, chloroform, alcohol, chlorinated hydrocarbons, amines, nitro pariffins lower weight fatty acids.

Stability and storage: PVP k30 darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–130°C; steam sterilization of an aqueous solution does not alter its properties. Aqueous solutions are susceptible to mold growth and consequently require the addition of suitable preservatives.

PVP k30 may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Incompatabilities: PVP k30 is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular

adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds. The efficacy of some preservatives, e.g. thiomersal, may be adversely affected by the formation of complexes with PVP k30.

Safety: When consumed orally, PVP k30 may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes. Povidone additionally has no irritant effect on the skin and causes no sensitization. Reports of adverse reactions to PVP k30 primarily concern the formation of subcutaneous granulomas at the injection site of intramuscular injections formulated with PVP k30. Evidence exists that PVP k30 may accumulate in the organs of the body following intramuscular injection.

Applications: Film-formers, thickeners, lubricants, and binders in hair-setting lotions, detoxifiers and detergents in shampoos and toothpastes. Stabilizers for suspensions, dispersions and emulsions. It is a very widely used excipient for the preparation of solid dosage forms. Main application is its function as a binder in wet granulation. It is also useful for the preparation of effervescent tablets or in direct compression applications.

2. MICROCRYSTALLINE CELLULOSE[169]

Synonym :

Avicel, Fibrocel, Cellulose crystalline, Tabulose.

Molecular Formula: ($C_6H_{10}O_5)_n$

Molecular weight: 3600

Description: Microcrystalline cellulose is a 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.

Solubility: insoluble in water,organic solvents,slightly soluble in 5% sodium hydroxide solution

Melting point: 260-270°C
True density: 1.512-1.668 g/ml
Bulk density: 0.32 g/ml
Tap density: 0.45 g/ml
Particle size: 20-200 μm

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.

Applications

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. It is also used as lubricant (5-20%) and disintegrant (5-15%) property.

3. SODIUM STARCH GLYCOLATE[168]

Synonyms: Carboxymethyl starch sodium salt; carboxy methylamylum natri-cum; Explosol; Explotab ; Glycolys; Primojel; starch carboxymethylether sodium salt; Tablo; Vivastar P.

Description: Sodium starch glycolate is a white or almost white free-flowing very hygroscopic powder and odour less

Molecular Weight: 500 000-11 000 000

Melting Point: Does not melt, but chars at approximately at 200^0C.

Solubility: Practically insoluble in water, insoluble in most organic solvents

Applications:

- Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is recommended to use in tablets prepared by either direct-compression or wet-granulation processes.

- The recommended concentration in a formulation is 2-8%, with the optimum concentration about 4% although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.

- The disintegrant efficiency of sodium starch glycolate is unimpaired in the presence of hydrophobic excipients, such as lubricants unlike many other disintegrants.

- Increasing the tablet compression pressure also appears to have no effect on disintegration time.

4. MAGNESIUM STEARATE[168]

Synonyms: Magnesium octadecanoate, Octadecanoic acid, Magnesium salt, Stearic acid.

Chemical Name: Octadecanoic acid magnesium salt.

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

Molecular formula: 591.34

Structural formula: $[CH_3 (CH_2)_{16}COO]_2Mg$

Category: Tablet and capsule lubricant.

Description: A very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

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

Melting point **:** 126-130°C
True density **:** 1.09 g/ml
Bulk density **:** 0.15 g/ml
Tap density **:** 0.28 g/ml

Applications: Widely used in cosmetics, foods, and pharmaceutical formulations. As a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. Also used in barrier creams.

Storage conditions :

Should be stored in well-closed container in a cool and dry place.

Incompatabilities :

With strong acids, alkalis, ion salts, strong oxidizing materials and products containing aspirin, some vitamins and most alkaloidal salts.

5. HYDROXYPROPYLMETHYL CELLULOSE (HPMC) [168]

Non-proprietary Name : P.Hydroxymethylcellulose.

Synonyms: Hydroxypropylmethylether, Methylhydroxy propylcellulose, methylcellulose, methocel, Hypromellose.

Chemical Name: Cellulose, 2-hydroxypropyl methylcellulose.

Description: Hydromellose is an odourless and tasteless, white or creamy or granular, powder.

Solubility: Soluble in cold water, forming a viscous colloidal solution, practically insoluble in chloroform, ethanol and ether. But it is soluble in mixtures of methanol and dichloromethane and mixtures of water and alcohol.

P^H : 5-8(1% w/w solution)

Viscosity: A wide range of viscosity type of HPMC is available (viscosity of 2% solution of HPMC K4M is 4000 mPa s.

True density **:** 1.326 g/ml
Bulk density **:** 0.341 g/ml
Tap density **:** 0.557 g/ml

Application:

- Hydromellose is widely used in oral and topical pharmaceutical formulations.
- Hydromellose is used as tablet binder, in film coating and as an extended release tablet matrix.
- Hydromellose is also used as an adhesive in plastic bandages and as a wetting agent for hard cotact lenses.

Stability and Storage: Hydromellose is a stable powder, but after drying it is hygroscopic. Solutions are stable at pH 3-11, increasing temperature reduced the viscosity of solutions. Hydromellose aqueous solutions are comparatively enzyme-resistance, providing good viscosity stability during long-term storage. It is liable to microbial spoilage; benzalkonium chloride is commonly used preservative. Stored in well closed container.

Incompatability : Hydromellose produces adducts with sodium salicylate, sulphathiazole and tannins.

6. COLLOIDAL SILICON DIOXIDE[168]

Description

Colloidal silicon dioxide is a submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, nongritty amorphous powder.

Synonym:

Aerosil; Cab-O-Sil; Cab-O-Sil M-5P; colloidal silica; fumed silica; light anhydrous silicic acid; silicic anhydride; silicon dioxide fumed; Wacker HDK.

Empirical formula and molecular weight

SiO_2 = 60.08

Structural formula

SiO_2

Functional category

Adsorbent; anticaking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent.

Applications in pharmaceutical formulation or technology

- Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting liquids.

- It is also used as a tablet disintegrant and as an adsorbent dispersing agent for liquids in powders.

- It is frequently added to suppository formulations containing lipophilic excipients to increase viscosity, prevent sedimentation during molding, and decrease the release rate.

Acidity/alkalinity: pH = 3.5–4.4 (4% w/v aqueous dispersion)
Density (bulk): 0.029–0.042 g/cm3
Density (tapped): 0.05 g/cm3
Flowability: 35.52% (Carrs compressibility index)
Particle size distribution: 7–16 nm.
Refractive index: 1.46

Solubility: Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water.

Specific gravity: 2.2

Specific surface area: 200–400 m2/g (Stroehlein apparatus, single point); 50–380 m2/g (BET method).

Incompatibilities:

Incompatible with diethylstilbestrol preparations.

Safety:

It is widely used in oral and topical pharmaceutical products and is generally regarded as an essentially nontoxic and nonirritant excipient. However, intraperitoneal and subcutaneous injection may produce local tissue reactions and/or granulomas. It should therefore not be administered parenterally. LD_{50} (rat, IV): 15 mg/kg LD_{50} (rat, oral): 3.16 g/kg

7. STARCH[168]

Description

Starch occurs as an odorless and tasteless, fine, white-colored powder comprising very small spherical or ovoid granules whose size and shape are characteristic for each botanical variety.

Nonproprietary Names

BP: Maize starch, Potato starch, Rice starch, Tapioca starch, Wheat starch,
JP: Corn starch, Potato starch, Rice starch, Wheat starch

PhEur: Maydis amylum (maize starch), Solani amylum (potato starch), Oryzae amylum (rice starch), Tritici amylum (wheat starch)

USPNF: Starch

Synonyms

Amido; amidon; amilo; amylum; Aytex P; Fluftex W; Instant Pure-Cote; Melojel; Meritena; Paygel 55; Perfectamyl D6PH; Pure-Bind; Pure-Cote; Pure-Dent; Pure-Gel; Pure-Set; Purity 21; Purity 826; Tablet White.

Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$ = 50 000–160 000, where n = 300–1000.

Functional Category

- Glidant
- Tablet and capsule diluents
- Tablet and capsule disintegrant
- Tablet binder.

Stability

Dry, unheated starch is stable if protected from high humidity. When used as a diluent or disintegrant in solid-dosage forms, starch is considered to be inert under normal storage conditions. However, heated starch solutions or pastes are physically unstable and are readily attacked by microorganisms to form a wide variety of starch derivatives and modified starches that have unique physical properties.

Storage Conditions

Starch should be stored in an airtight container in a cool, dry place.

Incompatibilities

Nil

Safety

Starch is widely used as an excipient in pharmaceutical formulations, particularly oral tablets. Starch is an edible food substance and is generally regarded as an essentially nontoxic and nonirritant material. However, oral consumption of massive doses can be harmful owing the formation of starch calculi, which cause bowel obstruction. Starch may also cause granulomatous reactions when applied to the peritoneum or the meninges.

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended. Excessive dust generation should be avoided to minimize the risks of explosion.

Related Substances

Amylopectin, α-amylose, Maltodextrin, Starch- pregelatinized, Sterilizable maize

8. HYDROXYPROPYL CELLULOSE, LOW-SUBSTITUTED[168, 170]

Description

Low-substituted hydroxypropyl cellulose occurs as a white to yellowish white powder or granules. It is odorless or has a slight, characteristic odour and it is tasteless.

Nonproprietary Names

JP: Low-substituted hydroxypropylcellulose
USPNF: Low-substituted hydroxypropyl cellulose

Synonyms

Hyprolose, low-substituted, L-HPC.

Chemical Name

Cellulose, 2-hydroxypropyl ether (low-substituted)

Empirical Formula and Molecular Weight

The USPNF 23 describes low-substituted hydroxypropyl cellulose as a low-substituted hydroxypropyl ether of cellulose. When dried at 105°C for 1 hour, it contains not less than 5.0% and not more than 16.0% of hydroxypropoxy groups (—OCH2CHOHCH3). Lowsubstituted hydroxypropyl cellulose is commercially available in a number of different grades that have different particle sizes and substitution levels.

Applications in Pharmaceutical Formulation or Technology

Low-substituted hydroxypropyl cellulose is widely used in oral solid-dosage forms. It is primarily used in tableting as a disintegrant, and as a binder in wet granulation.

It has been used in the preparation of rapidly disintegrating tablets produced by direct compression.

Solubility

Practically insoluble in ethanol (95%) and in ether. Dissolves in a solution of sodium hydroxide (1 in 10) and produces a viscous solution. Insoluble, but swells in water.

Melting point: decomposition at 275°C.
Acidity/alkalinity: pH = 5.0–7.5 for 1% w/v aqueous suspension.

Functional Category

- Tablet and capsule disintegrant
- Tablet binder.

Stability

Low-substituted hydroxypropyl cellulose is a stable, though hygroscopic, material

Storage Condition

The powder should be stored in a well-closed container.

Incompatibilities

Alkaline substances may interact. Such material may extend the disintegration.

Safety

Low-substituted hydroxypropyl cellulose is generally regarded as a nontoxic and nonirritant material.

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Excessive dust generation should be avoided to minimize the risk of explosions.

Related Substances

Hydroxy Propyl Cellulose.

9. TALC[168]

Description

Talc is a very fine, white to greyish-white, odourless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Non-proprietary Names

BP: Purified talc
JP: Talc
PhEur: Talcum
USP: Talc

Synonyms

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

Empirical Formula

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 diluent
- Tablet and capsule lubricant.

Stability

Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation.

Storage Conditions

Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Incompatible with quaternary ammonium compounds.

Safety

Intranasal or intravenous abuse of products containing talc can cause granulomas in body tissues, particularly the lungs. Contamination of wounds or body cavities with talc may also cause granulomas; therefore, it should not be used to dust surgical gloves. Inhalation of talc causes irritation and may cause severe respiratory distress in infants.

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Talc is irritant if inhaled and prolonged excessive exposure may cause pneumoconiosis.

Related Substances

Bentonite, Magnesium aluminum silicate, Magnesium silicate, Magnesium trisilicate.

10. Ethyl Cellulose[168, 170]

Synonym

Aquacoat ECD; Aqualon; E462; Ethocel; Surelease

Chemical Name

Cellulose ethyl ether

Functional Category

Coating agent; flavoring fixative; tablet binder; tablet filler; viscosity-increasing agent

Description

Ethyl cellulose is a tasteless, free-flowing, white to light tan colored powder.

Stability and Storage

Ethyl cellulose is a stable, slightly hygroscopic material.

Ethyl cellulose undergoes oxidative degradation in the presence of sunlight or UV light at elevated temperatures.

Ethyl cellulose should be stored at a temperature not exceeding 32^0C in a dry area away from all sources of heat. It should not be stored next to peroxides or other oxidizing agents.

Incompatibilities

Incompatible with paraffin wax and microcrystalline wax.

Safety

Ethylcellulose is widely used in oral and topical pharmaceutical formulations. It is also used in food products. Ethylcellulose is not metabolized following oral consumption and is therefore a noncalorific substance. Parenteral use may be harmful to the kidneys.

Applications

Ethyl cellulose is widely used in oral and topical pharmaceutical formulations. The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets and granules. Ethylcellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation; for example, where granules are coated with ethylcellulose to inhibit oxidation. Modified release tablet formulations may also be produced using ethylcellulose as a matrix former.

11. GLYCERYL BEHANATE[168, 170]

Synonyms

Glycerol behenate, Glyceroli dibehenas, Glyceryl mono behenate

Description

Glyceryl behenate occurs as a fine white-yellow powder, as a hard waxy mass or pellet, or as white or almost white unctuous flakes. It has a faint odour.

Chemical formula

$C_{69}H_{134}O_6$

Molecular weight

1059.9

HLB value

2

Melting point

65–77ºC

Solubility

Soluble when heated in chloroform and dichloro-methane and in many organic solvents, slightly soluble in hot ethanol (96%), practically insoluble in cold ethanol (95%), hexane, mineral oil and water.

Stability and Storage Conditions

Glyceryl behenate should be stored in a tightly closed container, at a temperature less than 35ºC

Applications

- Glycerylbehenate is mainly used as a lubricant in the preparation of oral tablets and capsules.
- Glyceryl behenate has been investigated for the encapsulation of various drugs such as retinoids.
- Glyceryl behenate is used in oral enteric-coated pellets, powders and suspensions.
- It is also used in controlled, extended-release and orally disintegrating tablets.

- For oral preparations, glycerylbehenate forms a lipidic matrix for sustained-release formulations.

- It has been used along with acid-soluble or swellable polymers to mask the bitter or unpleasant taste of the medicament with improved palatability.

12. SODIUM ALGINATE[168, 170]

Nonproprietary Names

BP: Sodium alginate
PhEur: Natrii alginas
USPNF: Sodium alginate

Synonyms

Algin; alginic acid, sodium salt; E401; Kelcosol; Keltone; Protanal; sodium polymannuronate.

Chemical Name

Sodium alginate

Empirical Formula and Molecular Weight

Sodium alginate consists chiefly of the sodium salt of alginic acid, which is a mixture of polyuronic acids composed of residues of D-mannuronic acid and L-guluronic acid.

Functional Category

Stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity increasing agent.

Applications in Pharmaceutical Formulation or Technology

- Sodium alginate is used in a variety of oral and topical pharmaceutical formulations.

- In tablet formulations, sodium alginate may be used as both a binder and disintegrant.

- It has been used as a diluent in capsule formulations. Sodium alginate has also been used in the preparation of sustained-release oral formulations since it can delay the dissolution of a drug from tablets, capsules, and aqueous suspensions.

- In topical formulations, sodium alginate is widely used as a thickening and suspending agent in a variety of pastes, creams, and gels, and as a stabilizing agent for oil-in-water emulsions.

- Recently, sodium alginate has been used for the aqueous microencapsulation of drugs in contrast with the more conventional microencapsulation techniques which use organic solvent systems.

- It has also been used in the formation of nanoparticles.

- Hydrogels prepared from sodium alginate has been investigated and drug release from oral mucosal adhesive tablets and buccal gels based on sodium alginate have been reported.

- Other novel delivery systems containing sodium alginate include ophthalmic solutions that form a gel in situ when administered to the eye; an *in situ* forming gel containing paracetamol for oral administration;and a freeze-dried device intended for the delivery of bone-growth factors.

- Hydrogel systems containing alginates have also been investigated for delivery of proteins and peptides.

Uses of sodium alginate

Pastes and creams 5–10 %
Stabilizer in emulsions 1–3%
Suspending agent 1–5%
Tablet binder 1–3%
Tablet disintegrant 2.5–10%

Description

Sodium alginate occurs as an odorless and tasteless, white to pale yellowish-brown colored powder.

Acidity/alkalinity
pH ≈7.2 for a 1% w/v aqueous solution.

Solubility

Practically insoluble in ethanol (95%), ether, chloroform, and ethanol/water mixtures in which the ethanol content is greater than 30%. Also, practically insoluble in other organic solvents and aqueous acidic solutions in which the pH is less than 3. Slowly soluble in water, forming a viscous colloidal solution.

Viscosity (dynamic)

20–400 mPa s (20–400 cP)-1% w/v aqueous solution at 20°C.

Stability and Storage Conditions

- Aqueous solutions of sodium alginate are most stable at pH 4–10. Below pH 3, alginic acid is precipitated.
- Solutions should not be stored in metal containers.
- Sodium alginate solutions are susceptible on storage to microbial spoilage, which may affect solution viscosity.

- Preparations for external use may be preserved by the addition of 0.1% chlorocresol, 0.1% chloroxylenol, or parabens. If the medium is acidic, benzoic acid may also be used.

- It should be stored in an airtight container in a cool, dry place.

Incompatibilities

Incompatible with acridine derivatives, crystal violet, phenylmercuric acetate and nitrate, calcium salts, heavy metals, and ethanol in concentrations greater than 5%. Low concentrations of electrolytes cause an increase in viscosity but high electrolyte concentrations cause salting-out of sodium alginate; salting-out occurs if more than 4% of sodium chloride is present.

Safety

Sodium alginate is widely used in cosmetics, food products, and pharmaceutical formulations, such as tablets and topical products, including wound dressings. It is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may be harmful.

Handling Precautions

Sodium alginate may be irritant to the eyes or respiratory system if inhaled as dust; Eye protection, gloves, and a dust respirator are recommended. Sodium alginate should be handled in a well-ventilated environment.

Related Substances

Alginic acid; calcium alginate; potassium alginate; propylene glycol alginate.

13. GELATIN [168,170]

Nonproprietary Names

BP: Gelatin
JP: Gelatin
PhEur: Gelatina
USPNF: Gelatin

Synonyms

Byco; Cryogel; gelatine; Instagel; Solugel.

Chemical Name

Gelatin

Empirical Formula and Molecular Weight

Gelatin is a generic term for a mixture of purified protein fractions obtained either by partial acid hydrolysis (type A gelatin) or by partial alkaline hydrolysis (type B gelatin) of animal collagen. Gelatin may also be a mixture of both types. The protein fractions consist almost entirely of amino acids joined together by amide linkages to form linear polymers, varying in molecular weight from 15 000–250 000.

Functional Category

Coating agent; film-former; gelling agent; suspending agent; tablet binder; viscosity increasing agent.

Applications in Pharmaceutical Formulation or Technology

- Biodegradable matrix material in an implantable delivery system
- Gelatin capsules are unit-dosage forms that are filled with an active drug and are generally designed for oral administration. Although gelatin is poorly soluble in cold water, a gelatin capsule will swell in gastric fluid to rapidly release its contents.

- Gelatin is also used for the microencapsulation of drugs.
- Low-molecular-weight gelatin has been prepared for the controlled release of the drug.
- Other uses of gelatin include the preparation of pastes, pastilles, pessaries, and suppositories. In addition, it is used as a tablet binder and coating agent, and as a viscosity-increasing agent for solutions and semisolids.

Description

Gelatin occurs as a light-amber to faintly yellow-colored, vitreous, brittle solid. It is practically odorless and tasteless and is available as translucent sheets and granules, or as a powder.

Acidity/alkalinity

1% w/v aqueous solution at 25°C
pH = 3.8–6.0 (type A);**pH** = 5.0–7.4 (type B).

Density

1.325 g/cm3 for type A;
1.283 g/cm3 for type B.

Isoelectric point

7–9 for type A;
4.7–5.3 for type B.

Moisture content:
9–11%

Solubility

Practically insoluble in acetone, chloroform, ethanol (95%), ether, and methanol. Soluble in glycerin, acids, and alkalis, although strong acids or alkalis cause

precipitation. In water, gelatin swells and softens, gradually absorbing between five and 10 times its own weight of water. Gelatin is soluble in hot water, forming a jelly, or gel, on cooling to 35–40°C.

Viscosity (dynamic)

4.3–4.7 mPa s (4.3–4.7 cP) for a 6.67% w/v aqueous solution at 60°C;
18.5–20.5 mPa s (18.5–20.5 cP) for a 12.5% w/v aqueous solution at 60°C.

Stability and Storage Conditions

Dry gelatin is stable in air. Aqueous gelatin solutions are also stable for long periods if stored under cool, sterile conditions. The bulk material should be stored in an airtight container in a cool, dry place.

Incompatibilities

Gelatin is an amphoteric material and will react with both acids and bases. It may be hydrolyzed by most proteolytic systems to yield its amino acid components. Gelatin will also react with aldehydes and aldehydic sugars, anionic and cationic polymers, electrolytes, metal ions, plasticizers, preservatives, and surfactants. It is precipitated by alcohols, chloroform, ether, mercury salts, and tannic acid.

Safety

It may be regarded as a nontoxic and nonirritant material. However, there have been rare reports of gelatin capsules adhering to the esophageal lining, which may cause local irritation. Hypersensitivity reactions, including serious anaphylactoid reactions, have been reported for the use of gelatin in parenteral products.

Handling Precautions

Eye protection and gloves are recommended. Gelatin should be handled in a well ventilated environment.

RATIONALE BEHIND THE DEVELOPMENT OF PULSATILE DRUG DELIVERY FOR ANTI DIABETIC DRUG MIGLITOL:

Miglitol is a drug commonly used in the management of Type 2 diabetes mellitus which belongs to the category of alpha-glucosidase enzyme inhibitor. Miglitol delay the absorption of carbohydrates from the gastrointestinal tract, thereby limiting postmeal plasma glucose excursions. The following are the various reasons for the need of development of pulsatile drug delivery systems for the anti diabetic drug Miglitol.

- The biological half life of Miglitol is 2 hrs. Hence, by conventional dosage form it needs to be administered three times a day. The development of pulsatile drug delivery systems will help to reduce the frequency of drug administration, as the novel dosage form encompass three pulses of drug in an unit dosage forms

- Miglitol is well absorbed from intestine. Hence the delivery of Miglitol in the intestine helps to improve absorption and improve the efficacy.

- In view of the limitations of the conventional oral Miglitol tablets, which are required to be administered at different time intervals leading to inconvenience to the patients, demands the development of Pulsatile drug delivery of Miglitol. Administration of Miglitol in pulsatile drug delivery system will help to release the drug in the pre determined time which improves the patient compliance as well as therapeutic efficacy.

- The oral route is the most often used for administration of drugs. Tablets and Capsules are the most popular oral formulations available in the market and are preferred by most of patients and physicians. Hence the pulsatile drug delivery of Miglitol by oral route is ideal.

- Pulsatile drug delivery system for anti diabetics has more market opportunities due to the simplicity in design and reliable in functioning.

6. MATERIALS AND METHODS

Table 6.1. Materials used

S.NO	MATERIAL	SOURCE
1	Miglitol	Micro labs Pvt.ltd, Bangalore
2	Avicel PH 102	Indian research products, Chennai
3	Magnesium stearate	Loba chemie pvt.ltd, Chennai
4	Aerosil	Otto chemical-biochemika reagents, Mumbai
5	Talc	Otto chemical-biochemika reagents, Mumbai
6	PVP	Sisco research laboratories, Mumbai
7	Lactose	Otto chemical-biochemika reagents, Mumbai
8	Starch	Otto chemical-biochemika reagents, Mumbai.
9	Sodium starch glycollate	Otto chemical-biochemika reagents, Mumbai.
10	HPMC	Central drug house pvt.ltd, New Delhi.
11	Gelatin	HIMEDIA.
12	Sodium alginate	Central drug house pvt.ltd, New Delhi.
13	HPMC K4M	β- pura laboratories pvt.ltd., Chennai.
14	L- Hydroxy propyl cellulose	Central drug house pvt.ltd, New Delhi.
15	Glecyryl behenate	HIMEDIA.
16	Ethyl cellulose	β- pura laboratories pvt.ltd., Chennai.
17	Potassium bromide(IR grade)	Merck limited, Mumbai.
18	Hydrochloric acid	RFCL limited,Rankem, NewDelhi.
19	Potassium dihydrogen phosphate	Central drug house pvt.ltd, New Delhi.
20	Sodium hydroxide pellets	Merck limited, Mumbai.
21	Disodium hydrogen phosphate	Central drug house pvt.ltd, New Delhi.
22	Acetonitrile	Ranchem , New Delhi.
23	Sodium dihydrogen phosphate	Central drug house pvt.ltd, New Delhi.

Table 6.2. Equipments used

S.NO	EQUIPMENTS	MODEL
1	Rotary tablet punch machine	Rimek,minipress, UK.
2	Electronic balance	Sartoroius, Germany.
3	Mechanical sieve shaker	Hicon,grover Enterprises, New Delhi.
4	Hot air oven	Hicon,grover Enterprises, New Delhi.
5	Bulk density apparatus	Veego, Mumbai.
6	Vernier calliper	Mitutoyo cd-6cs, Japan.
7	FTIR	Alphar T0, Bruker, New Delhi.
8	DSC	Schimadzu DSC-60.
9	HPLC	Schimadzu LC2010 CHT, Mumbai.
10	UV spectrophotometer	Schimadzu 1710, Mumbai.
11	USP dissolution apparatus	Lab india, DS8000.
12	Ultra centrifuge	Remi instruments, Mumbai.
13	Hardness tester	Pfizer.
14	Disintegration apparatus	Electrolab, Mumbai.
15	Friabilator	EF2, Electrolab, Mumbai.
16	pH meter	DI-707 Digisun electronics, Hyderabad.
17	Stability chamber	Thermolab scientific equipments pvt.ltd, Mumbai.

I. PREFORMULATION STUDIES

Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It is defined as an investigation of physical and chemical properties of a drug substance. The overall objective of preformulation testing is to generate information useful to the formulation in developing stable and bioavailable dosage forms.

Analysis of Miglitol

Description

Physical appearance and form of the Miglitol were observed.

Solubility

The quantitative determination of solubility was made by preparing saturated solution of drug in a constant volume of pH 1.2, 7.4 and 6.8 buffers and resulting solutions were kept at room temperature for 24 hours with intermediate shaking. The resulting solutions were filtered and analyzed for dissolved drug by measuring absorbance at 232 nm.[172]

Identification

IR Spectroscopy

IR spectrum of Miglitol was obtained by KBr pellatisation technique using an instrument "Perkin-elmer FTIR".[173] The pellets were prepared by mixing the sample with KBr in the ratio of 1:100 and scanned in the range of 4000 to 400 $cm.^{-1}$. The obtained IR spectrum of Miglitol was compared with IR spectrum of Miglitol standard.

HPLC[172]

The retention time of the chromatogram obtained with the sample preparation was compared with the retention time of the chromatogram obtained with the standard preparation.

Melting point

The melting point of Miglitol was measured by capillary tube method.[173]

Loss on drying

1 gm of Miglitol was kept in a hot air oven at 60^0C for 2 hrs and the percentage of loss was calculated by using the formula given below, [173]

Percentage LOD=Initial weight-Final weight /Initial weight X 100

Bulk density and Tapped density

Weighed quantity of Miglitol was placed in a calibrated measuring cylinder, the initial volume(untapped) was noted and then the measuring cylinder was tapped until the volume remains constant.[174] The following formulae were used to calculate the bulk and tapped density of Miglitol,

Bulk density = weight of the powder / bulk volume of the powder

Tapped density = weight of powder /tapped volume of powder

Hausner's ratio

Hausner's ratio was determined as the ratio between the tapped density to that of the bulk density and it was calculated by substituting the bulk and tapped density values of Miglitol in the following formula[174],

Hausner's ratio = Taped Density/Bulk Density

Carr's index

Carr's index was measured using the values of the bulk density and tapped density of Miglitol in the following equation, [174]

$$\textbf{Carr's index} = \textbf{(TD-BD)/ TD X100}$$

Where, TD - Tapped density

BD - Bulk density

Angle of Repose

Angle of repose of Miglitol was determined by fixed funnel technique. In this technique Miglitol was placed in a funnel which was kept at a fixed height. Then the sample was allowed to flow to the surface of the ground which contains a graph paper. The height (h) and radius (r) of the sample was measured and calculated the angle of repose by using the following formula[174],

$$\theta = \tan^{-1} h/r$$

Where, h – Height of the heap

r – Radius of the heap

DRUG-EXCIPIENT COMPATIBILITY STUDIES[175, 176, 177]

Each excipient used in the formulations was blended thoroughly with Miglitol to increase drug-excipient molecular contacts to accelerate the reactions if possible. Each drug- excipient blend was taken separately into the vials and kept for a month and two months study at 40ºC. After, that each blend was tested for stability by physical observation and assay. The details of the sample used for the compatibility studies were given in **table 6.3.**

Table 6.3. List of drug-excipients and their ratio used in accelerated compatibility study

S.No	Sample ID	Ratio
1.	Miglitol	-
2.	Miglitol+ Avicel pH 102	1:5
3.	Miglitol+ SSG	1:5
4.	Miglitol+ Magnesium stearate	1:5
5.	Miglitol+ Aerosil	1:10
6.	Miglitol+ Lactose	1:10
7.	Miglitol+ PVP	1:5
8.	Miglitol+ Starch	1:5
9.	Miglitol+ Talc	1:5
10.	Miglitol+ Gelatin	1:5
11.	Miglitol+ HPMC K4M	1:5
12.	Miglitol+ Sodium alginate	1:5
13.	Miglitol+HPMC	1:5
14.	Miglitol+ L-HPC	1:5
15.	Miglitol+ Ethylcellulose	1:5
16.	Miglitol+ Glycerylbehenate	1:5

Fourier Transform infra Red spectroscopy

TIR spectroscopy was used to ensure that no chemical interaction between Miglitol and the other excipients used in the formulation. IR spectra of Miglitol and other excipients used in the formulation were recorded by using"Perkin-elmer FTIR." The sample for the IR spectroscopy was prepared by mixing the samples with spectroscopic grade KBr and compressed in to transparent pellets, then scanned in the IR range from 500 to 4000 cm^{-1} with a resolution of 4 cm.

Differential Scanning calorimetry(DSC technique)

Differential Scanning Calorimetry studies for Miglitol, excipients and combinations of Miglitol with excipients were carried out using "Schimadzu DSC-60. In this study Miglitol was mixed with the excipients used in the formulation and thermal analysis of each sample was carried out. During the study, the temperature ranges from 25 to 400º C, heating rate 10ºC/min and flow rate of nitrogen 30 ml/min were maintained. The samples approximately 5 mg were taken in aluminium pan, sealed and recorded the thermogram.

PREPARATION OF STANDARD GRAPH OF MIGLITOL

Standard graph of the drug was obtained using standard Miglitol solution pepared using buffer pH 1.2, pH 7.4 and pH 6.8. In this the concentration of standard Miglitol was maintained from 5 µg to 50 µg/ml.

Preparation of hydrochloric acid buffer pH 1.2

8.9 ml of concentrated HCl was diluted in 1000 ml volumetric flask with distilled water.

Preparation of phosphate buffer pH 6.8

28.80 gm of disodium hydrogen phosphate and 11.45 gm of potassium dihydrogen phosphate was weighed and dissolved in 1000ml volumetric flask with distilled water.

Preparation of phosphate buffer pH 7.4

8 gm of sodium hydroxide pellets and 27.212 gm of Potassium dihydrogen phosphate was weighed and dissolved in 1000 ml volumetric flask with distilled water.

Linear plot of Miglitol in pH 1.2 buffer

50 mg of Miglitol standard was dissolved in pH 1.2 buffer in a 100 ml standard flask, which gives 500 µg/ml. From this stock solution suitable dilutions were made to get the concentration of solution from 5 µg to 50 µg/ml. Absorbance of these solutions were measured at 232 nm using UV- visible spectrophotometer and standard graph was plotted.

Linear plot of Miglitol in pH 7.4 phosphate buffer

50 mg of Miglitol standard was dissolved in pH 7.4 buffer in a 100 ml standard flask, which gives 500 µg/ml. From this stock solution suitable dilutions were made to get the concentration of solution from 5 µg to 50 µg/ml. Absorbance of these solutions were measured at 232 nm using UV- visible spectrophotometer and standard graph was plotted.

Linear plot of Miglitol in pH 6.8 phosphate buffer

50 mg of Miglitol standard was dissolved in pH 6.8 buffer in a 100 ml standard flask, which gives 500 µg/ml. From this stock solution suitable dilutions were made to get the concentration of solution from 5µg to 50 µg/ml. Absorbance of these solutions were measured at 232 nm using UV- visible spectrophotometer and standard graph was plotted.[172]

II. FORMULATION OF MIGLITOL PULSINCAPS[178,179,180]

Stage 1: Preparation of insoluble body of the capsule

The solubility of the hard gelatin capsules are modified by exposing the body of the capsules to the formaldehyde vapors produced by the reaction between formaldehyde solution and potassium permanganate. For this body of the capsules were placed on a wire mesh and kept inside a desiccator containing formaldehyde 15% and potassium permanganate. The vapors of formaldehyde formed were exposed to body of the capsule until the body with sufficient solubility was achieved. Then the body of the capsules were removed and dried at 50˚C to ensure completion of reaction between formaldehyde and gelatin. Finally the bodies of the capsule were dried at room temperature to remove the excess of formaldehyde vapor

Stage 2: Preparation of Miglitol immediate release tablets

The immediate release tablets were prepared by using direct compression method. Powder mixtures of Miglitol, avicel PH102, aerosil and sodium starch glycollate were dry blended for 20 minutes followed by addition of magnesium stearate. The mixtures were then further blended for 10 minutes and compressed to obtain immediate release core tablets of Miglitol. The optimum concentration of sodium starch glycollate was selected by conducting various trials (MCT1-MCT6) with different concentrations (0, 2, 4, 6, 8 and 10mg / tablet). The optimized Miglitol immediate release tablets were selected for the preparation of Miglitol pulsincaps. The formula used for the preparation of Miglitol immediate release tablets were given in **table 6.4**.

Table 6.4.Formula used in the preparation of Miglitol immediate release tablets

Ingredients	MCT1	MCT2	MCT 3	MCT 4	MCT 5	MCT 6
Miglitol (mg)	25	25	25	25	25	25
Avicel PH102 (mg)	73.25	71.25	69.25	67.25	65.25	63.25
Sodium starch glycollate (mg)	0	2	4	6	8	10
Magnesium stearate (mg)	0.25	0.25	0.25	0.25	0.25	0.25
Aerosil (mg)	1.5	1.5	1.5	1.5	1.5	1.5

Stage 3: Preparation of hydrogel plug using different and various concentration of hydrophilic polymers [179,180]

Hudrogel plugs of various polymers were prepared by compression of various hydrophilic polymers such as gelatin, HPMC K4M and sodium alginate in different concentrations (30, 40, 50, 60 and 70 mg) with equal proportion of lactose.

Stage4: Preparation of Miglitol pulsincaps and optimization of hydrogel plug based on its *invitro* drug release profile and lag time (MPC1-MPC15).[179, 181,182,183]

The optimized immediate release Miglitol tablets were selected for the preparation of Miglitol pulsincaps. These selected three doses of immediate release tablets were kept inside the body of the capsule and each dose was plugged with hydrogel plug prepared with gelatin, HPMC K4M and sodium alginate, separately in various concentrations. Then the body of the capsule was closed with the cap of normal gelatin capsule (Soluble). The prepared each pulsincap consisted of three layers of Miglitol immediate release tablets and two layers of hydrogel plug. The formula used for the preparation of hydrogel plug in the preparation of Miglitol pulsincaps were given in **table 6.5** and the images of prepared Miglitol pulsincaps were shown in **fig.6.1 to 6.4**.

Table 6.5. Formula for different batches of hydrogel plug used in the preparation of pulsincaps

Trials	Hydrogel plug used		
	Gelatin (mg)	**HPMC K4M (mg)**	**Sodium alginate (mg)**
MPC1	30	_	_
MPC 2	40	_	_
MPC 3	50	_	_
MPC 4	60		
MPC 5	70	-	_
MPC 6	_	30	_
MPC 7	_	40	_
MPC 8		50	-
MPC 9	_	60	-
MPC10	_	70	-
MPC11	_	_	30
MPC12			40
MPC13	_	_	50
MPC14	_	_	60
MPC15	_	_	70

MIGLITOL PULSINCAPS

Fig.6.1.Preparation of insoluble body of capsule

Fig.6.2.Hydrogel plug

Fig.6.3 and 6.4. Miglitol pulsincaps inserted with hydrogel plug

EVALUATION[184, 185,186,187,188]

Evaluation of formaldehyde treated capsules

Solubility test

The empty formaldehyde treated capsules were stirred in a 250 ml beaker containing 100 ml of buffer solutions. The different buffer solutions such as pH 1.2, pH 7.4 and pH 6.8 were used for this study. The time taken for capsule to dissolve or form soft mass was noted.

Chemical test for free formaldehyde

Standard formaldehyde reparation

Diluted suitable volume of formaldehyde solution with water to obtain a solution containing 25 µg/ml concentration of formaldehyde.

Sample preparation

Formaldehyde treated 25 body of the capsules were cut in to small pieces and taken in to a beaker and dissolved with 40 ml of water. Then the solution was filtered and diluted to 50 ml with water.

Procedure

1ml of the sample solution was added with 4 ml of water and 5 ml of acetyl acetone reagent and kept in a water bath at 40^0C for 40 mts. The same procedure was followed for 1 ml of standard formaldehyde solution. The colour produced in the sample solution was compared with the colour produced with the standard solution.

Evaluation of precompression parameters of granules of Miglitol[173,174]

The powder blend used for the preparation of Miglitol immediate release tablets were evaluated for its physical characteristics such as bulk density, tapped density, angle of repose, compressibility index and hausner's ratio.

Evaluation of post compression parameters[175, 176,177]

The immediate release tablets were evaluated for thickness, hardness, friability, weight variation, disintegration, content uniformity, drug content and *in vitro* drug release.

Thickness

Thickness of tablet was measured by using vernier caliper.

Hardness test

Hardness of the tablets depends on the concentration of binder, superdisintegrant, distance between the upper and lower punches. Hardness of the prepared Miglitol immediate release tablets were carried out by Pfizer hardness tester.

Friability test

Friability test for the Miglitol immediate release tablets were carried out in a friabilator to check the ability of the tablet to with stand the pressure during handling and transportation. Twenty tablets were weighed and kept inside the rotating chamber and the apparatus was operated at a speed of 25 rpm for 4 minutes. At the end of the operation, the tablets were removed, dedusted and the final weight of the 20 tablets were taken. The percentage of drug loss was calculated from these intial and final weights of tablets by using the following formula,

Percentage of drug loss = (initial weight-final weight) 100 /Initial weight

Weight variation test

Weight variation test was carried out for plain Miglitol immediate release tablets and Miglitol pulsincaps. In this test twenty Miglitol immediate release tablets or Miglitol pulsincaps were weighed and the average weight was calculated. Then they were weighed individually. The percentage deviation of individual tablet or pulsincap from the average weight was calculated.

Disintegration test

Disintegration test was carried out for plain Miglitol immediate release tablets. Six randomly selected tablets from each formulation were placed in each of the 6 tubes of basket rack. A disc was added to each tube and was positioned in a 1 L beaker filled with 800 ml of disintegration medium. This study was carried out using different buffer solutions such as pH 1.2 for 2 hrs, pH 6.8 for 3 hrs and pH 7.4 buffers for subsequent hrs at a temperature of 37± 2^0C. The times taken for all the six tablets to disintegrate completely were noted.

Content uniformity test[172]

Content uniformity test for plain Miglitol immediate release tablets and Miglitol pulsincaps were carried out by chromatographic technique.

Mobile phase preparation

0.96 gm of Potassium dihydrogen phosphate was weighed and dissolved in 1000 ml of water. 850 ml of this solution was mixed with 150 ml of acetonitrile, sonicated for 10 minutes and filtered.

Chromatographic conditions

Instrument- Shimadzu LC2010
Stationary phase- C8X150 x 4.6 mm i.d; 5µm
Mobile phase-850 ml buffer +150ml acetonitrile
Flow rate-1ml / mt**; Injection volume-**20 µl
Detection wave length-232nm

Standard preparation

25 mg of Miglitol standard weighed and transferred to 25 ml volumetric flask and dissolved with 5 ml of water and diluted up to the volume with acetonitrile. From this stock solution suitable dilution was made to obtain final standard concentration of 100 µg/ ml. Then the final solution was filtered.

Sample preparation

Samples were kept individually in a 25 ml volumetric flask and dissolved with 5 ml of water and diluted up to the volume with acetonitrile. From this sample solution suitable dilution was made to obtain final standard concentration of 100 µg/ ml. Then the final solution was filtered.

Procedure

The standard and sample solutions were injected and the amount of Miglitol was estimated by measuring the peak areas of standard and sample preparations.

Drug content[172]

Drug content study was carried out for plain immediate release Miglitol tablets and Miglitol pulsincaps. Standard preparation, chromatographic condition and the procedure as given in content uniformity determinations were applied for this drug content study also. For the Sample preparation twenty Miglitol immediate release tablets or Miglitol pulsincaps were weighed and powdered in a mortar. Weighed accurately the powdered sample equivalent to 25 mg of Miglitol and transferred in to a 25 ml standard flask. The sample was dissolved with 5 ml of water and diluted to 25 ml with actonitrile. Then the standard and samples were injected and the amount of Miglitol present was calculated by measuring peak areas of standard and sample.

***Invitro* drug release study**[172, 186,187,188]

The *In vitro* drug release study were performed for plain immediate release Miglitol tablets and Miglitol pulsincaps using different dissolution medium such as pH 1.2 for 2 hrs, pH 6.8 for 3 hrs and pH 7.4 buffers for subsequent hrs. The samples were taken at regular time intervals and the amount of drug released was calculated by measuring the areas of standard and sample preparation.

III. FORMULATION OF MIGLITOL PRESS COATED TABLETS

Stage1: Preparation of Miglitol core tablets for the third pulse[173, 174, 175]

The optimized formula **MCT5** used in the preparation of Miglitol immediate release tablets were selected for the preparation of core tablets in the formulation of press coated tablet of Miglitol. The formula used for the preparation of core tablet was given in **table 6.6**.

Table 6.6.Formula used for the preparation of Miglitol immediate release core tablets

S.No	Ingredients	Quantity (mg)
1	Miglitol	25
2	Avicel PH102	65.25
3	Sodium starch glycollate	8
4	Magnesium stearate	0.25
5	Aerosil	1.5

Stage 2: Press coating of Miglitol immediate release core tablets with barrier layer[189, 190, 191]

The press-coating of Miglitol immediate release core tablets with barrier layer were performed using different hydrophilic and hydrophobic polymers in various concentrations. The barrier layer was prepared by compression coating of immediate release Miglitol core tablets with various polymers such as L-hydroxy propyl cellulose, hydroxy propyl methyl cellulose, glyceryl behenate and ethyl cellulose in different ratios (MPT1-MPT26). 200 mg of this powder mixture of polymers were used for the outer shell (Barrier layer). A half amount of powder was filled into the die to make a powder bed, on the centre of which Miglitol immediate release tablet was placed. Then, the remaining half of the powder was filled in the die, and the contents were compressed. The formula used for the preparation of barrier layer was given in **table 6.7**.

Table 6.7. Formula used for the preparation of barrier layer

Trials (MPT1-22)	GLYCERYL BEHENATE (mg)	ETHYL CELLULOSE (mg)	HPMC (mg)	L-HPC (mg)
1.	200	_	_	
2.	_	200	_	
3.	_	_	200	
4.				200
5.	100	100	_	-
6.	100	_	100	
7.	100	-	-	100
8.	_	100	100	
9.	-	100	-	100
10.	-	-	100	100
11.	50	-	150	-
12.	50	-	-	150
13.	-	50	150	-
14.	-	50	-	150
15.	50	-	100	50
16.	50	-	50	100
17.	-	50	100	50
18.	-	50	50	100
19.	25	-	150	25
20.	25	-	25	150
21.	-	25	150	25
22.	-	25	25	150
23.	25	-	175	-
24.	25	-	-	175
25.	-	25	175	-
26.	-	25	-	175

Stage 3: Press coating of barrier layer with Miglitol immediate release layer for the second pulse[175,176,177]

Immediate release layer of Miglitol for second pulse was prepared by direct compression method. A half amount of immediate release powder was filled into the die to make a powder bed; on the centre the press coated tablet was placed. Then, the remaining half of the powder was filled in the die, and the contents were compressed.

Stage 4: Press coating of immediate release layer for the second pulse with second barrier layer[192-196]

The same procedure as given in the stage 2 was followed for the preparation of second barrier layer.

Stage 5: Coating of second barrier layer with immediate release layer of Miglitol for first pulse[197, 198]

The Second barrier layer was coated with immediate release layer of Miglitol using 6% PVP as adhesive by spray coating. Then tablet was rolled well over the required quantity of Miglitol-starch powder mixture to get a uniform coating and dried for 5 minutes at 40^0C in a hot air oven. The formula used for the immediate release layer of Miglitol for first pulse release was given in **table 6.8** and the images of prepared Miglitol press coated tablets were shown in **fig.6.5** to **6.8**.

Table 6.8. Formula for the immediate release layer of Miglitol for first pulse

S.No	Ingredients	Quantity (mg)
1	Miglitol	25
2	Starch	60
3	PVP	6%

MIGLITOL PRESS COATED TABLETS

Fig.6.5.Miglitol immediate release tablets

Fig.6.6.Miglitol immediate press coated tablets with single barrier layer

Fig.6.7.Miglitol immediate press coated tablets with double barrier layer

Fig.6.8.Miglitol immediate release tablets encapsulated in barrier layer

EVALUATION OF MIGLITOL PRESS COATED TABLETS[199, 200,201,202]

The prepared press coated tablets were evaluated for hardness, friability, thickness, drug content, and *in vitro* drug release studies.

Thickness

Thickness of Miglitol press coated tablet was measured by using vernier caliper.

Hardness test

Hardness of the prepared Miglitol press coated tablets were carried out by Pfizer hardness tester.

Friability test

Twenty Miglitol press coated tablets were weighed and kept inside the rotating chamber and the apparatus was operated at a speed of 25 rpm for 4 minutes. At the end of the operation, the tablets were removed, dedusted and the final weight of the 20 tablets were taken. The percentage of drug loss was calculated from these intial and final weights of tablets by using the following formula,

Percentage of drug loss = (initial weight-final weight) 100 /Initial weight

Weight variation test

In this test twenty Miglitol press coated tablets were weighed and the average weight was calculated. Then they were weighed individually. The percentage deviation of individual tablet o from the average weight was calculated.

Content uniformity

Content uniformity test for Miglitol press coated tablets were carried out in the same procedure as followed in content uniformity test for Miglitol pulsincaps.

In vitro dissolution studies

The *in vitro* dissolution studies for the prepared press coated tablets were carried out in the same procedure as followed in *in vitro* dissolution studies for Miglitol pulsincaps.

IV. PERFORMANCE EVALUATION OF OPTIMIZED MIGLITOL PULSINCAPS AND MIGLITOL PRESS COATED TABLETS

Pharmacokinetic Parameter Studies

RP-HPLC Assay of Miglitol - Chromatographic conditions[172, 203,204,205]

Instrument- Shimadzu LC2010

Stationary phase- C8X150 x 4.6 mm i.d; 5µm

Mobile phase-850 ml buffer +150ml acetonitrile

Flow rate-2ml / mt**; Injection volume-**20 µl

Detection wave length-232nm

The stock solution of Miglitol was prepared by accurately weighing 25 mg Miglitol, transferring to 25 ml volumetric flask, dissolving in 5 ml of water and diluting it up to the mark with acetonitrile. Appropriate aliquot of this solution was further diluted to 10 ml with acetonitrile to obtain final standard solution of 100 µg/ ml of Miglitol. Resultant solution was filtered through Whatman filter paper No.1. All the stock solutions were refrigerated (2-8^{0}C when not in use).

The mobile phase consisted of sodium dihydrogen phosphate: acetonitrile (85:15, v/v) in Milli-Q water and the pH adjusted to 6.2 using 2MOPA. The flow rate was fixed to 2ml/min with sample volume 20 µl and the mobile phase was filtered through a 0.22µ membrane and degassed using ultra sonicator injected into HPLC system using rheodyne injector and all determinations were performed at ambient column temperature. The wave length used to read the values was 232 nm. The run time was set at 10 minutes.

Preparation of standard solutions for calibration curve[172.206, 207,208]

Appropriate aliquots of standard Miglitol stock solution (100 µg/ml) were taken in different 10 ml volumetric flasks and resultant solution was diluted up to the mark with mobile phase to obtain final concentration of 5, 10, 15, 20, 25 and 50 µg/ ml of Miglitol. These solutions were injected into chromatographic system and chromatograms were obtained and peak area was determined for each concentration

of drug solution. Calibration curve of Miglitol was constructed by plotting peak area Vs applied concentration of Miglitol and regression equation was computed. Similarly the sample solution was chromatographed and concentrations of Miglitol in samples were found out using regression equation.

Analysis of data[172.206, 207,208]

The concentrations of Miglitol were quantified using HPLC technique. Consequently, based on the drug concentrations the AUC, C_{max} and other pharmacokinetic parameters were calculated by using "KINETICA" software. The results were compared statistically by using "graph pad prism" software.

Pharmacokinetic study *in vivo* [209,210,211,212,213]

Study design

The pharmacokinetic study was performed using the open labeled parallel study design i.e. Miglitol pure in first group, Miglitol pulsincap in second group and Miglitol press coated tablets in third group[211].

Animals

The male rabbits (2000-2600 gms) were selected from the animal housing facility of Vel's college of pharmacy, Chennai. They were maintained under controlled lab environment and fed with standard pellet diet (Sai Durga Foods PVT Limited, Bangalore) and water *ad libidum*. All the animals were quarantined for one week before commencement of study. For each combinational sets of study, three groups of rabbits consisting of six animals each were used (n=6). **(No. XII/VELS/ PCOL/22/2000/CPCSEA/IAEC/10.06.2010)**

Collection of blood sample and processing[214]**:**

The appropriate drug treatment in the respective groups was continued for one-week period. In the first phase of work, i.e. On day 1, the animals were administered with respective drugs and the blood samples (500 µl) were collected at different time

intervals (0, 0.5, 1, 2, 4, 6, 8 and 24 hrs) through ear marginal vein using fine butterfly needle with the diameter of 0.5 mm from each animal into the heparinized eppendorff tubes and equal amount of saline were administered to replace blood volume at every blood withdrawal time. Centrifugation was performed at 3000 rpm for 10 minutes and plasma was isolated carefully and every time the plasma collecting tube was labeled (tarsons micro centrifuge tube 2 ml) appropriately at sampling time and kept ready. The upper-layer plasma was transferred from the centrifuged tube to the labeled plasma collecting tube without air bubbles using adjustable micropipette (500 µl) by placing the tip (tarsons micro tip, 200-1000 µl) of the pipette under the surface of the plasma.

All this procedure was done within half an hour of blood collection. The separated plasma samples were stored in the deep freezer at about -20^0C, to allow sufficient number of samples to accumulate to perform the analysis as well as to avoid degradation. The plasma samples were removed from the freezer just before 5 minutes to inject the sample for analysis. Animals were allowed for food after second hour (2 hr) sampling. After 24h sample collection, the treatment was continued till 7th day and again the samples were collected in the same pattern after administration of last dose. The reason for one-week treatment is that, in long term therapy the rate of enzyme inhibition/induction may develop slowly.

Pharmacokinetic parameters[212, 213]

The pharmacokinetic parameters, peak plasma concentrations (C_{max}) and time to reach peak concentration (t_{max}) were directly obtained from concentration time data. In the present study, AUC_{0-t} refers to the AUC from 0 to 24 hrs, which was determined by linear trapezoidal rule and $AUC_{0-\alpha}$ refers to the AUC from time at zero hours to infinity.

The $AUC_{0-\alpha}$ was calculated using the formula AUC_{0-t} + [Clast/K] where C last is the concentration in µg/ml at the last time point and K is the elimination rate constant.[212, 213]

Various pharmacokinetic parameters like area under the curve [AUC], elimination half life [$t_{½}$]. Volume of distribution (V/f) total clearance (Cl/f) and mean residence time for each subject using a pharmacokinetic software programme KINETICA based on the following equations.

Treatment of Bio availability Data[215]

The various pharmacokinetic parameters were calculated through model independent or non-compartmental model. Although it is customary to fit the data into compartment model, there are some indications by earlier workers that pharmacokinetics of certain drug revealed alterations in the compartment model to which they adhere as a function of time of administration**.**[215]

The various pharmacokinetic parameters like elimination half-life ($t_{½}$), overall elimination rate constant (K_e), area under concentration time curve (AUC), area under the first moment curve (AUMC), apparent volume of distribution for fraction of dose absorbed (Vd/f), total clearance (Cl/f) for the drug under consideration were obtained in each subject from serum concentration verses time profile on a IBM compatible personal computer using KINETICA, a program developed based on the equations described in the following paragraphs.

1. Peak time (T_{max}) and peak levels (C_{max})

These parameters were obtained from the observed concentrations verses time data in each subject.

2. Overall elimination rate constant (K_e)

The overall elimination rate constant is the sum of individual rate constant associated with the loss of parent drug in the body and is calculated from the slope of the terminal elimination phase of a semi logarithmic plot of concentration of the drug in biological fluid verses time, after subjecting it to linear regression analysis.

$$\text{Slope} = \frac{n[\Sigma^{n}_{i=1} T_i \ (\log Ci)] - [\Sigma^{n}_{i=1} \times \log Ci]}{n[\Sigma T_i^2] - [\Sigma T_i]^2}$$

Where n is the number of points in the terminal phase and

$$Ke = \text{-slope x } 2.303$$

3. Half Life ($t_{½}$)

Half-life of the drug is defined as the time required to reduce the concentration of drug in the body by 50%. It can be calculated from elimination rate constant, assuming the elimination to be a first order process.

$$t_{½} = 0.693 / Ke$$

Whereas Ke is the overall elimination rate constant.

4. Area under the curve (AUC)

The area under the concentration time curve extended to infinite time represents bioavailability of the drug. It is calculated by means of trapezoidal rule. It is area under the zero moment curves.

$$AUC_{0\text{-}t} = \int_0^t C.dt.$$

$$= \Sigma [(ti+1 - ti) / 2 \times (Ci + Ci+1)]$$

$$AUC_{0\text{-}\infty} = AUC0\text{-}t + C/Ke$$

Where C is the concentration at last point t.

5. Area under first moment curve (AUMC)

This is again computed by means of trapezoidal rule and it is the area under the curve resulting upon plotting the product of concentration and time verses time.

$$AUMC_{0\text{-}t} = {}_0\int^t Ct.dt.$$

$$= \Sigma [(ti+1 - ti) /2 \times (Ci + Ci+1)]$$

$$AUMC_{0\text{-}\infty} = AUMC_{0\text{-}t} + [Ct/K_e \cdot C/K_{e2}]$$

6. Mean Residence time (MRT)

Mean residence time represents the time for 63.2% of the administered dose to be eliminated. It is statistical moment analog of half-life.

$$MRT = \frac{AUMC}{AUC} = \frac{{}_0\int^t Ct.dt.}{{}_0\int^t C.dt.}$$

Mean residence time is the function of route of drug administration thus MRT values for extra vascular drug administration are always greater than the MRT following intravenous bolus administration. MRT of a drug can be described by one compartment model after intravenous administration is given by

$$MRT \text{ i.v.} = 1/K_e$$

$$\& \quad t_{½} = 0.693 \text{ MRT i.v.}$$

7. Absorption rate Constant

Statistical moment method for estimating rates of absorption after oral or intramuscular administration of a drug are based on the differences in mean residence time after extra vascular and intra vascular routes.

$$MAT = MRTev - MRT \text{ iv}$$

Where MAT is the mean absorption time.

When drug absorption can be describe by a first order process.

$$MAT = 1/ Ka$$

In this study Ka is calculated from the equation

$$Ka = \frac{4.61}{T_a} h^{-1}$$

Where T_a is the absorption time obtained from a semi logarithmic plot of concentration verses time data.

8. Apparent Volume of Distribution (Vd/f)

Once a drug attains distribution equilibrium, there exists a relation between the concentration of drug in plasma and total amount of drug in the body. The proportionality constant relating these two quantities is called the apparent volume of distribution. This conventional parameter gives an understanding of drug reaching tissue level and is calculated in several ways. However the volume parameter obtained for any drug by administering through any route other than intravenous will never represent the real apparent volume of distribution. In the present study the apparent volume of distribution for fraction of drug absorbed (Vd/f) was calculated using the equation.

$$Vd/f = \frac{Dose}{AUC_{0-\infty} \times K_e} \ ml/hr$$

9. Clearance (Cl_s / f)

Systemic clearance represents the sum of individual processes like renal clearance, hepatic clearance, salivary clearance, etc., involved in the elimination of drug from the body and is calculated using the equation.

$$Cls/f = \frac{Dose}{AUC_{0-\infty}} \ ml/hr$$

PHARMACODYNAMIC STUDY[216,217,218,219,220,221]

Animals

Male Albino rabbits were obtained from the animal house of School of Pharmacy, Vels University, Chennai. Before and during the experiment, animals were fed with standard diet (Sai durga foods, Bangalore). After randomization into various groups and before initiation of experiment, the rabbits were acclimatized for a period of 7 days under standard environmental conditions of temperature, relative humidity and dark/light cycle. Animals described as fasting were deprived of food and water for 16 hours ad libitum.

Drug administration

The pure drug Miglitol was suspended in vehicle (2% w/v suspension of carboxy methyl cellulose (CMC) in water 10 ml/kg b.w). and was administered continuously for 14 days orally using an oral feeding tube. Similarly the other formulations were administered in rabbits directly with the help of specially designed oral gavage tube continuously for 14 days.

Experimental Design

Induction of Diabetes in Experimental Animals

Rabbits were made diabetic by a single intraperitoneal injection of alloxan monohydrate (150mg/kg). Alloxan was first weighed individually for each animal according to the body weight and then solubilized with 0.2ml saline just prior to injection. Two days after alloxan injection, rabbits with plasma glucose levels of >150mg/dl were included in the study. Treatment with Miglitol pure, marketed Miglitol tablet, Miglitol pulsincap (MPC 9), Miglitol press coated tablet (MPT 24), were started 48 h after alloxan injection.

Six groups of rabbits, six in each received the following treatment schedule,

Group I : Normal control (saline).
Group II : Alloxan treated control (150 mg/kg.ip).
Group III : Alloxan (150 mg/kg.i.p) + Miglitol Marketed 25 mg/kg, p.o,
Group IV : Alloxan (150 mg/kg.ip) + Miglitol Press coated 25 mg/kg, p.o
Group V : Alloxan (150 mg/kg.ip) + Miglitol pulsicap (25 mg/kg, p.o).
Group VI : Alloxan (150 mg/kg.ip) + Miglitol Pure (25 mg/kg, p.o).

Miglitol pure, marketed Miglitol tablet, Miglitol pulsincap (MPC 9), Miglitol press coated tablet (MPT 24) and saline were administered with the help of feeding cannula. Group I serve as normal control, which received saline for 14 days. Group II to Group V are diabetic control rabbits. Group III to Group V (which previously received alloxan) are given a fixed dose Miglitol different formulations (25 mg/kg, p.o), for 14 consecutive days. Group VI was treated with miglitol pure.

Collection of Blood Sample and Blood Glucose Determination[214]

Blood samples were drawn from ear marginal vein of rabbits at weekly intervals till the end of study. Fasting blood glucose estimation and body weight measurement were done on day 1, 5, 10 and 14 of the study. Blood glucose estimation was done by one touch electronic glucometer using glucose test strips. On day 14, blood was collected from retro-orbital plexus under mild ether anesthesia from overnight fasted rabbits and fasting blood sugar was estimated. Serum was separated and analyzed for serum cholesterol, serum triglycerides.

Statistical Analysis

All the values were expressed as mean±standard error of mean (S.E.M.) and analyzed for ANOVA and Dunnet's *t*-test. Differences between groups were considered significant at $P < 0.01$. Plasma concentrations of test samples were quantified using HPLC technique. Consequently, based on the drug concentrations the AUC and other pharmacokinetic parameter were calculated by using "KINETICA" software. The results were compared statistically by using "graph pad prism" software. Pharmacodynamic data were expressed as Mean ± Standard Error of Mean. Statistical analysis was done by using student's unpaired t-test.

V. STABILITY EVALUATION OF OPTIMIZED MIGLITOL PULSINCAPS AND MIGLITOL PRESS COATED TABLETS [123,222]

The optimized formulation of Miglitol pulsincap (MPC9) and press coated tablets (MPT24) were subjected to stability studies as per ICH guidelines. Samples were withdrawn at predetermined time intervals and subjected to various quality control tests such as weight variation, hardness, friability, weight variation, content uniformity, drug content and *in vitro* drug release. The conditions used for stability studies of Miglitol pulsincap and press coated tablets were given in **table 6.9**

Table 6.9. Conditions for stability studies of Miglitol pulsincap and press coated tablets

Storage temperature(°C)	Relative humidity (%)	Minimum time period covered by data at submission(months)
Accelerated :40±2	75±5	6
Intermediate: 30±2	65±5	12
Long term: 25±2	60±5	12

VI. COMPARISON OF *IN VITRO* DRUG RELEASE PROFILE OF OPTIMIZED MIGLITOL PULSINCAPS (MPC9) AND MIGLITOL PRESS COATED TABLETS (MPT24) WITH MARKETED MIGLITOL TABLETS

The *in vitro* drug release profile of the optimized formulations of Miglitol pulsincap (MPC9) and press coated tablets (MPT24) were compared with the *in vitro* drug release profile of marketed Miglitol tablets. The *in vitro* drug release studies were carried out in three different buffer solutions such as pH 1.2, pH 7.4 and pH 6.8.

7. RESULTS AND DISCUSSION

1. PREFORMULATION STUDIES

The preformulation results obtained for the drug Miglitol was found to within the limits and desirable standards for the preparation of pulsincaps and press coated tablets.

1.1. Characterization of Miglitol

Description

The physical appearance of Miglitol was found to be white crystalline powder. The solubility results of Miglitol in different buffer solutions were given below,

Solubility studies

Solubility of Miglitol in pH 1.2 was found to be 31.42mg/ml
Solubility of of Miglitol in pH 6.8 was found to be 33.25mg/ml
Solubility of Miglitol in pH 7.4 was found to be 32.39mg/ml
As evident from the solubility profile study, Miglitol was soluble in pH 1.2, pH 6.8 and pH 7.4

Identification

The IR, HPLC and melting point results were used to identify the Miglitol. The IR spectrum and retention time of sample were similar to that of IR spectrum and retention time of standard Miglitol. The IR spectrum and HPLC chromatogram were given in **Fig.7.1 to Fig 7.4**

Physical characteristics

Physical characteristics results of Miglitol indicated that, it possesses poor flow property and needs to be improved. The results were given in **table 7.1**

1.2. Drug –Excipients accelerated compatibility study based physical observation and assay

Upon analysis of the drug excipient mixture for their physical characteristics no colour change was observed. Based on the chemical evaluation it was found that there was no significant change observed indicating that the drug is compatible with the added ingredients. The results of this study were given in **Table 7.2 to 7.4**.

1.3. Compatibility study using IR and DSC

- In the IR spectrum of Miglitol standard consists of characteristics band values at 3865 cm^{-1}(C-H-bending), 2816 cm^{-1}(C-H-stretching) and 1589. $2cm^{-1}$ (N-H-stretching). These characteristic band values were observed in all the recorded IR spectra.

- DSC of Miglitol showed a sharp endothermic peak at147.17^0C (melting point). The physical mixture of Miglitol and other excipients also showed the same thermal behavior as the individual component.

- DSC results also revealed that the physical mixture of Miglitol with excipients showed superimposition of the thermograms. There was no significant change observed in melting endotherm of physical mixture of Miglitol and excipients.

- From the IR and DSC studies, it was found that there were no interaction took place between Miglitol and the other ingredients used in the formulation of pulsincaps and press coated tablets. The IR spectra and DSC images were shown from **Fig.7.5 to Fig.7.56**

1.4. Standard graph of Miglitol

The linear plot was obtained for the aliquot concentration of 5, 10, 15 20, 25 30, 35 40, 45 and 50 µg/ml with absorbance seen at 232 nm. The results were given in **Table 7.5** and the standard graph was shown in F**ig.7.57 to 7.59**

1.5. Evaluation of Formaldehyde Treated Capsules

Solubility test

The solubility study results for the formaldehyde treated capsules showed that, only the cap dissolved within 10 mts but the body of the capsules remained intact for about 24 hrs.

Chemical test for free formaldehyde

The chemical test was carried out to check the presence of free formaldehyde in body of the capsules. The results of chemical test for free formaldehyde showed that the intensity of colour produced in the sample solution was not more intensely colored than the colour produced in the standard solution.[223] This result confirmed that less than 25 µg/ml concentration of free formaldehyde was present in the 25 capsules body.

1.5. Pre Compression Parameters of Miglitol Immedite Release Tablets

The precompression parameter results of Miglitol granules for all the six trials indicated that the powder was freely flowing. As the granules showed good flow properties, it was found to be suitable for compression. The results were given in **table 7.6.**

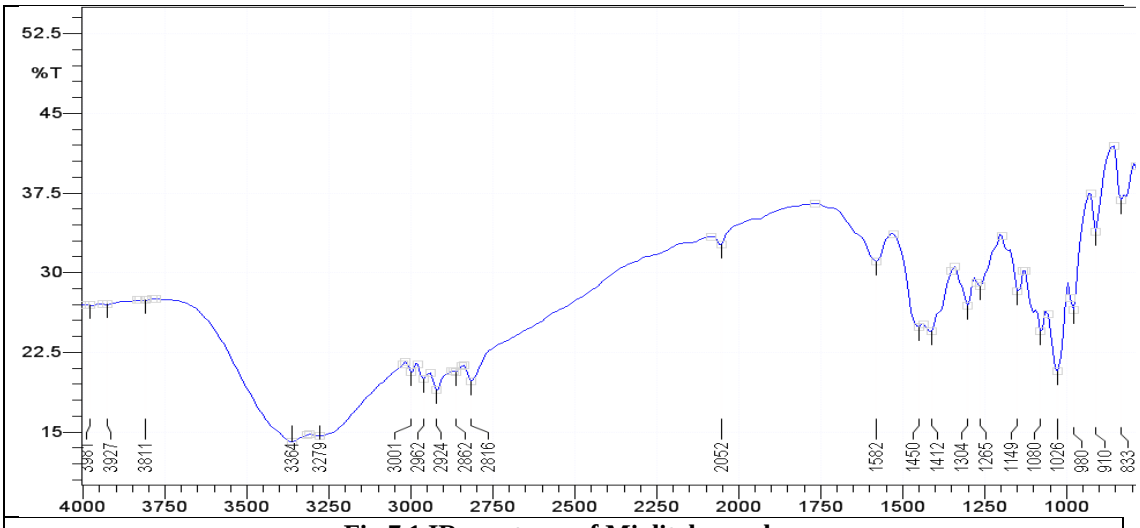


Fig.7.1.IR spectrum of Miglitol sample

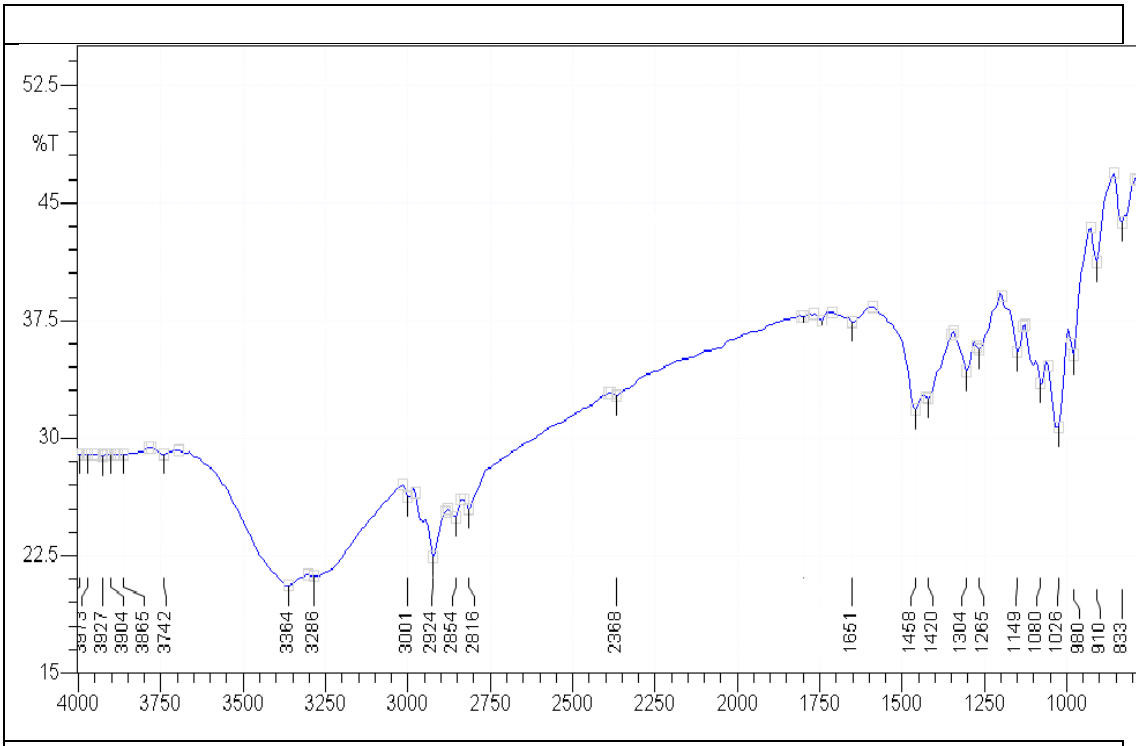


Fig.7.2.IR spectrum of Miglitol standard

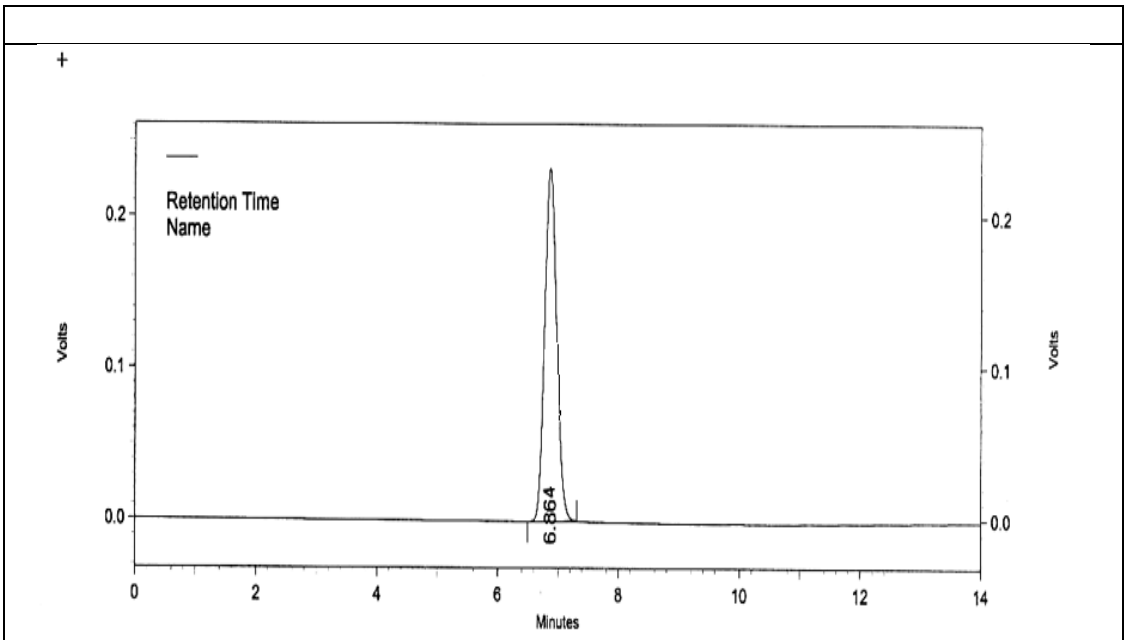


Fig.7.3.Chromatogram of Miglitol sample

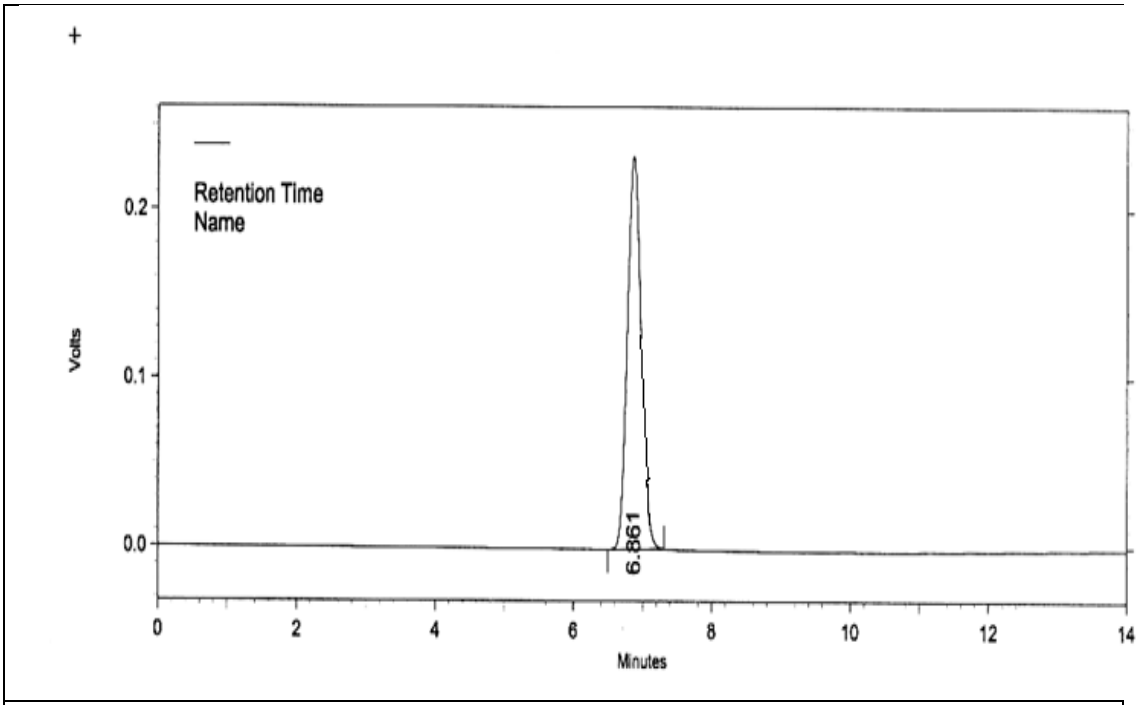


Fig.7.4.Chromatogram of Miglitol standard

Table 7.1. Physical characteristics of Miglitol

S.No	Physical parameters	Results
1	Description	White crystalline powder
2	Melting point	144-147^{0}C
3	Loss on drying	0.02%
4	Angle of repose	41.76 ±0.12
5	Bulk density	0.554±0.012
6	Tapped density	0.715±0.019
7	Compressibility index	22.52±0.3
8	Hausner's ratio	1.291±0.015

Table 7.2. Physical characteristics of individual drug and excipients

S.No	Sample ID	Initial description	Final description
17.	Miglitol	White crystalline powder	No change
18.	Avicel pH 102	Fine white crystalline powder	No change
19.	SSG	Fine white powder	No change
20.	Magnesium stearate	Very fine white powder	No change
21.	Aerosil	White amorphous powder	No change
22.	Lactose	White powder	No change
23.	PVP	Creamy white powder	No change
24.	Starch	Very fine white powder	No change
25.	Talc	Very fine white crystalline powder	No change
26.	Gelatin	Faintly yellow powder	No change
27.	HPMC K4M	White powder	No change
28.	Sodium alginate	Off white powder	No change
29.	HPMC	White powder	No change
30.	L-HPC	White powder	No change
31.	Ethylcellulose	White powder	No change
32.	Glycerylbehenate	Fine white powder	No change

Table 7.3. Physical characteristics of drug-excipient mixture

S.No	Sample ID	Initial description	Final description
1	Miglitol	White crystalline powder	No change
2	Miglitol+ Avicel pH 102	White crystalline powder	No change
3	Miglitol+ SSG	Fine white powder	No change
4	Miglitol+ Magnesium stearate	Very fine white powder	No change
5	Miglitol+ Aerosil	White amorphous powder	No change
6	Miglitol+ Lactose	White powder	No change
7	Miglitol+ PVP	Off white powder	No change
8	Miglitol+ Starch	Very fine white powder	No change
9	Miglitol+ Talc	Fine white crystalline powder	No change
10	Miglitol+ Gelatin	Off white powder	No change
11	Miglitol+ HPMC K4M	White powder	No change
12	Miglitol+ Sodium alginate	Off white powder	No change
13	Miglitol+HPMC	White powder	No change
14	Miglitol+ L-HPC	White powder	No change
15	Miglitol+ Ethylcellulose	White powder	No change
16	Miglitol+ Glycerylbehenate	White powder	No change

Table 7.4. Chemical characteristics of drug-excipient mixture

S.No	Sample ID	Initial assay (%)	Final assay (%)
1.	Miglitol	99.87±0.05	99.85±0.12
2.	Miglitol+ Avicel pH 102	99.83±0.07	99.82±0.04
3.	Miglitol+ SSG	99.84±0.08	99.83±0.07
4.	Miglitol+ Magnesium stearate	99.85±0.12	99.84±0.08
5.	Miglitol+ Aerosil	99.83±0.07	99.81±0.11
6.	Miglitol+ Lactose	99.84±0.08	99.83±0.07
7.	Miglitol+ PVP	99.86±0.06	99.82±0.04
8.	Miglitol+ Starch	99.87±0.05	99.84±0.08
9.	Miglitol+ Talc	99.82±0.04	99.81±0.11
10.	Miglitol+ Gelatin	99.81±0.11	99.81±0.11
11.	Miglitol+ HPMC K4M	99.83±0.07	99.84±0.08
12.	Miglitol+ Sodium alginate	99.86±0.06	99.86±0.06
13.	Miglitol+HPMC	99.84±0.08	99.83±0.12
14.	Miglitol+ L-HPC	99.85±0.12	99.84±0.08
15.	Miglitol+ Ethylcellulose	99.86±0.06	99.85±0.12
16.	Miglitol+ Glycerylbehenate	99.84±0.08	99.83±0.07

n = 3; Mean ± S.E.M.

Table 7.5. Concentration and absorbance of Miglitol in pH 1.2, pH 7.4 and pH 6.8 buffers

S.No	Concentration (µg/ml)	Absorbance		
		pH 1.2	pH 7.4	pH 6.8
1	5	0.044	0.052	0.039
2	10	0.082	0.106	0.080
3	15	0.124	0.157	0.118
4	20	0.172	0.202	0.156
5	25	0.214	0.252	0.195
6	30	0.258	0.304	0.234
7	35	0.302	0.358	0.279
8	40	0.346	0.408	0.312
9	45	0.392	0.464	0.351
10	50	0.434	0.512	0.392

Table 7.6. Precompression parameters of Miglitol immediate release granules

Trials	Angle of repose(^{0})	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner's ratio
MCT1	27.12±0.05	0.632±0.02	0.708±0.04	10.73±0.02	1.12±0.02
MCT2	27.24±0.12	0.628±0.12	0.703±0.06	10.66±0.05	1.12±0.02
MCT3	27.18±0.13	0.643±0.06	0.717±0.02	10.32±0.03	1.12±0.02
MCT4	27.42±0.18	0.639±0.08	0.711±0.05	10.13±0.04	1.11±0.04
MCT5	27.24±0.11	0.642±0.03	0.709±0.04	9.44±0.01	1.10±0.01
MCT6	27.25±0.09	0.627±0.04	0.695±0.02	9.78±0.02	1.11±0.04

n = 3; Mean ± S.E.M.

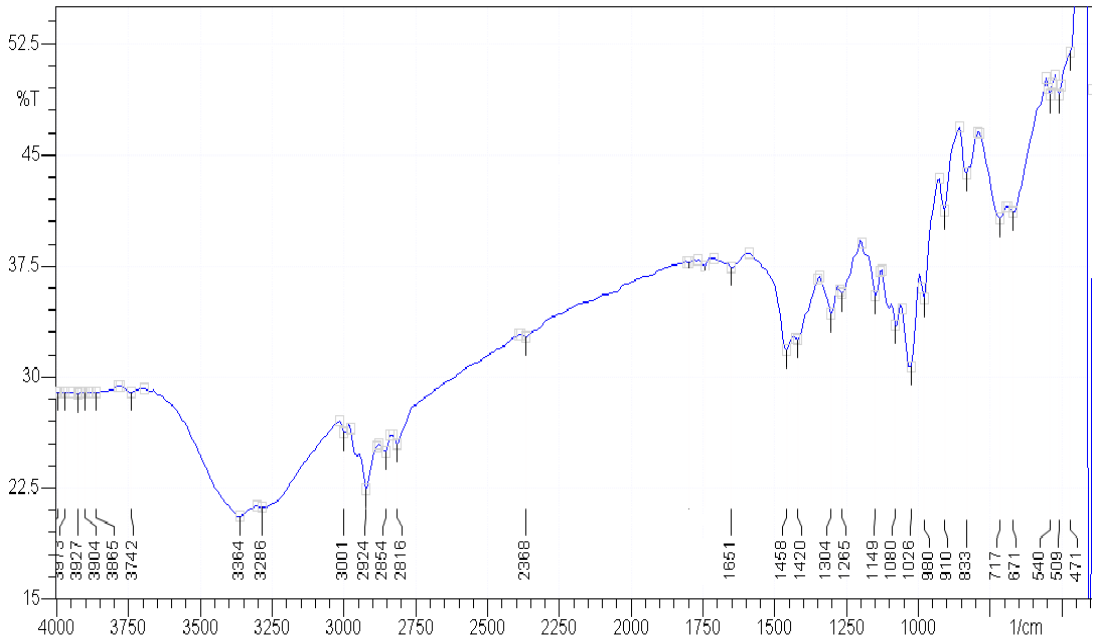


Fig.7.5.IR spectrum of miglitol standard

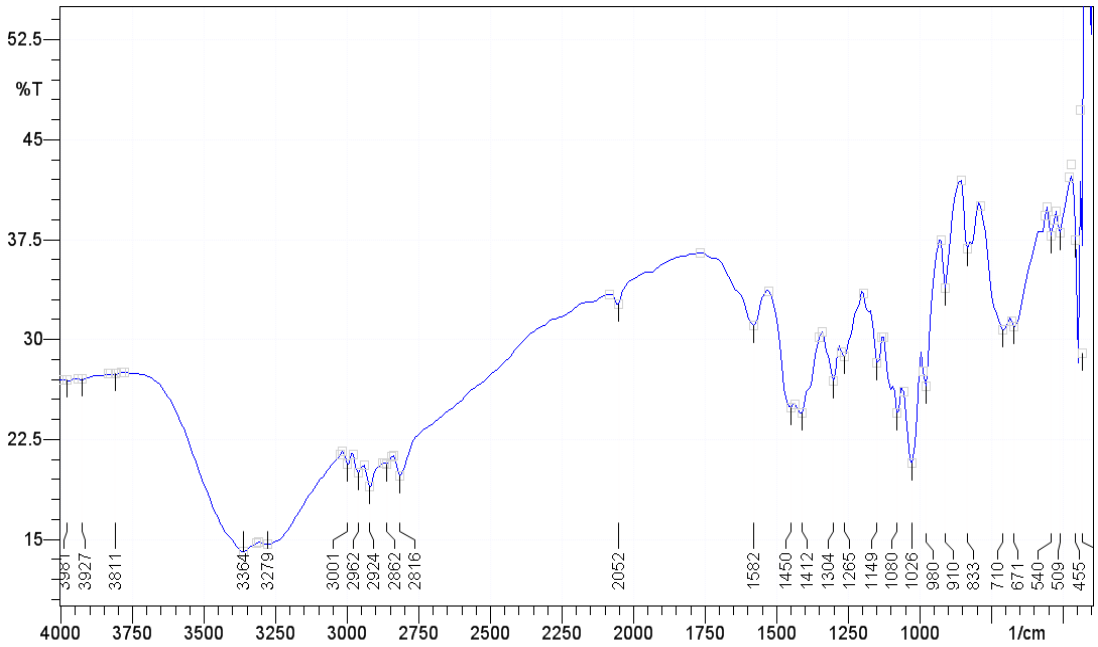


Fig.7.6.IR spectrum of miglitol sample

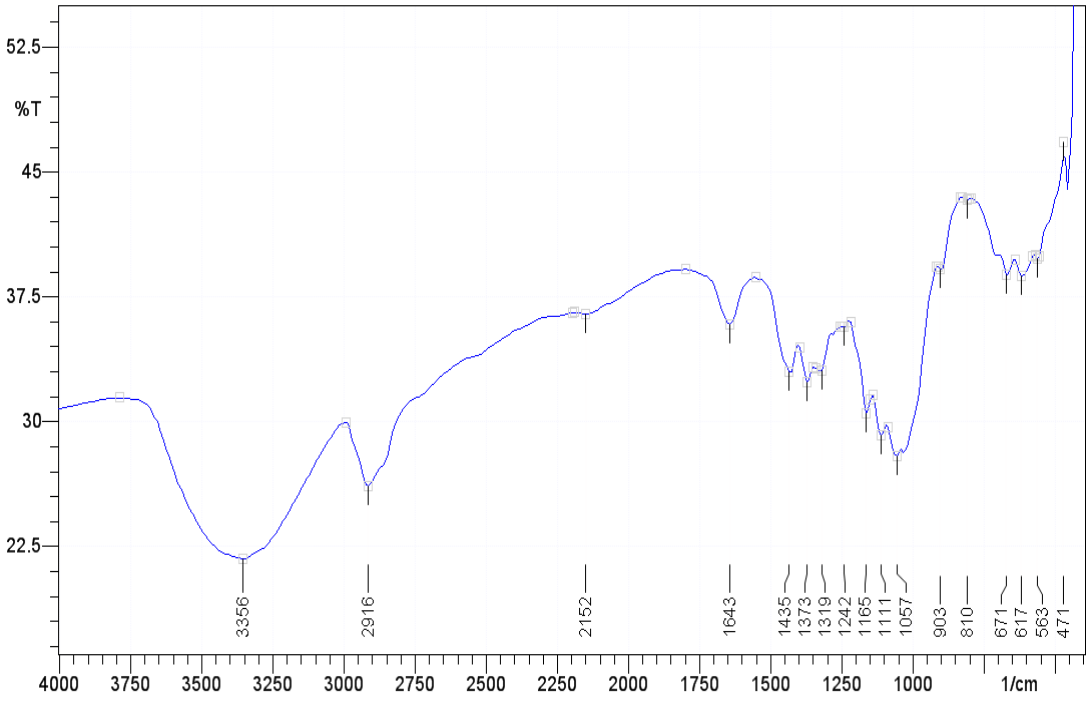


Fig.7.7. IR spectrum of Avicel

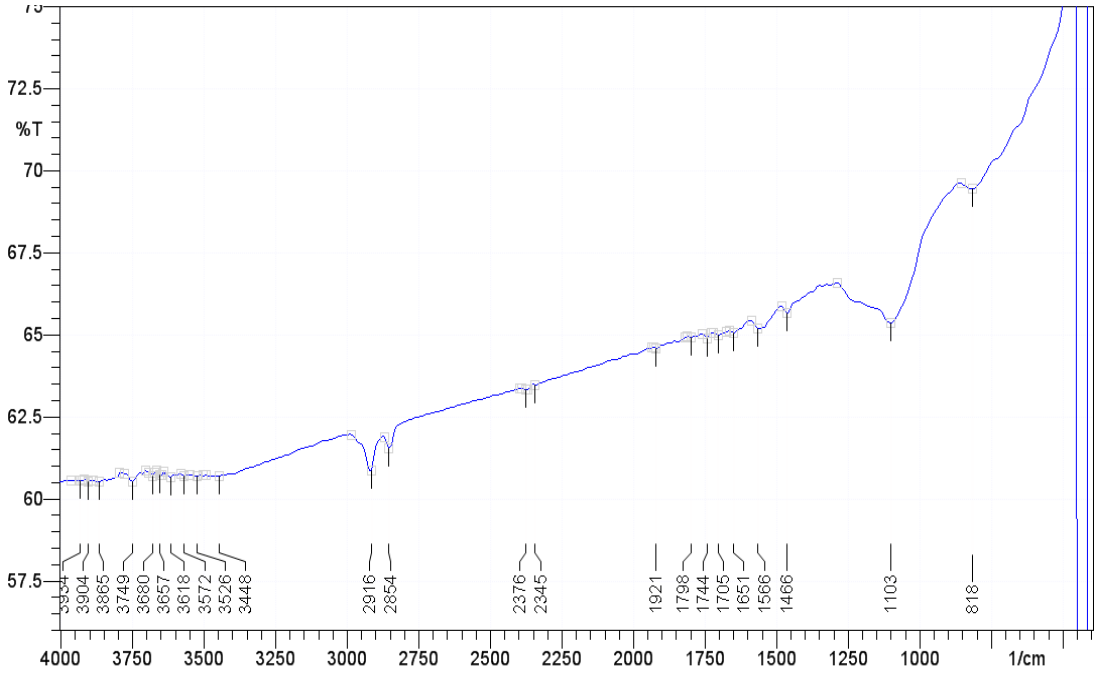


Fig.7.8.IR spectrum of Aerosil

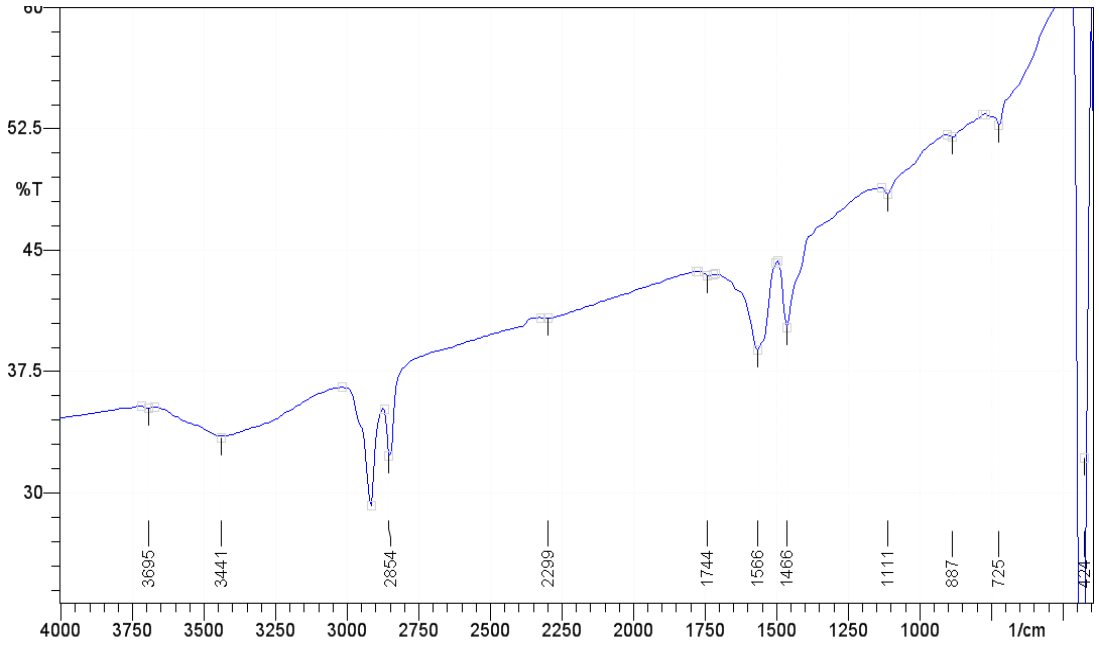


Fig.7.9. IR spectrum of Magnesium stearate

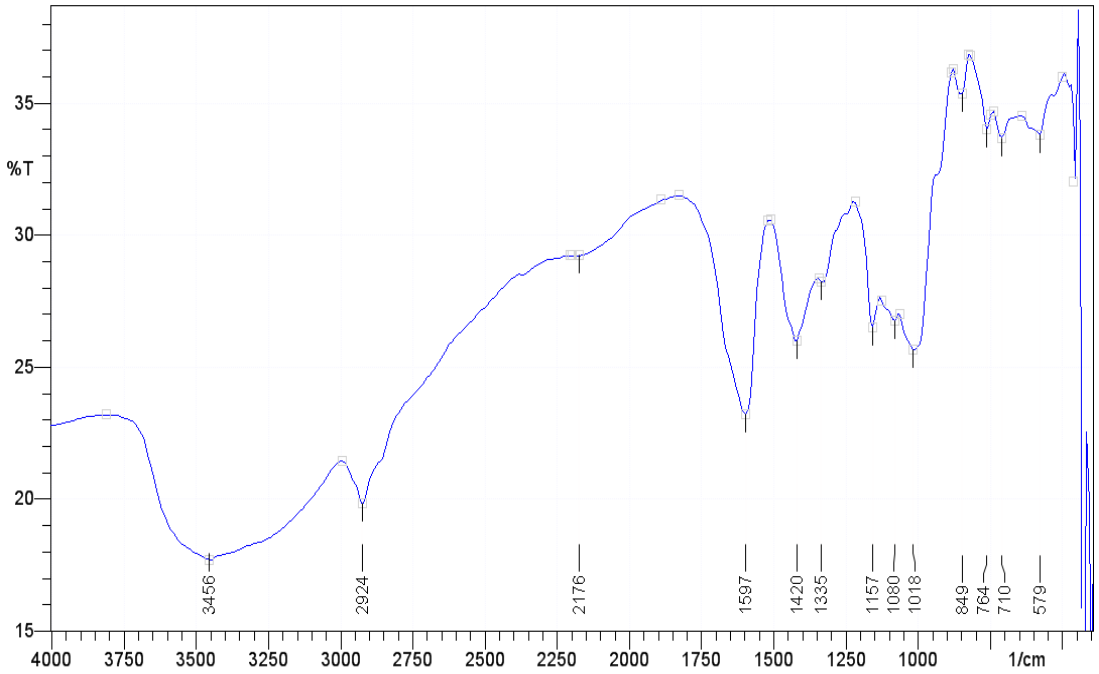


Fig.7.10.IR spectrum of Sodium starch glycollate

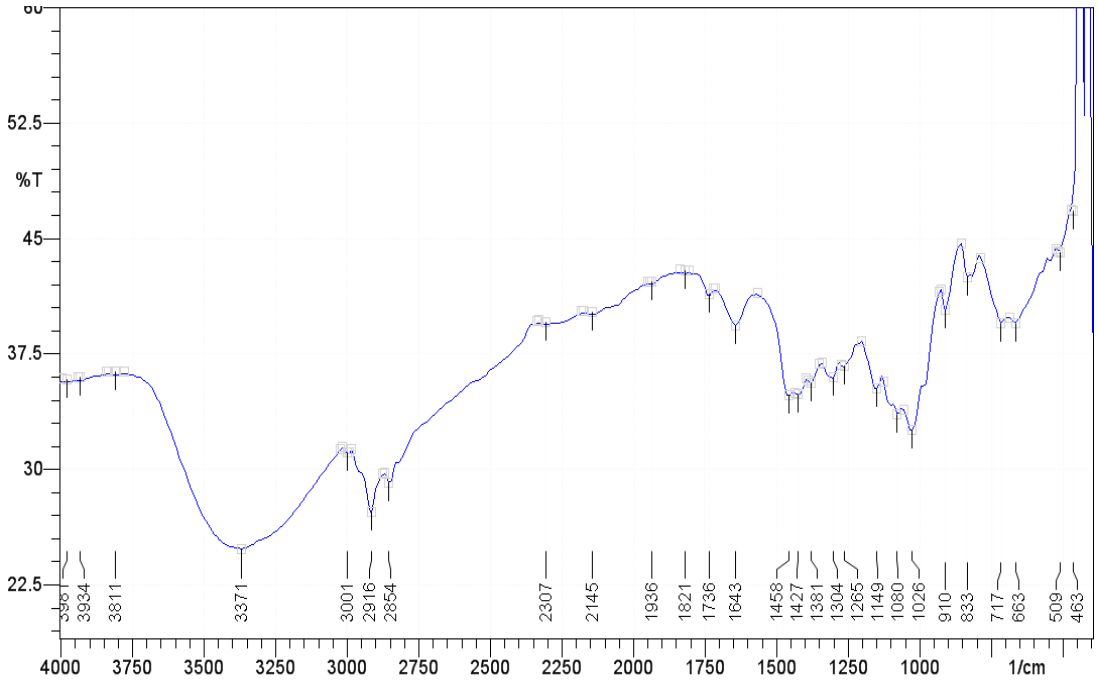


Fig.7.11. IR spectrum of Miglitol-Avicel

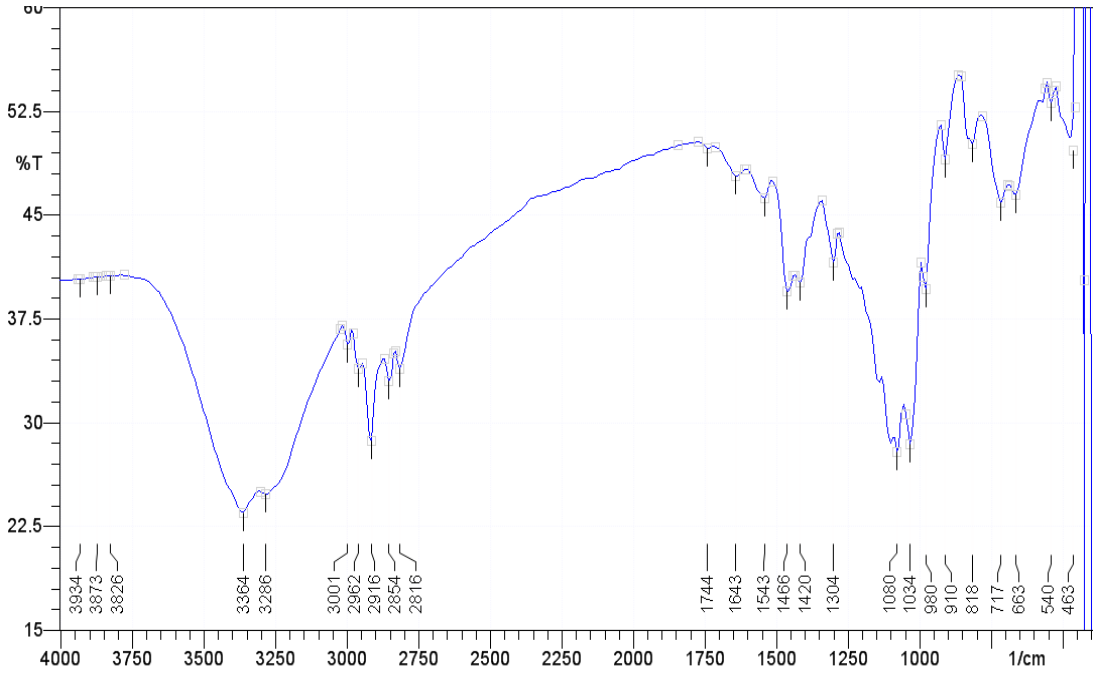


Fig.7.12. IR spectrum of Miglitol-Aerosil

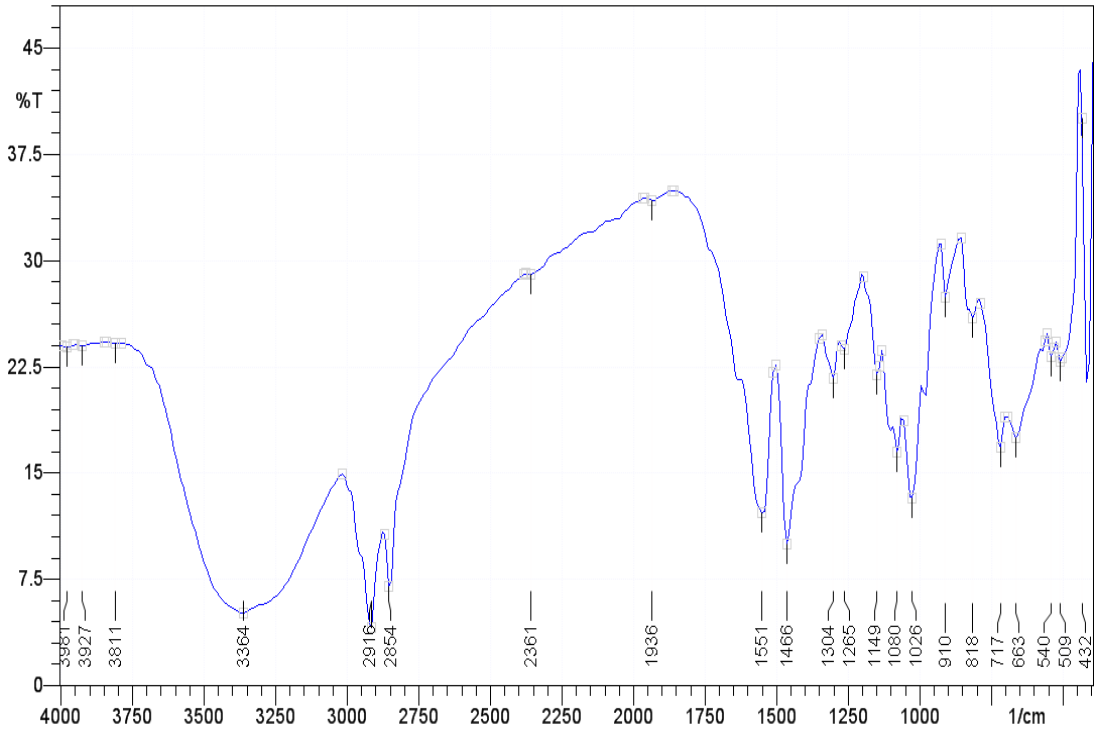


Fig.7.13. IR spectrum of Miglitol-Magnesium stearate

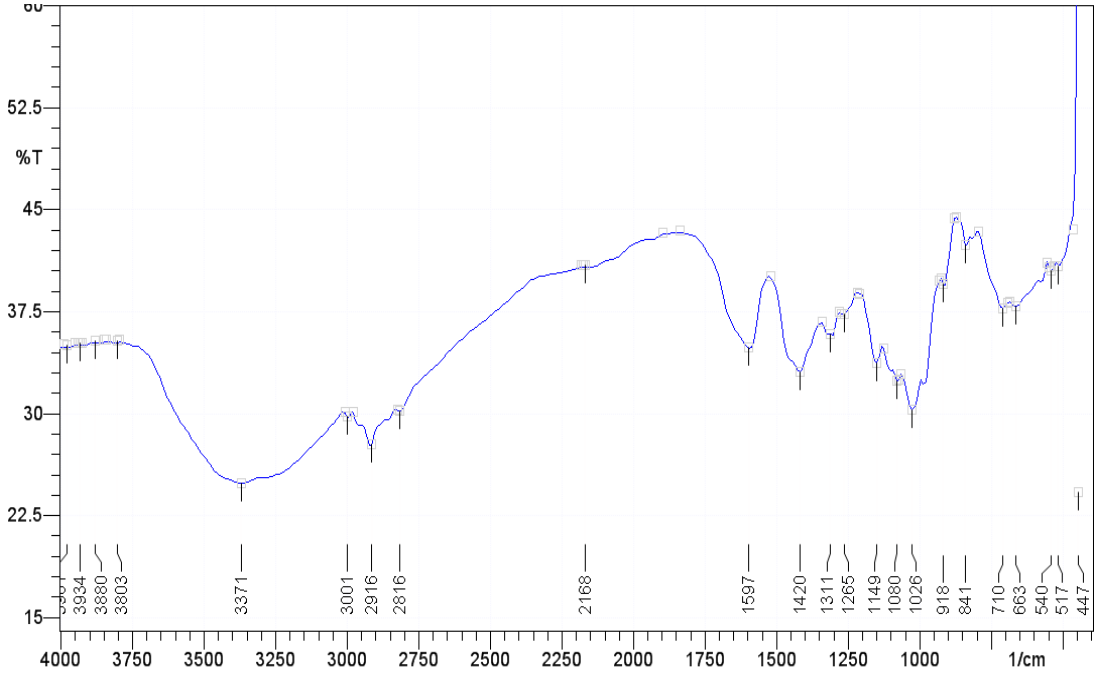


Fig.7.14.IR spectrum of Miglitol-Sodium starch glycollate

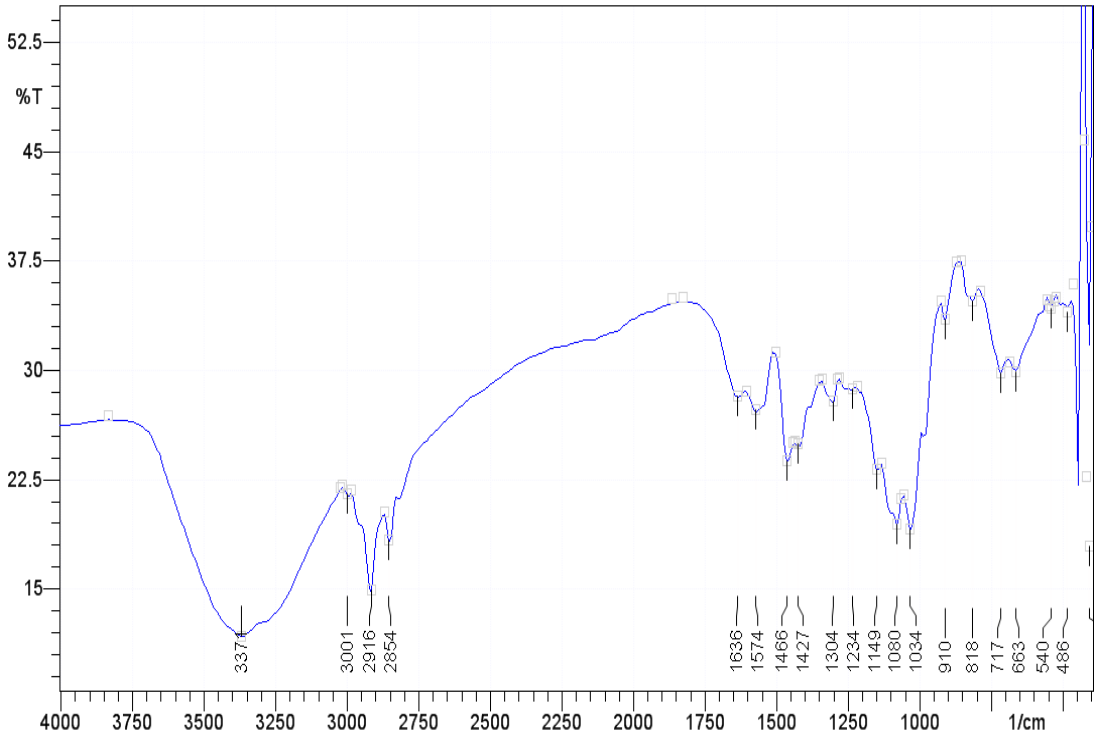


Fig.7.15. IR spectrum of Miglitol blend

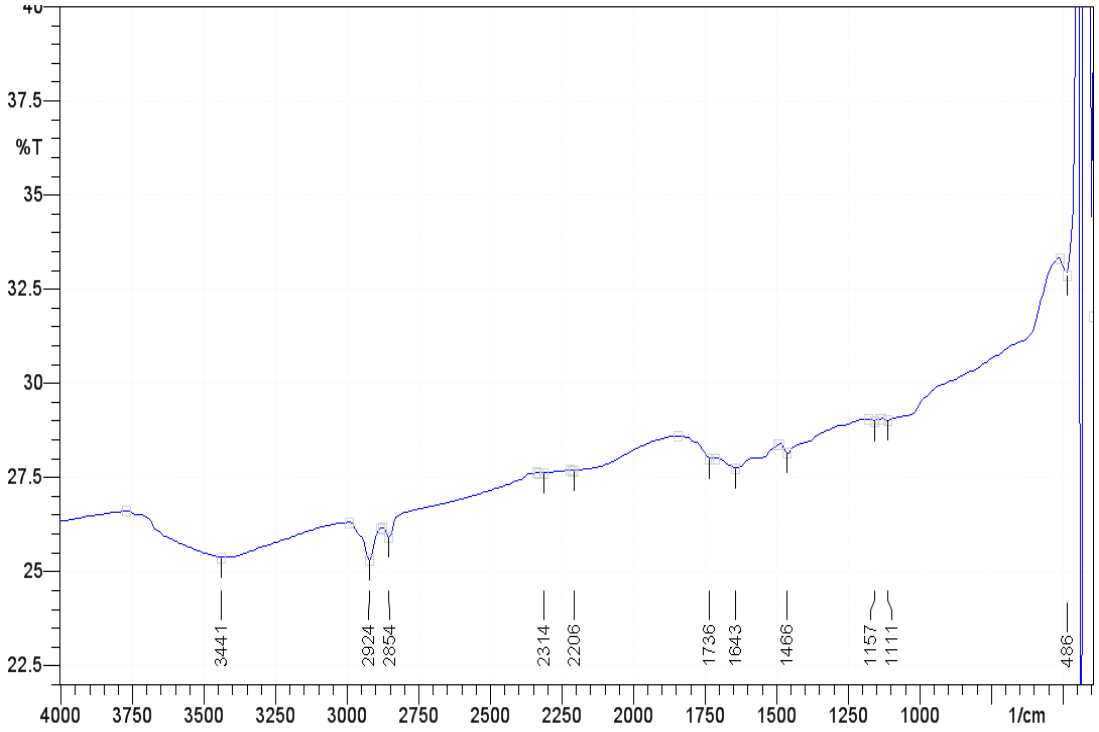


Fig.7.16. IR spectrum of Gelatin

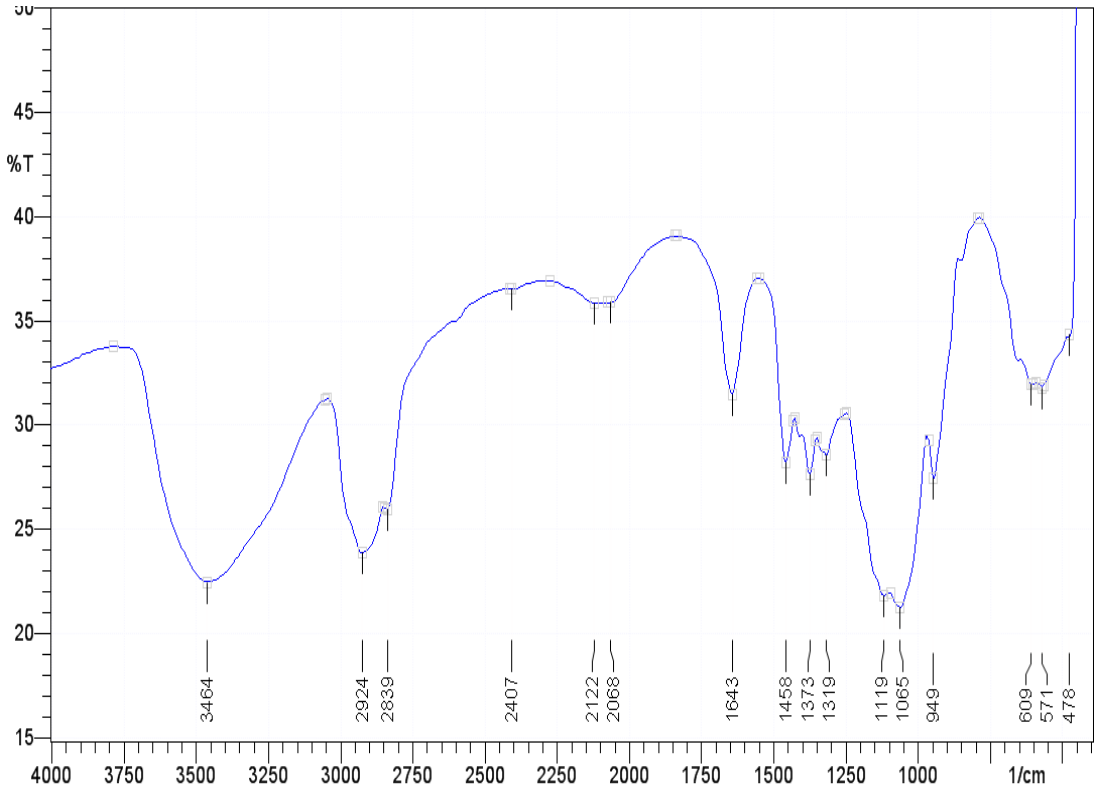


Fig.7.17.IR spectrum of HPMC K4M

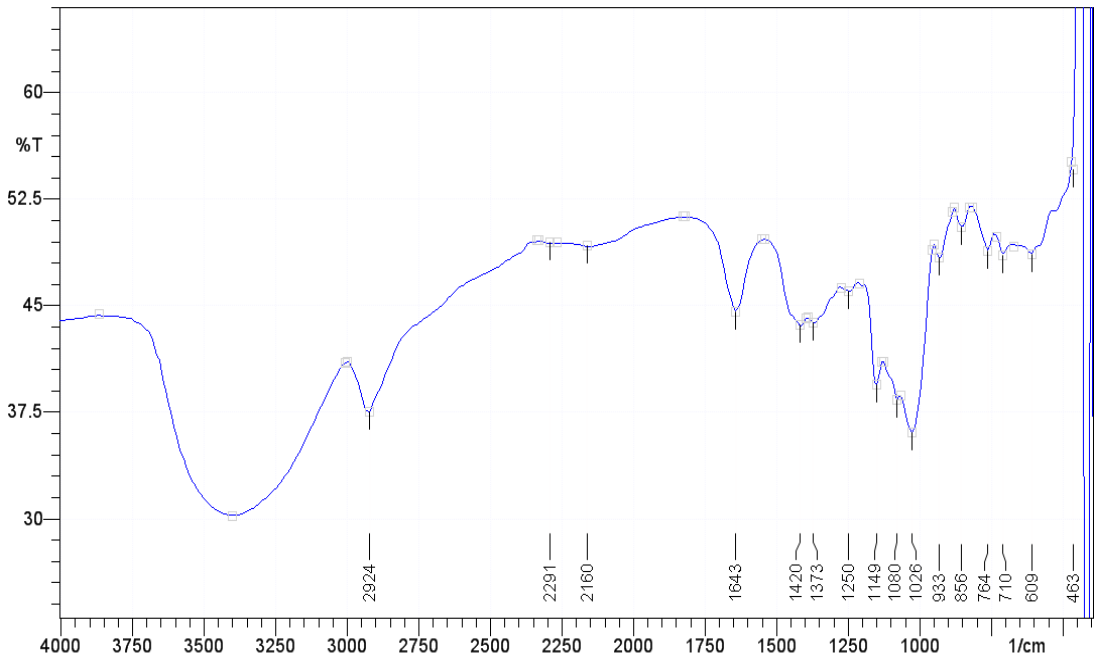


Fig.7.18.IR spectrum of Sodium alginate

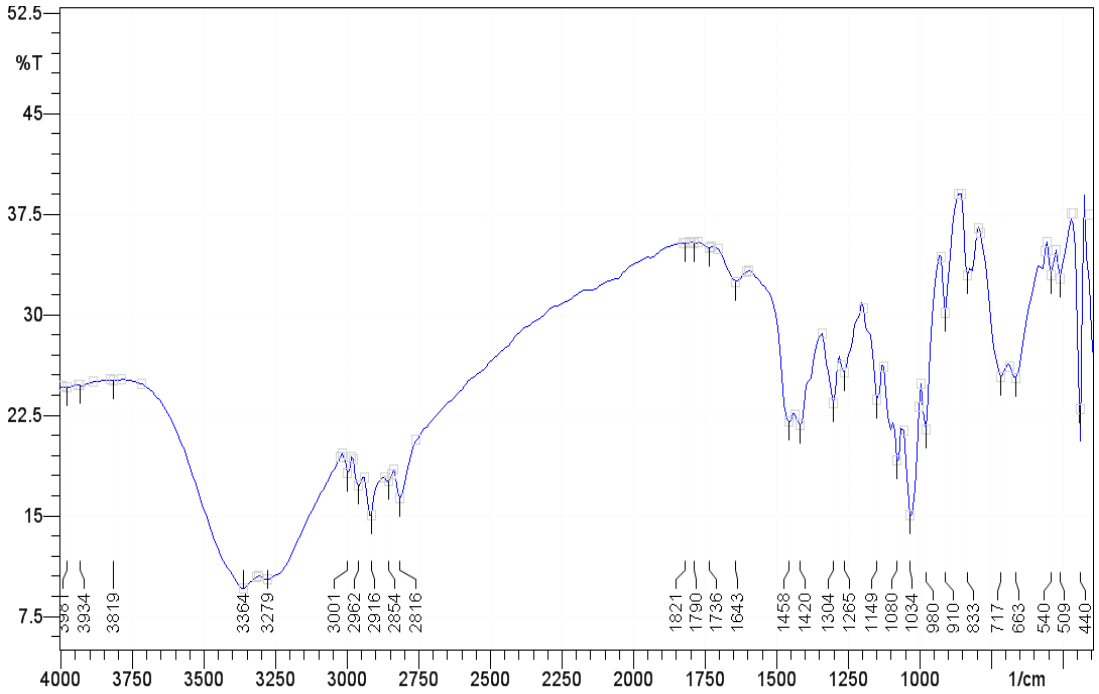


Fig.7.19.IR spectrum of Miglitol-gelatin

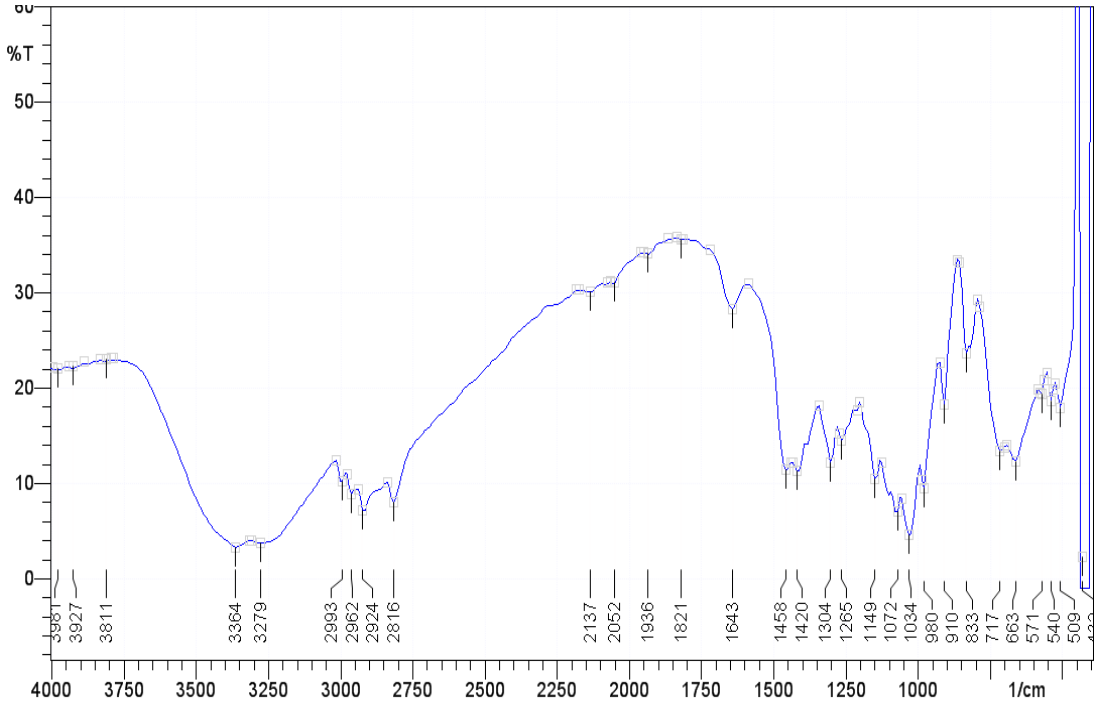


Fig.7.20.IR spectrum of Miglitol HPMC K4M

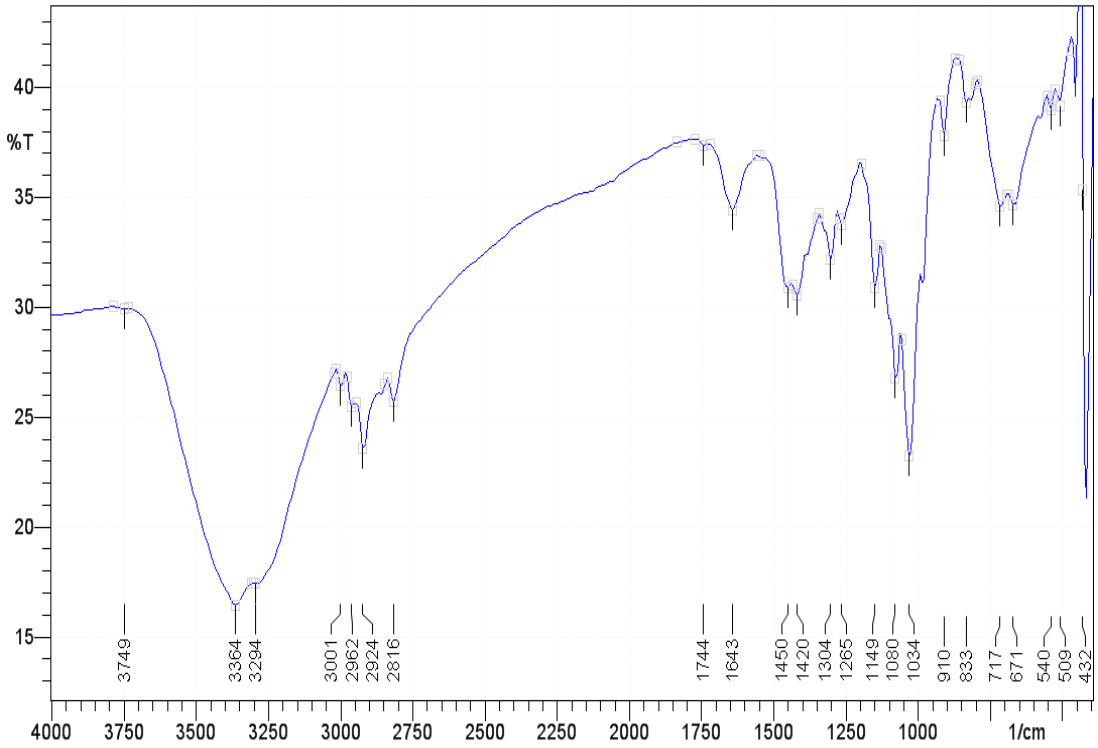


Fig.7.21. IR spectrum of Miglitol-sodium alginate

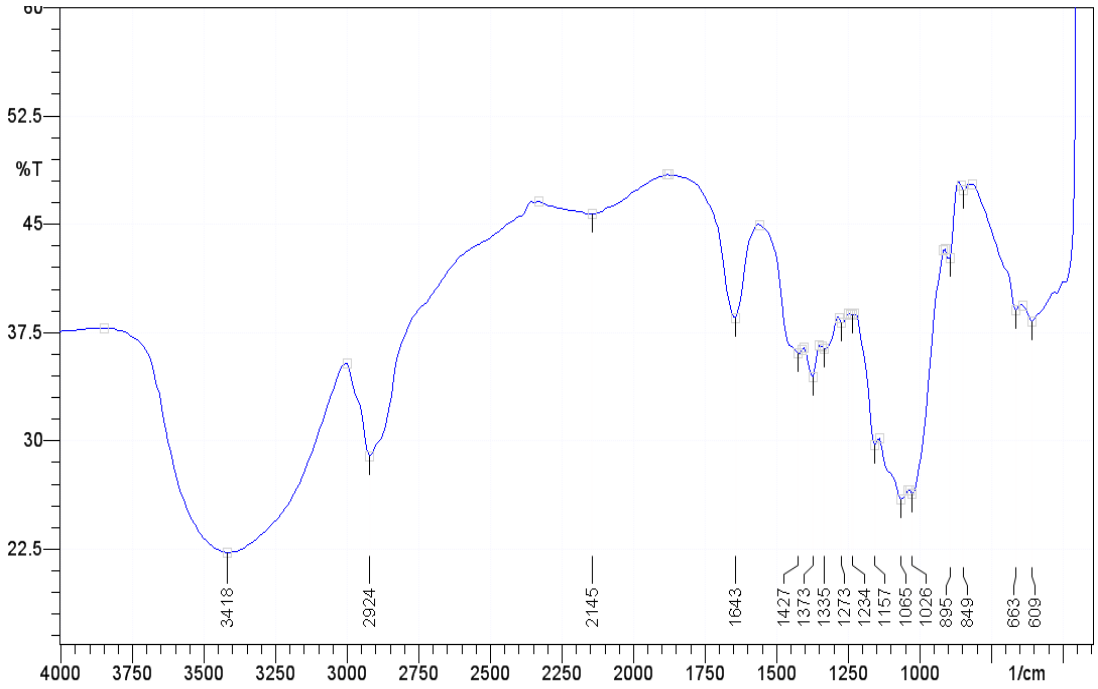


Fig.7.22. IR spectrum of L-HPC

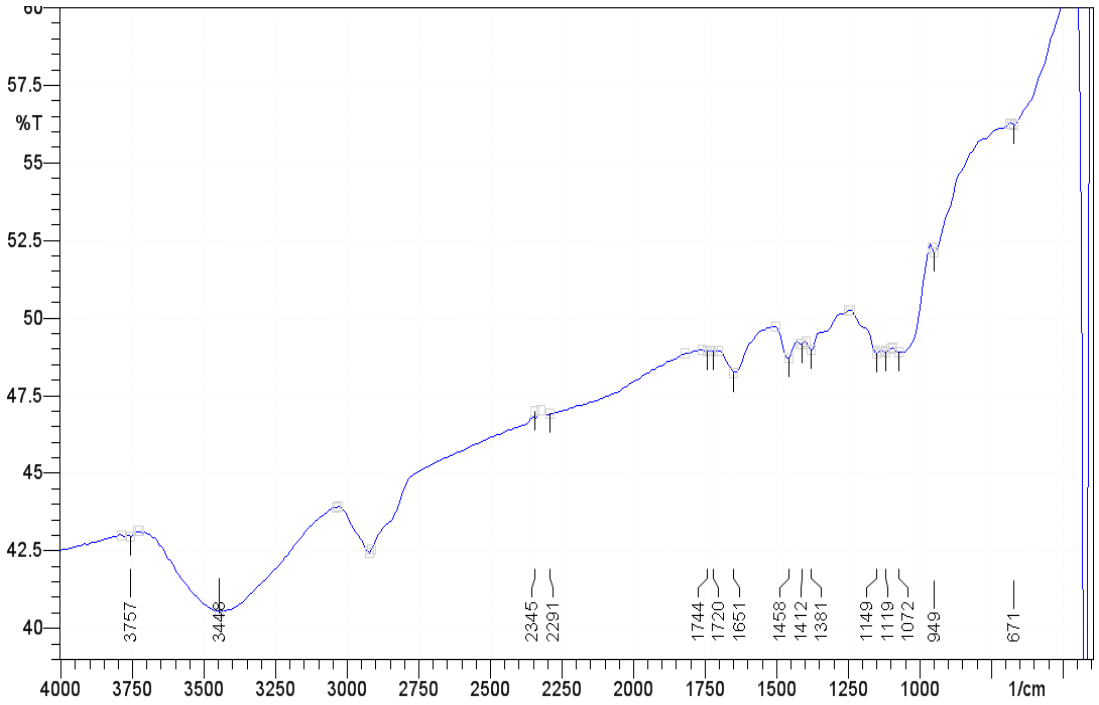


Fig.7.23.IR spectrum of HPMC

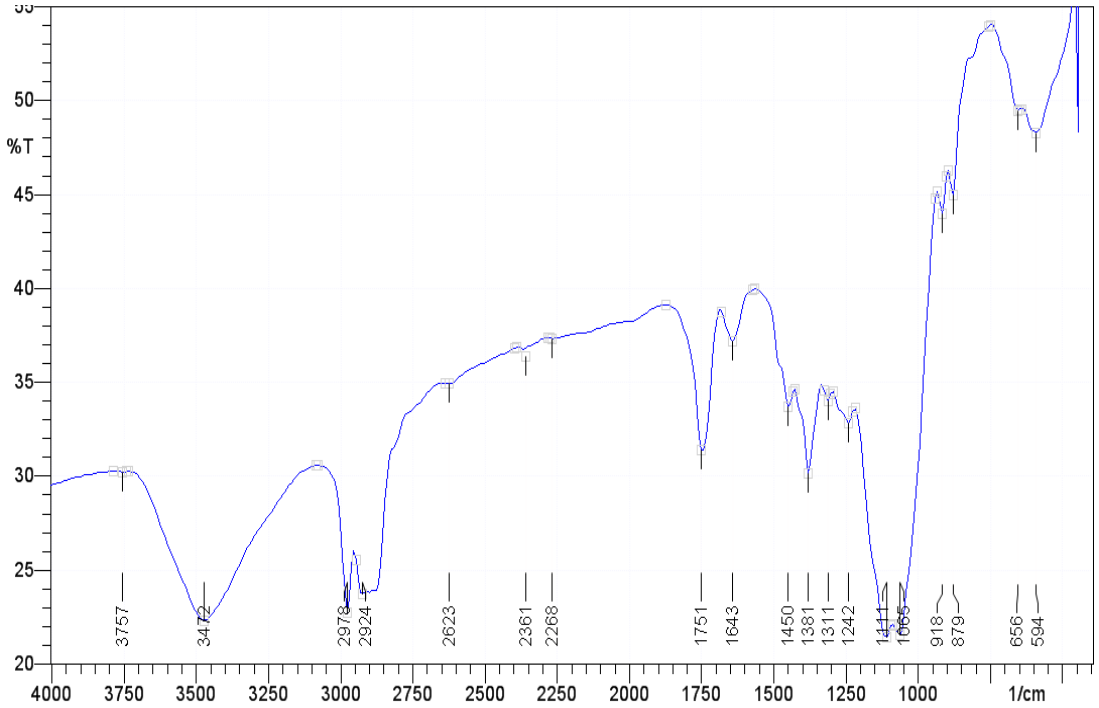


Fig.7.24. IR spectrum of Ethylcellulose

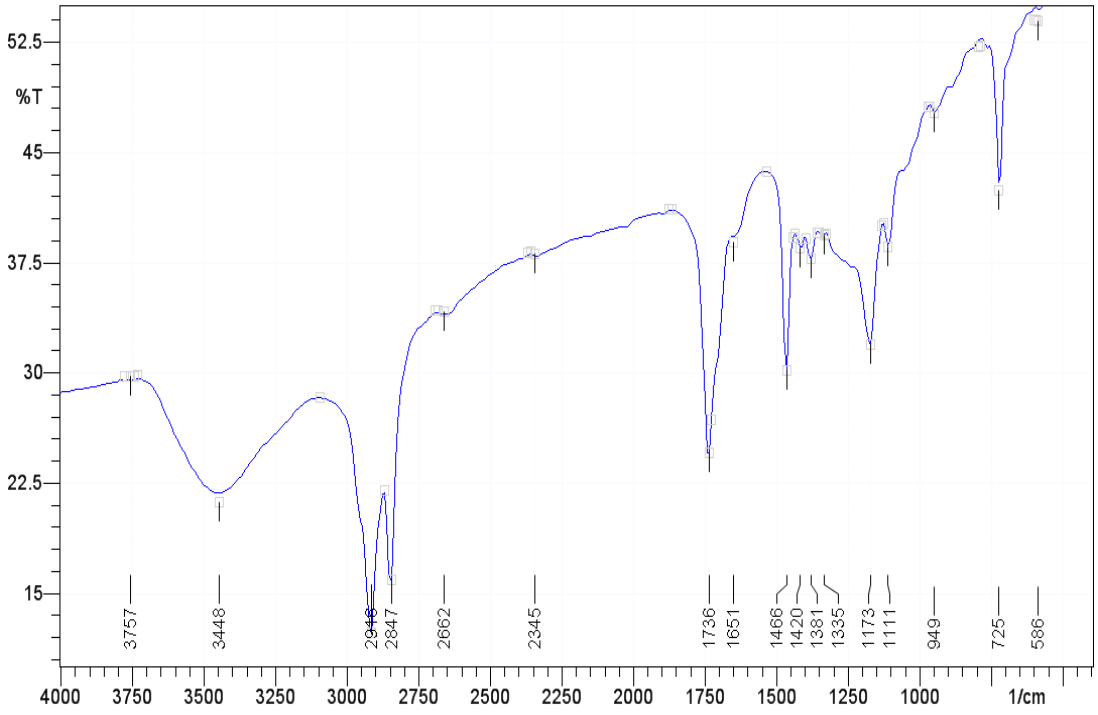


Fig.7.25. IR spectrum of Glyceryl behenate

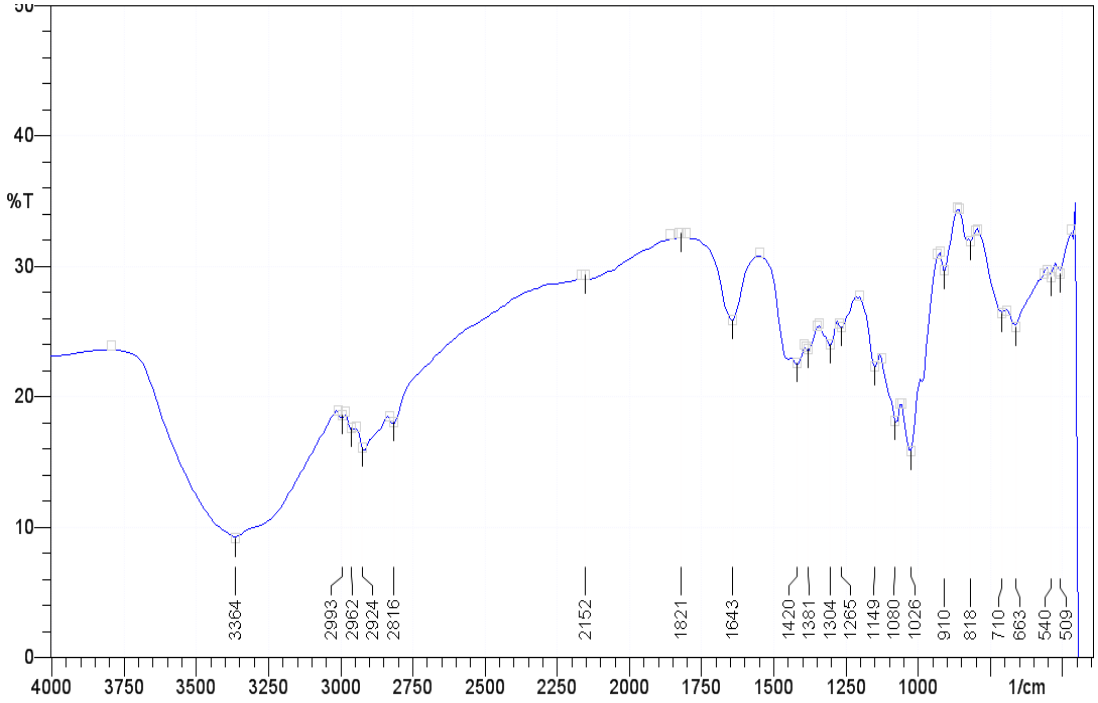


Fig.7.26.IR spectrum of Miglitol-L-HPC

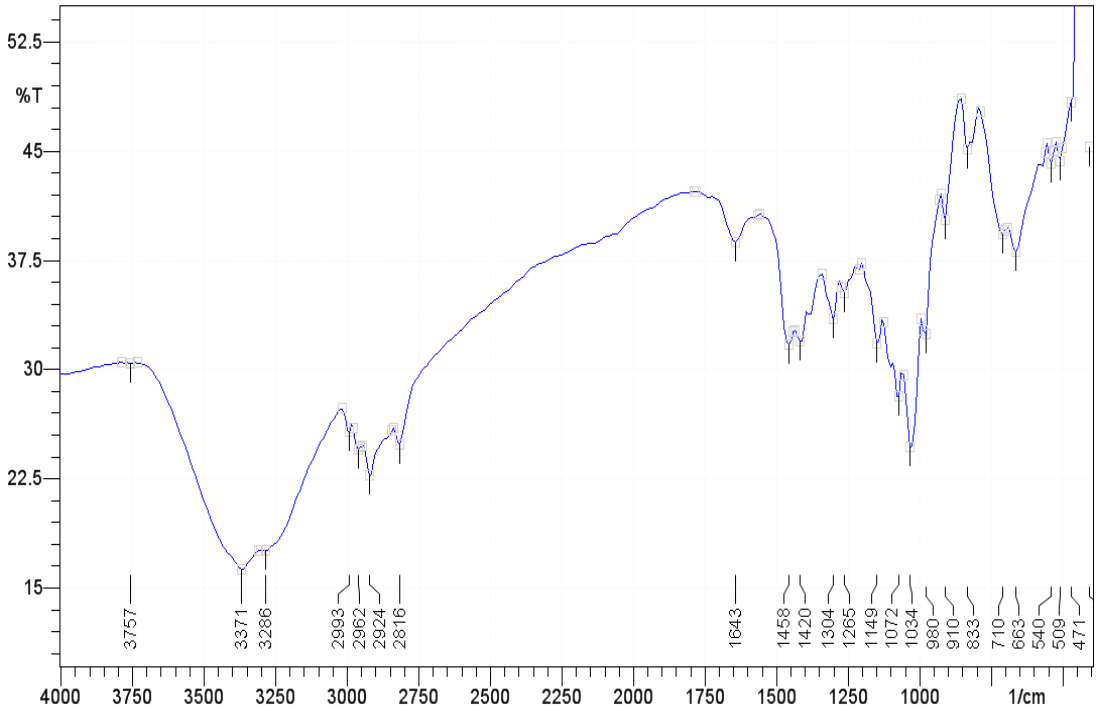


Fig.7.27.IR spectrum of Miglitol-HPMC

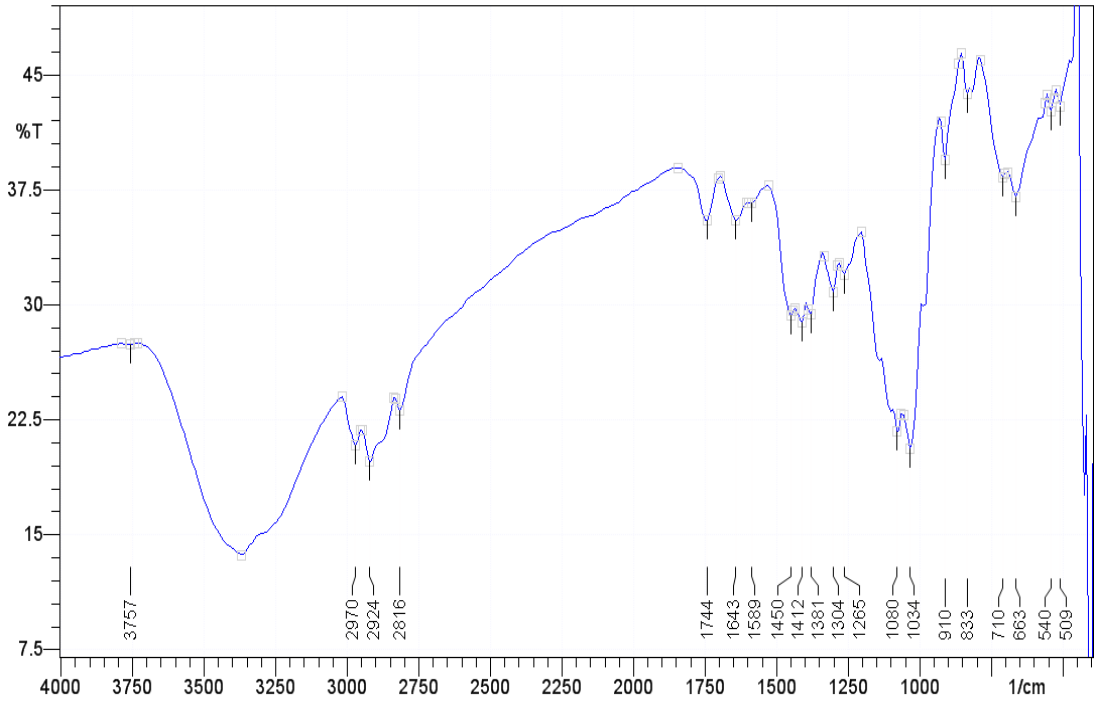


Fig.7.28.IR spectrum of Miglitol-Ethylcellulose

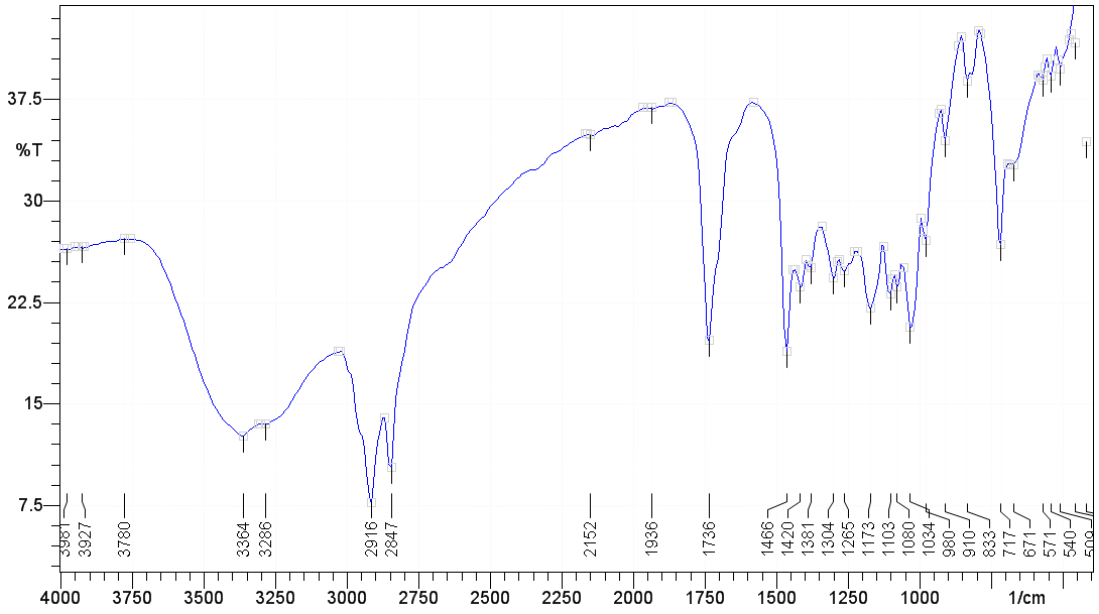


Fig.7.29.IR spectrum of Miglitol-glycerylbehenate

DIFFERENTIAL SCANNING CALORIMETRY THERMOGRAMS

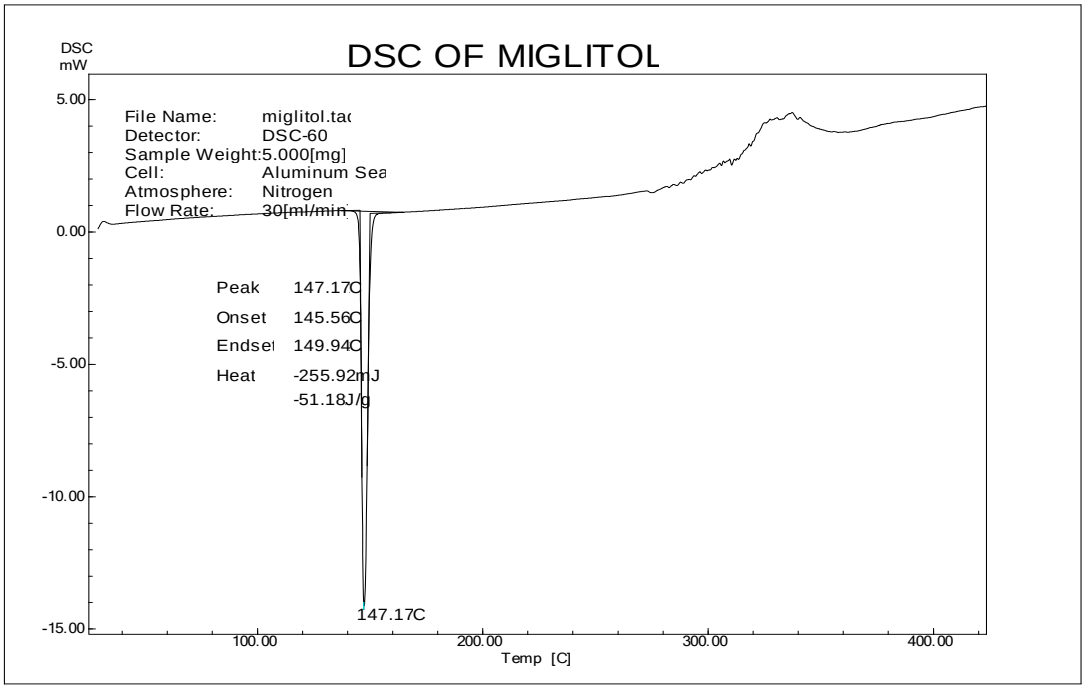


Fig.7.30

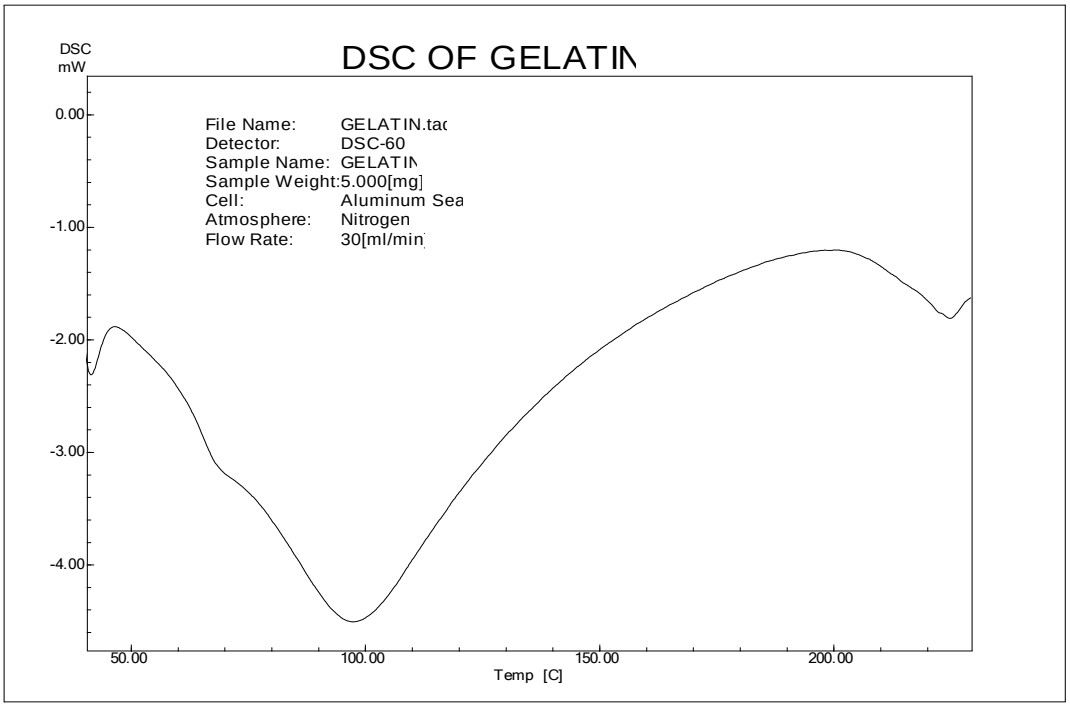


Fig.7.31

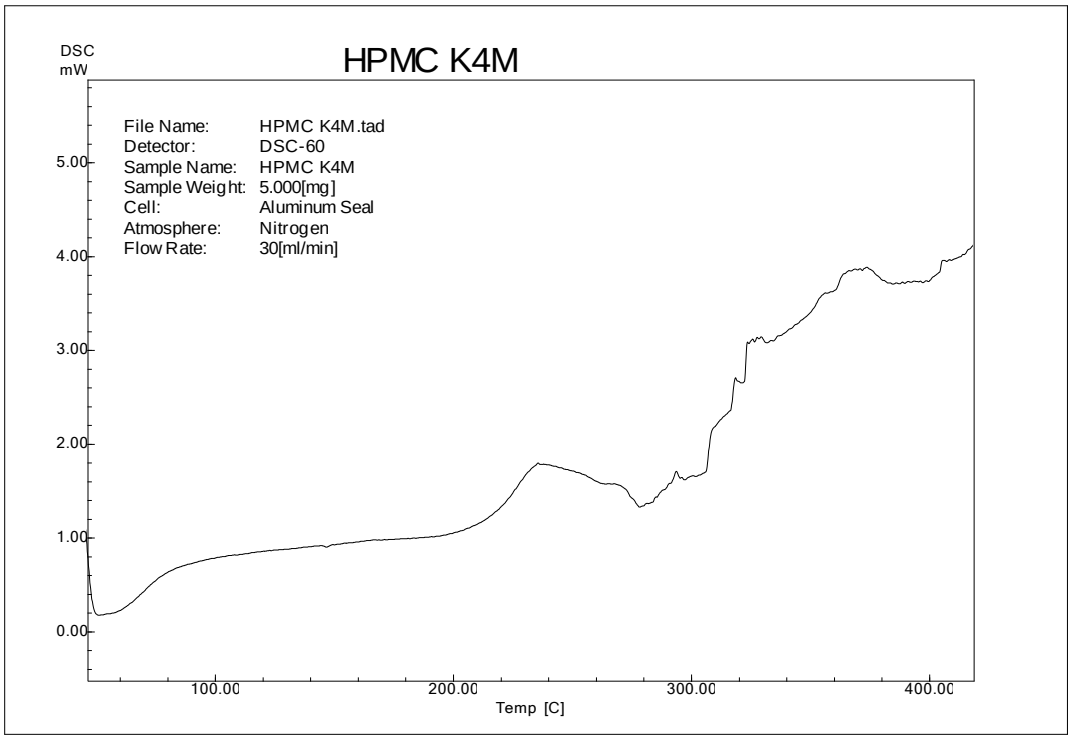


Fig.7.32

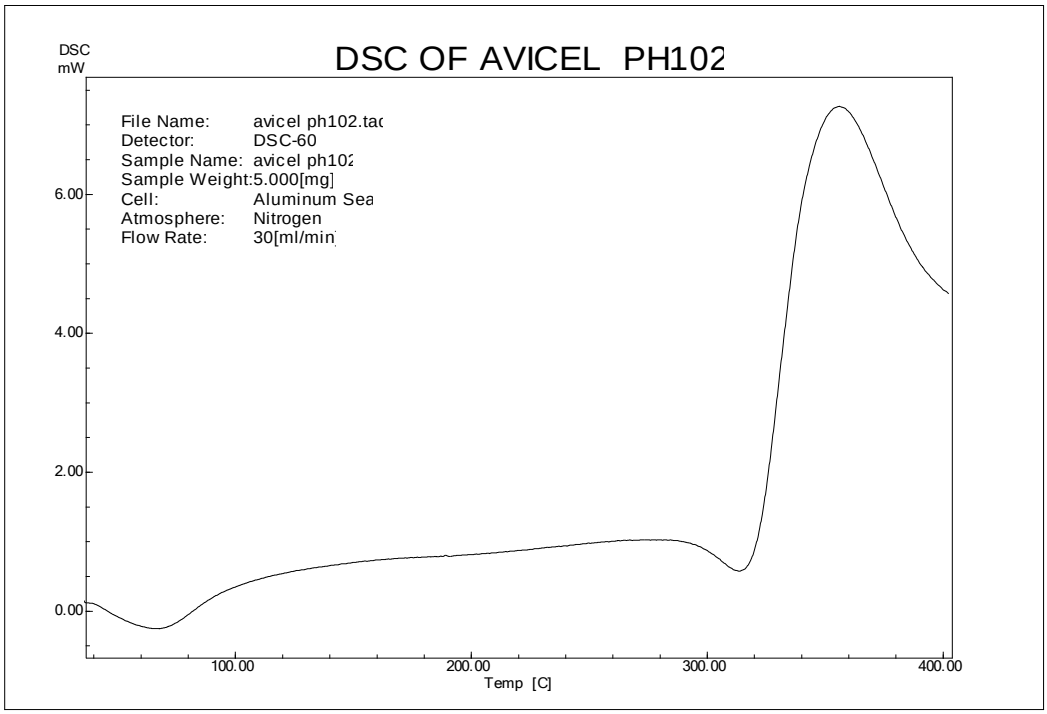


Fig.7.33

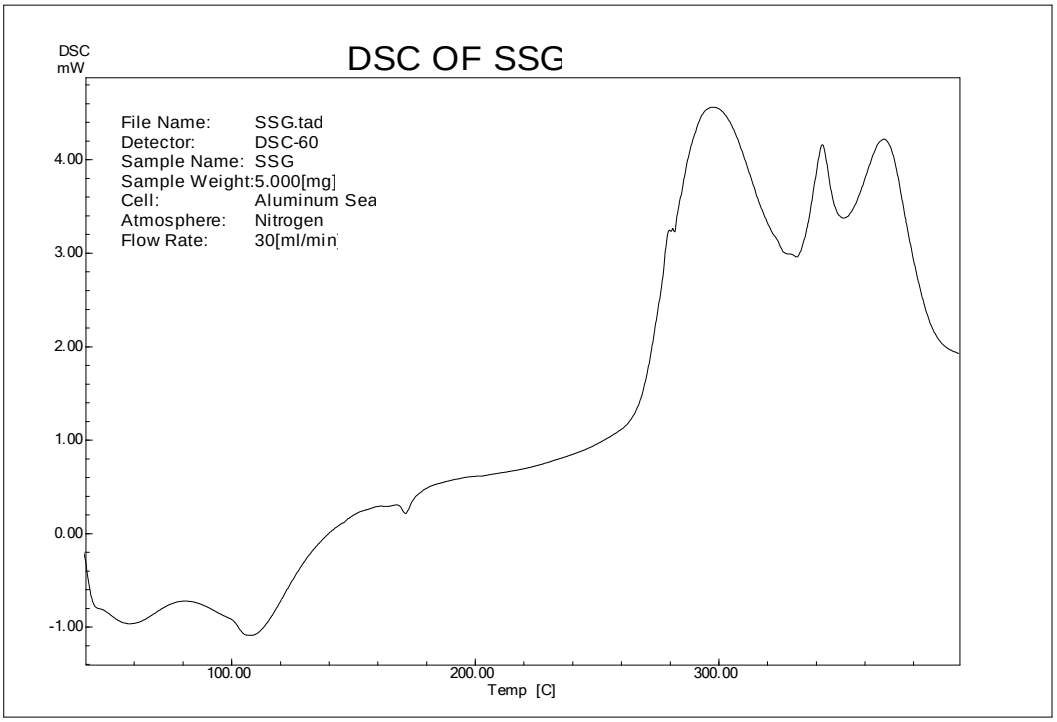


Fig.7.34

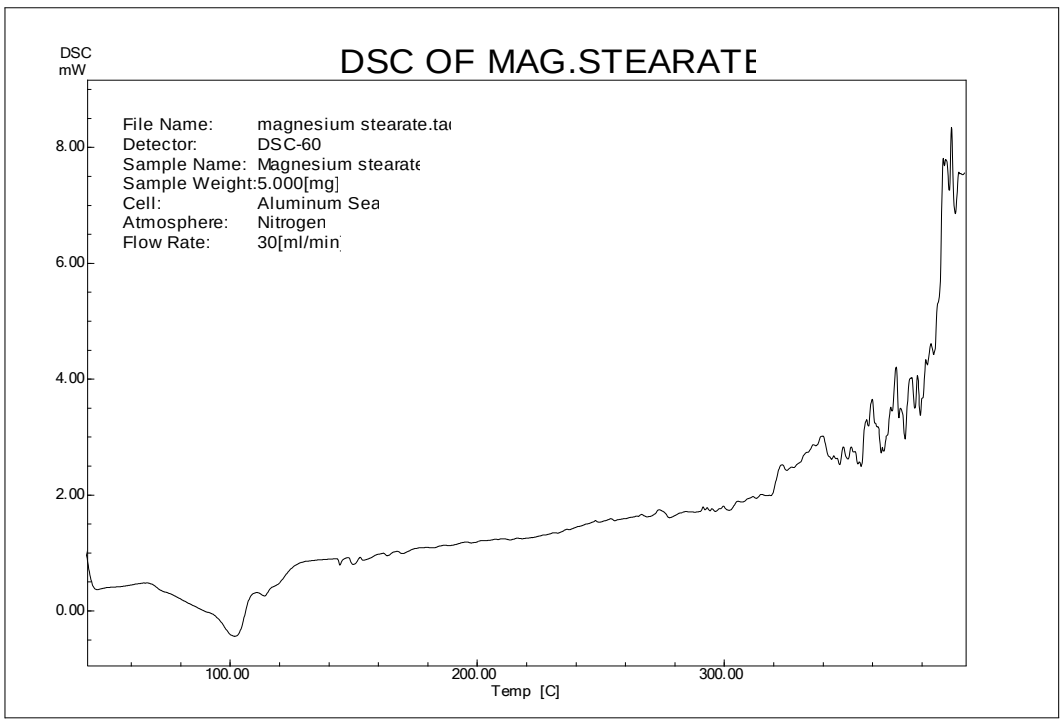


Fig.7.35

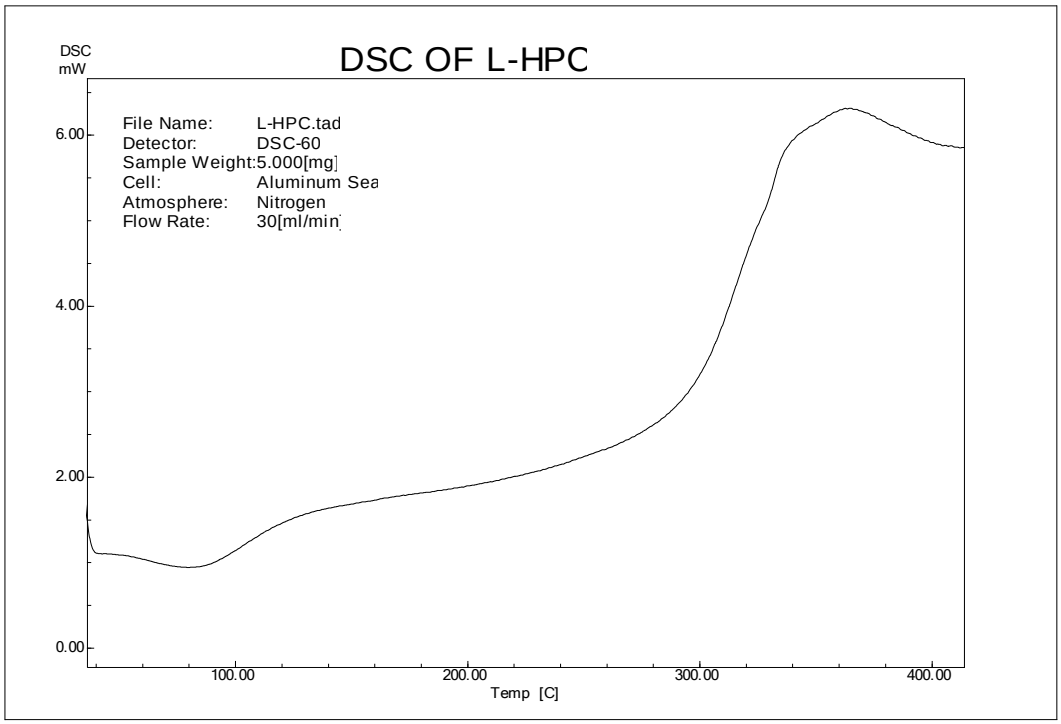


Fig.7.36

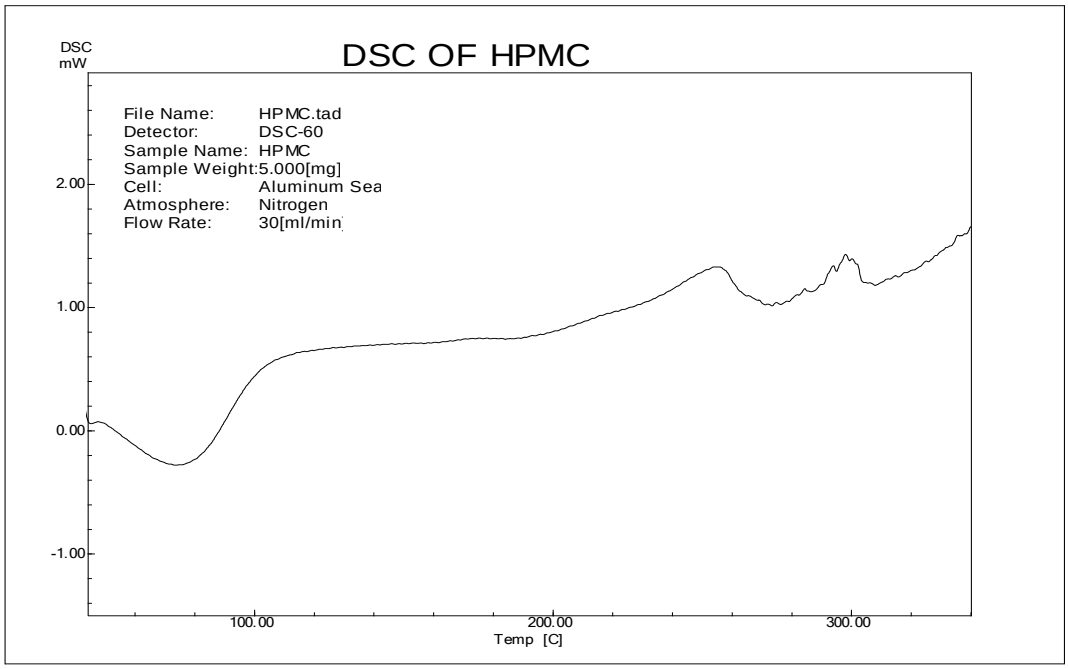
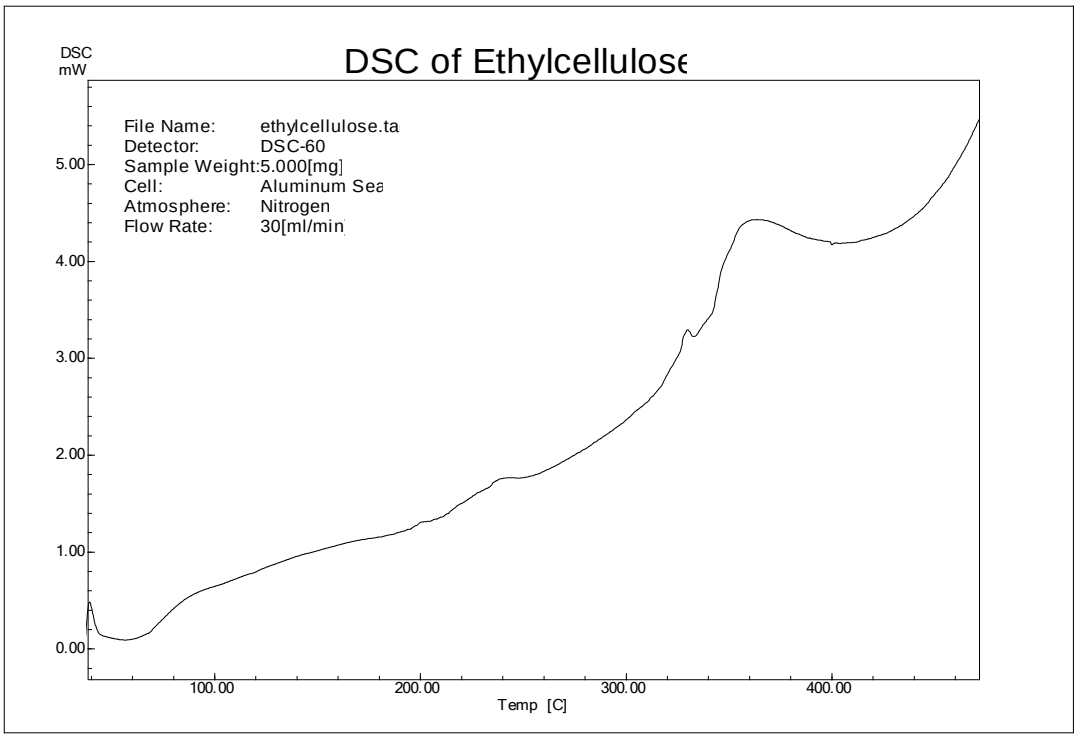


Fig.7.37



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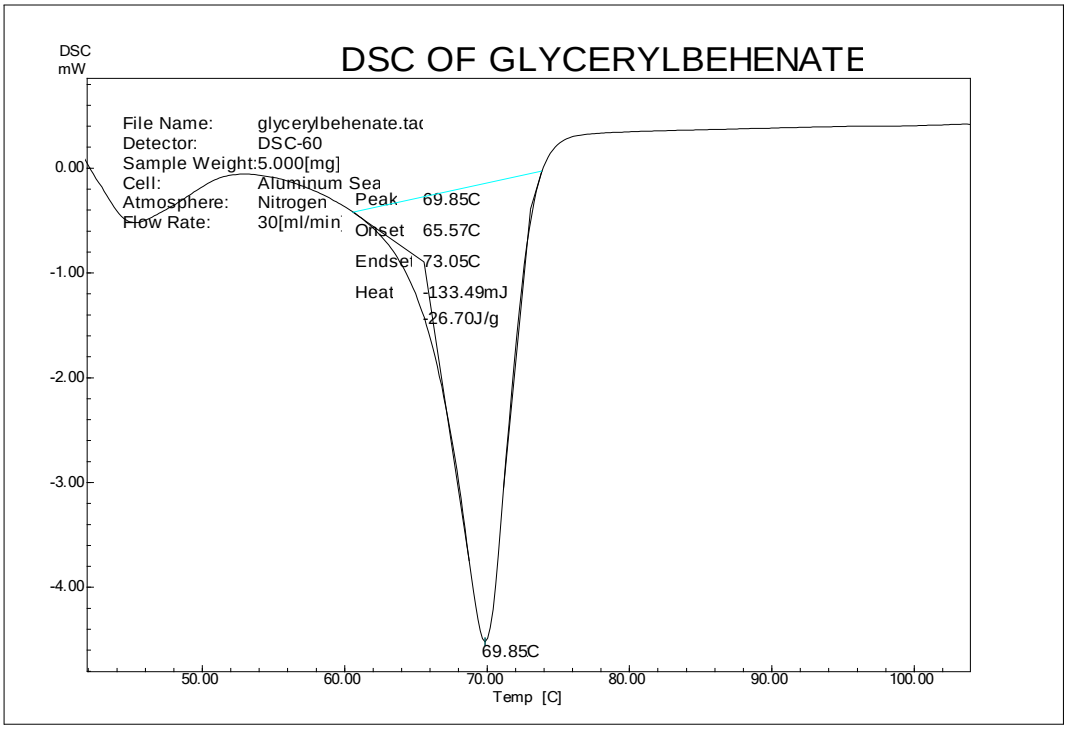


Fig.7.39

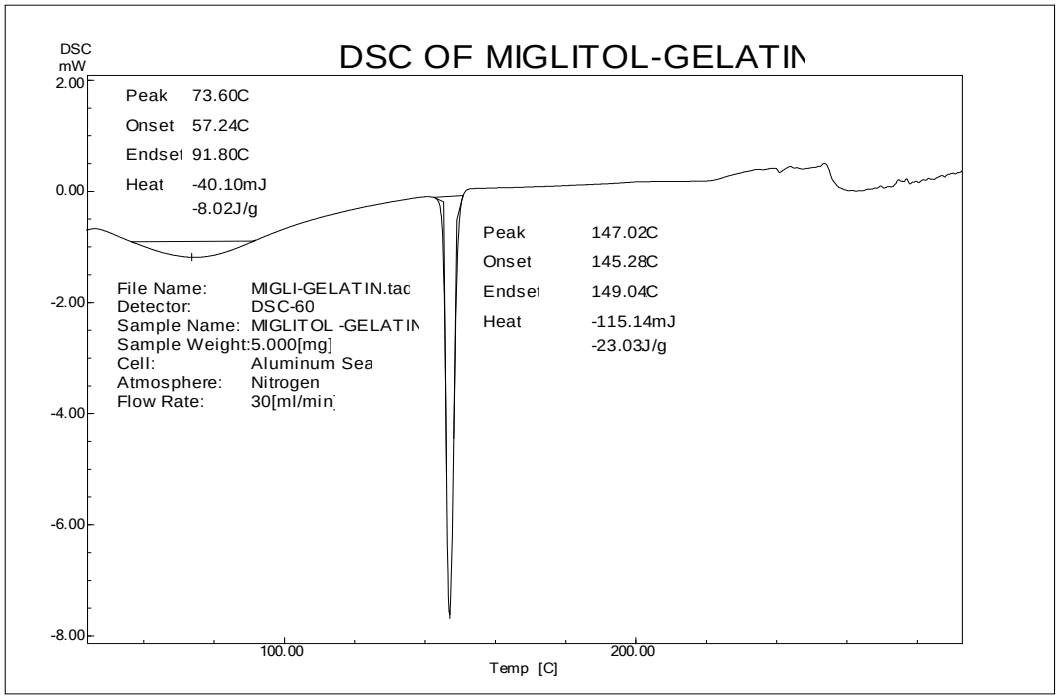
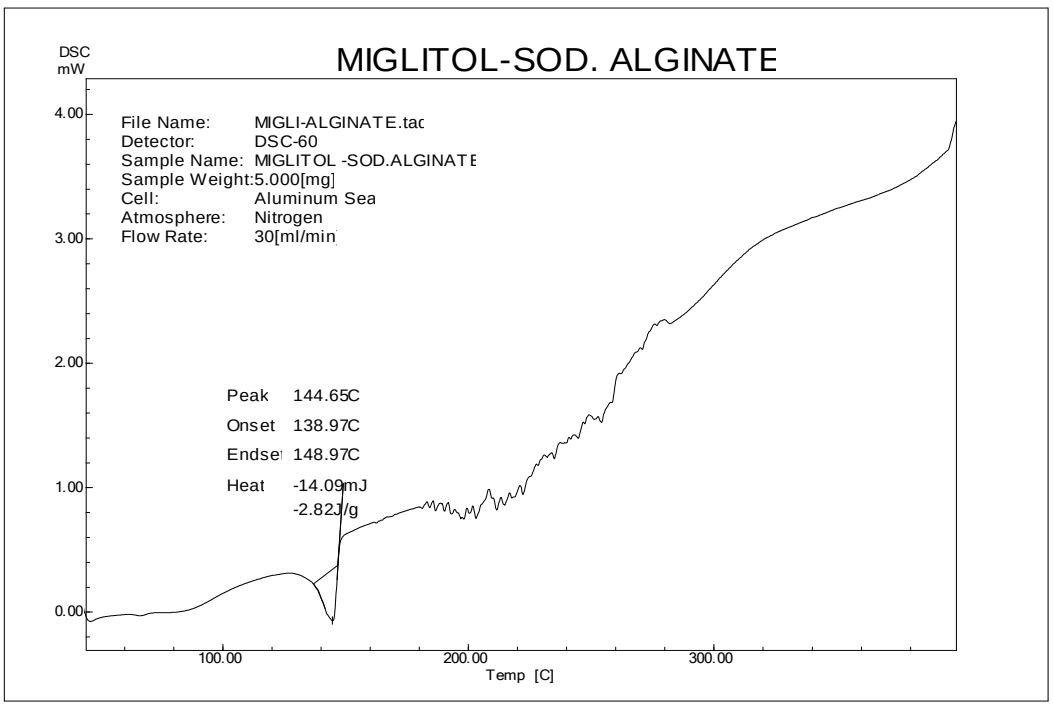


Fig.7.40



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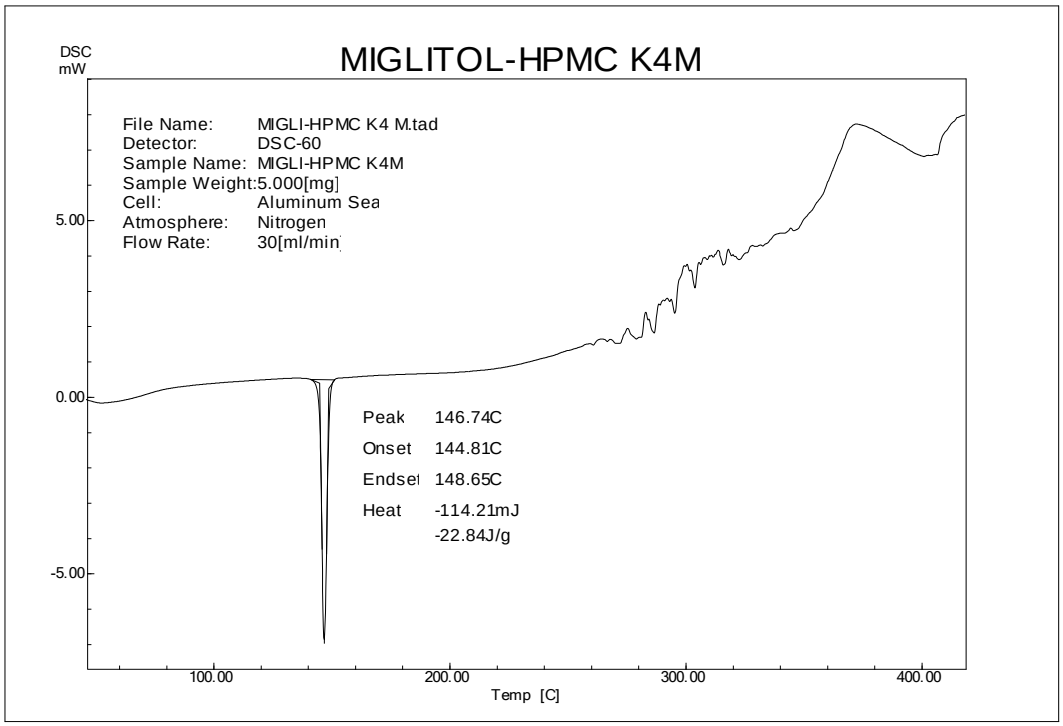

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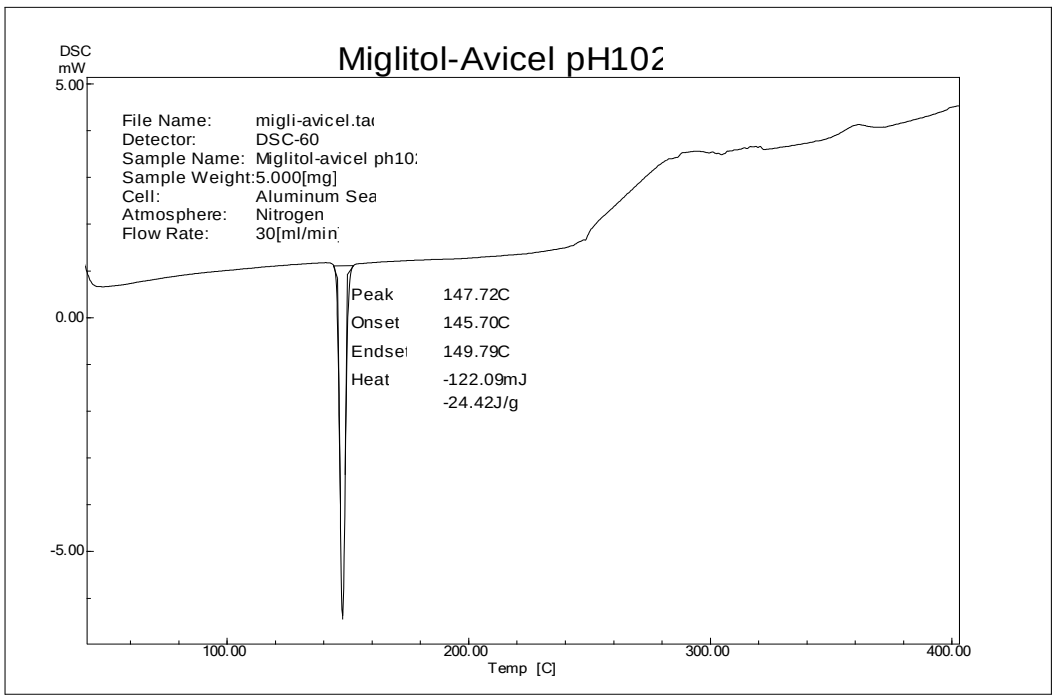

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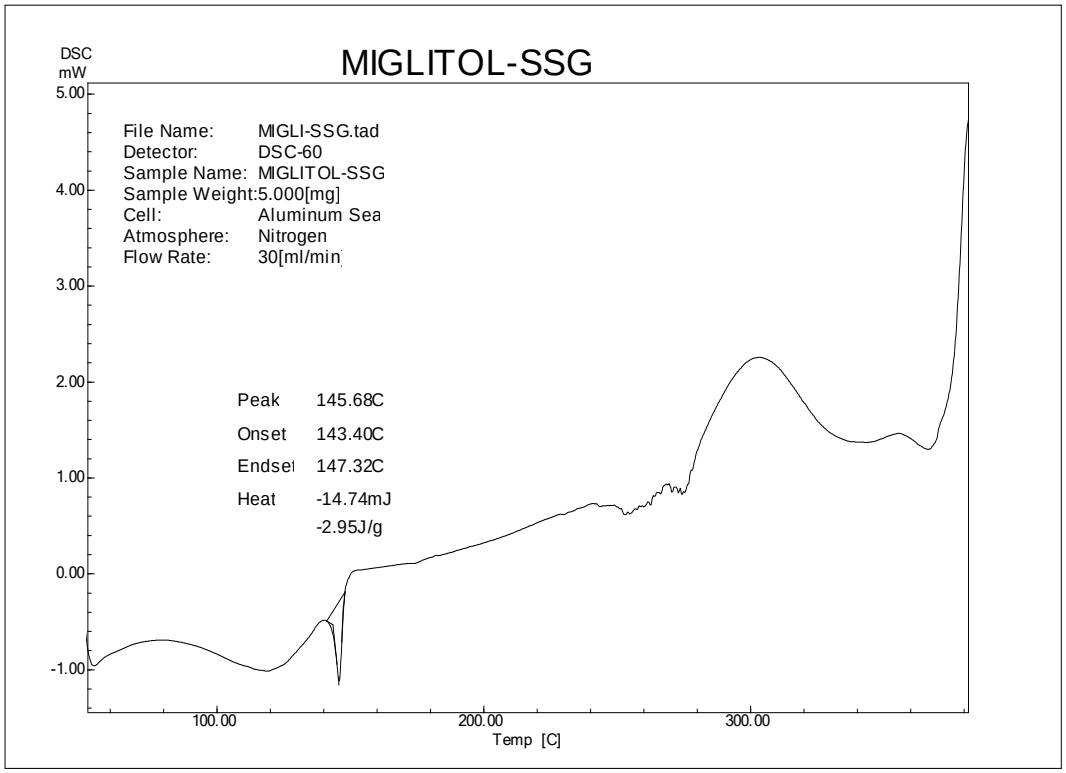

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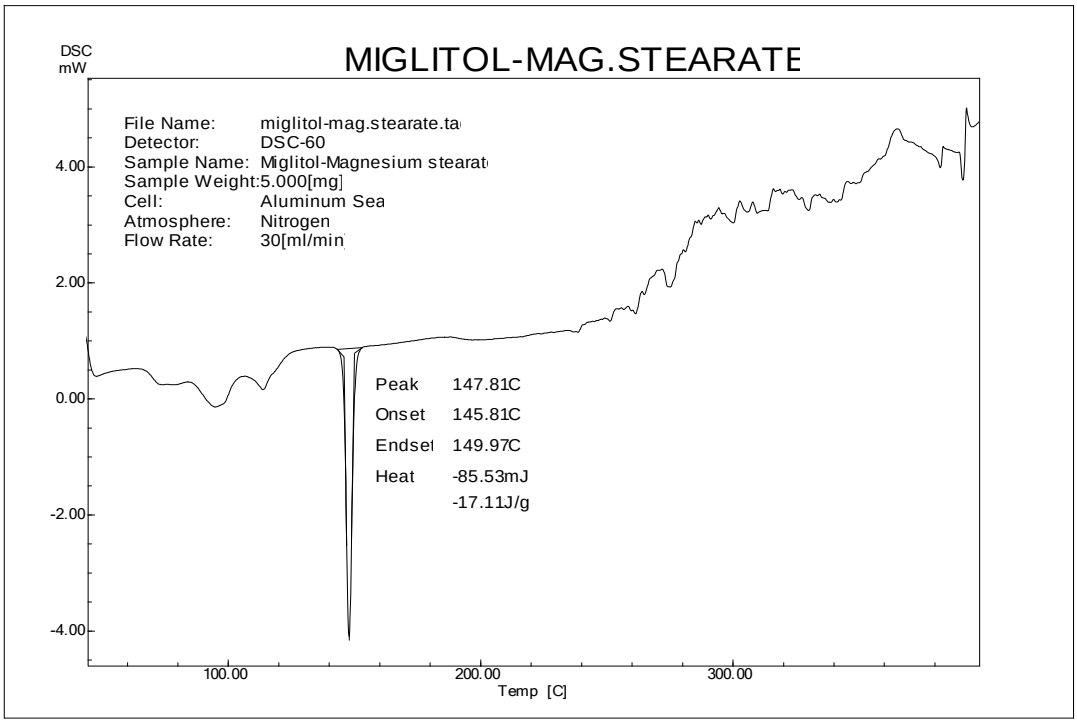


Fig.7.45

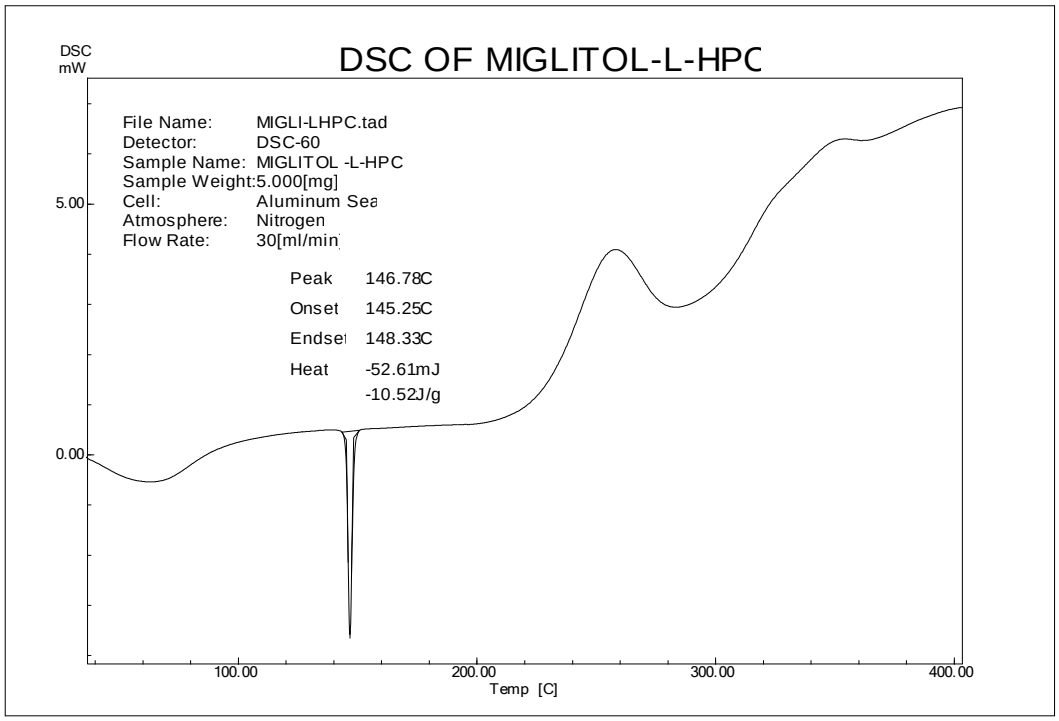
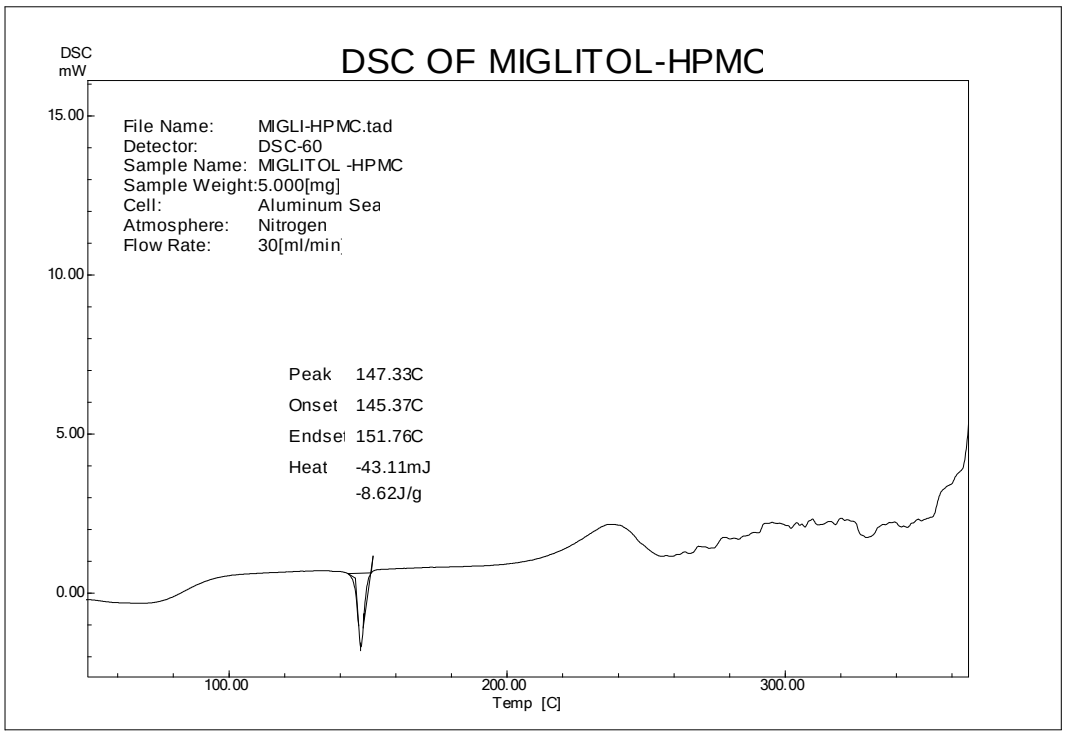


Fig.7.46



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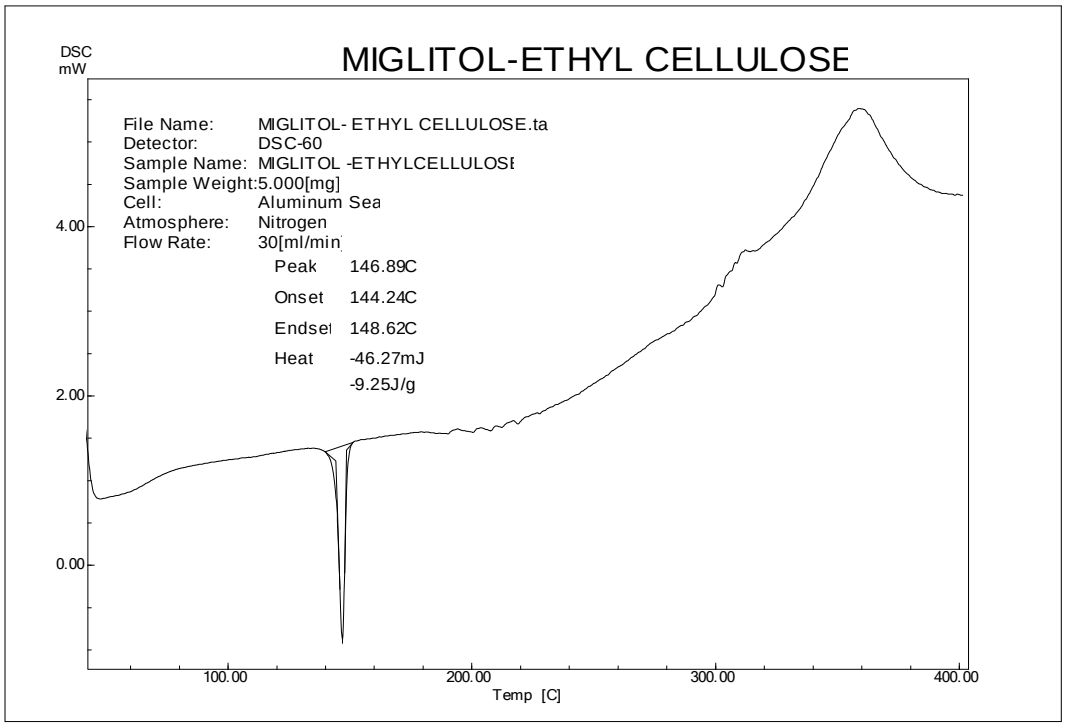

Fig.7.48

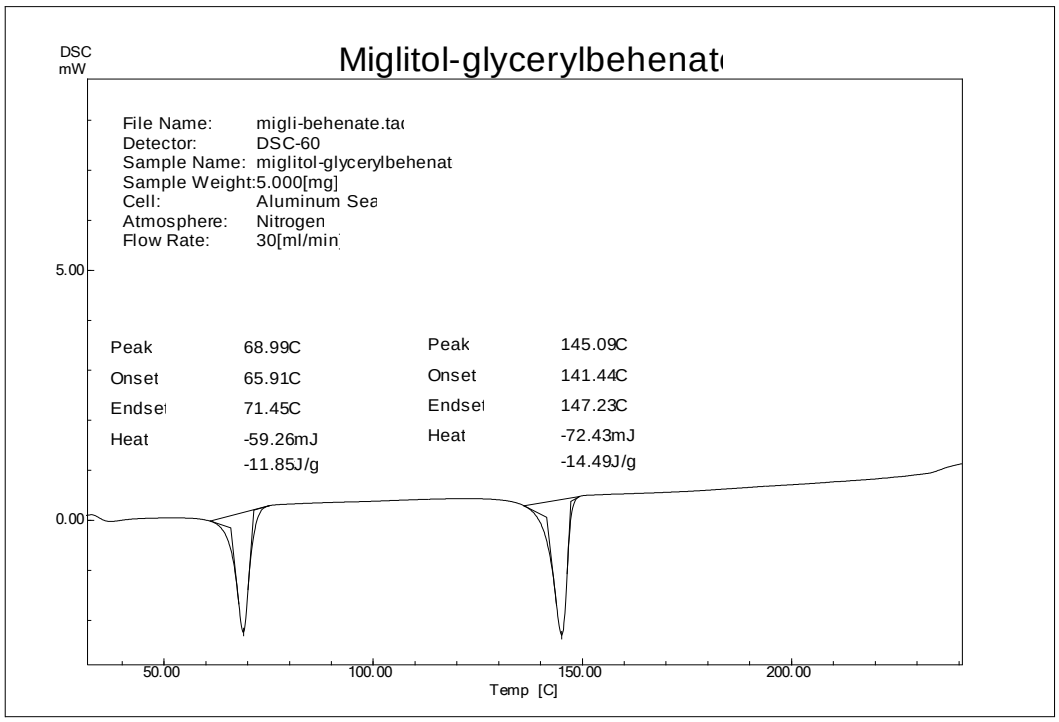

Fig.7.49

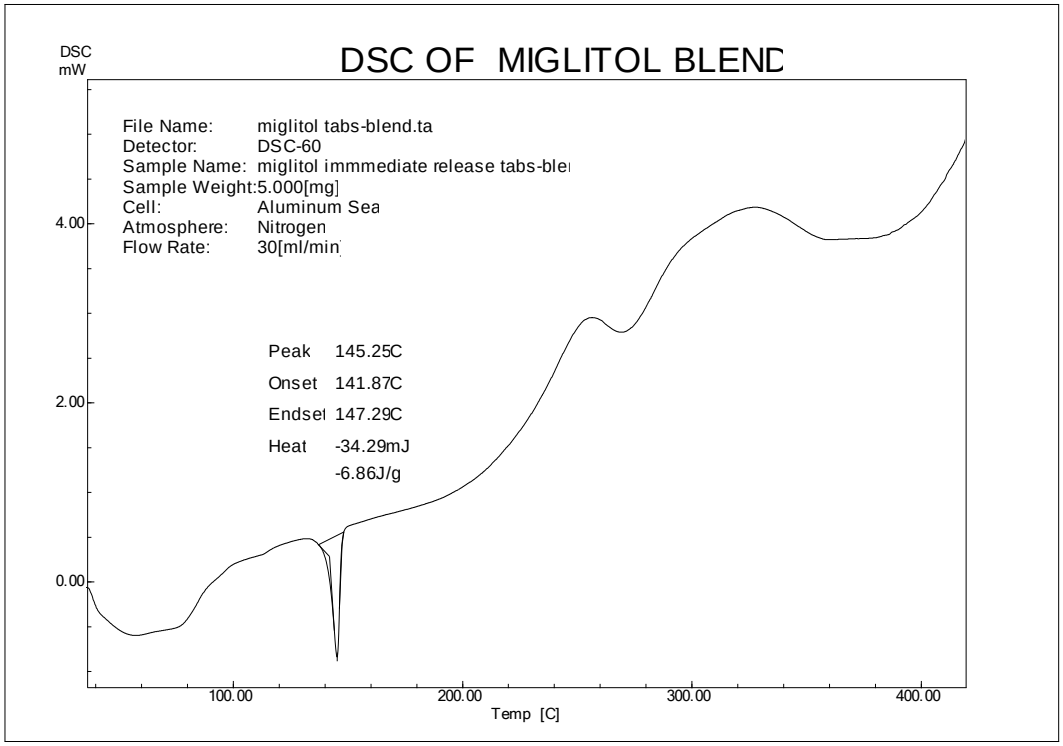

Fig.7.50

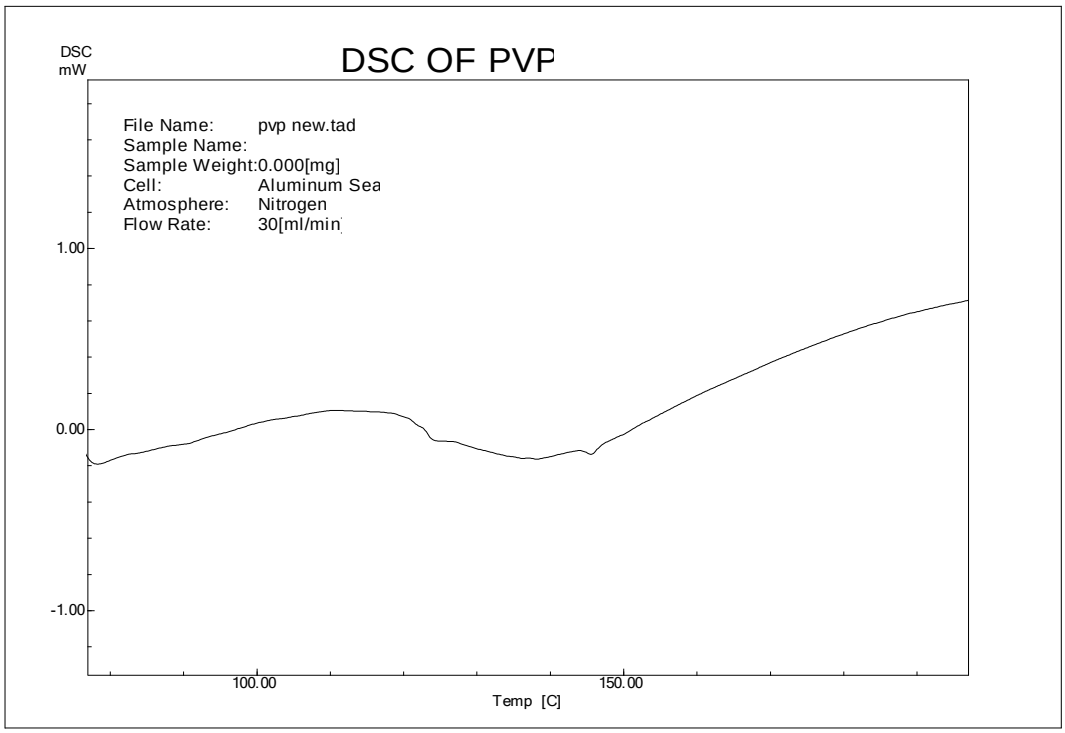

Fig.7.51

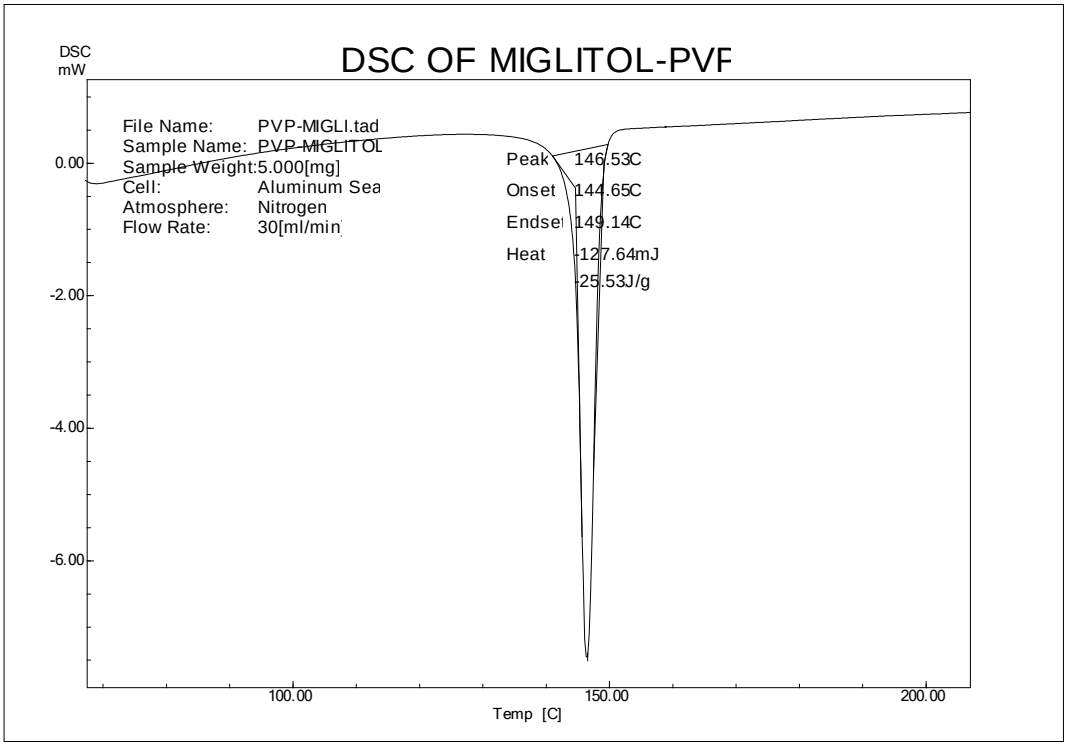

Fig.7.52

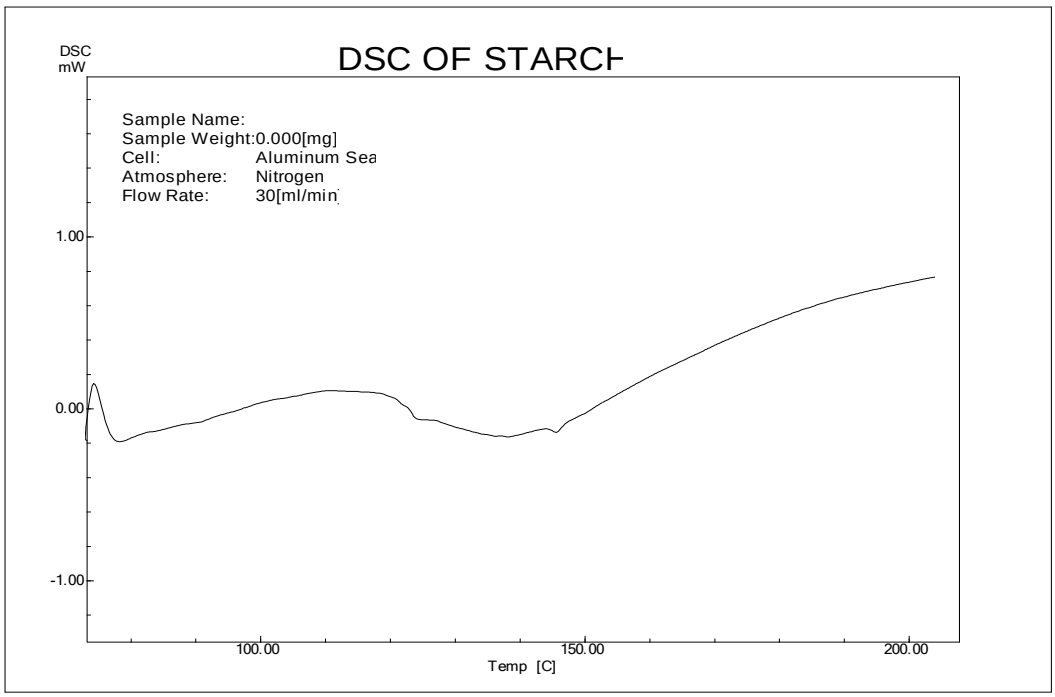

Fig.7.53

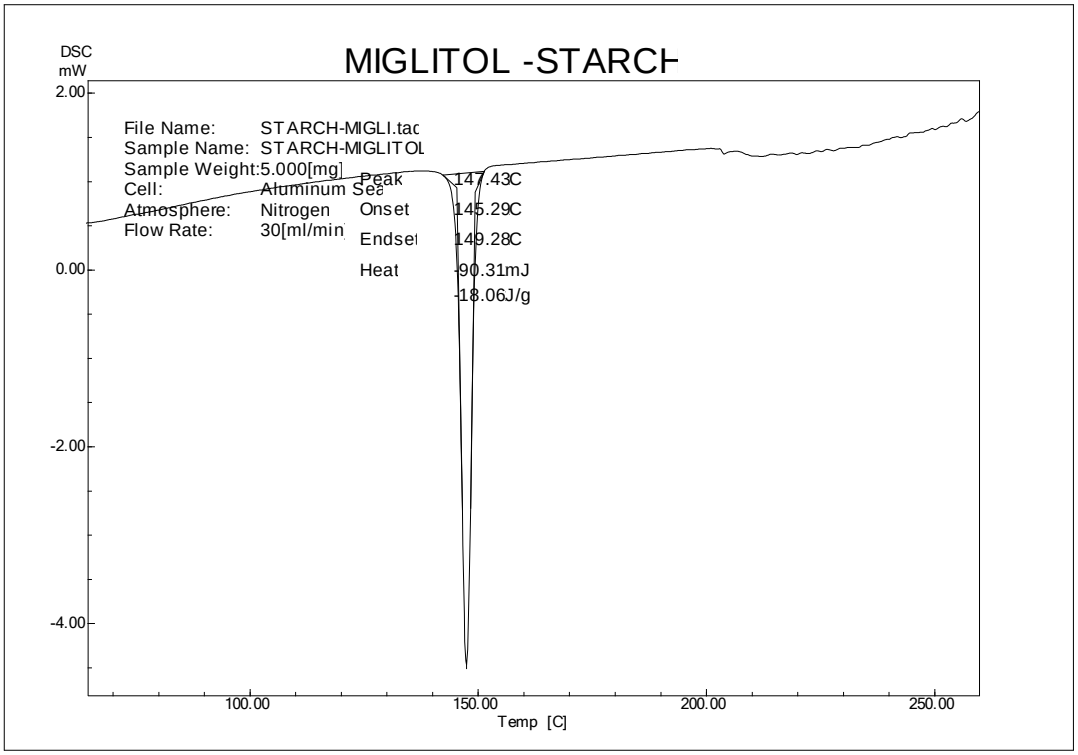

Fig.7.54

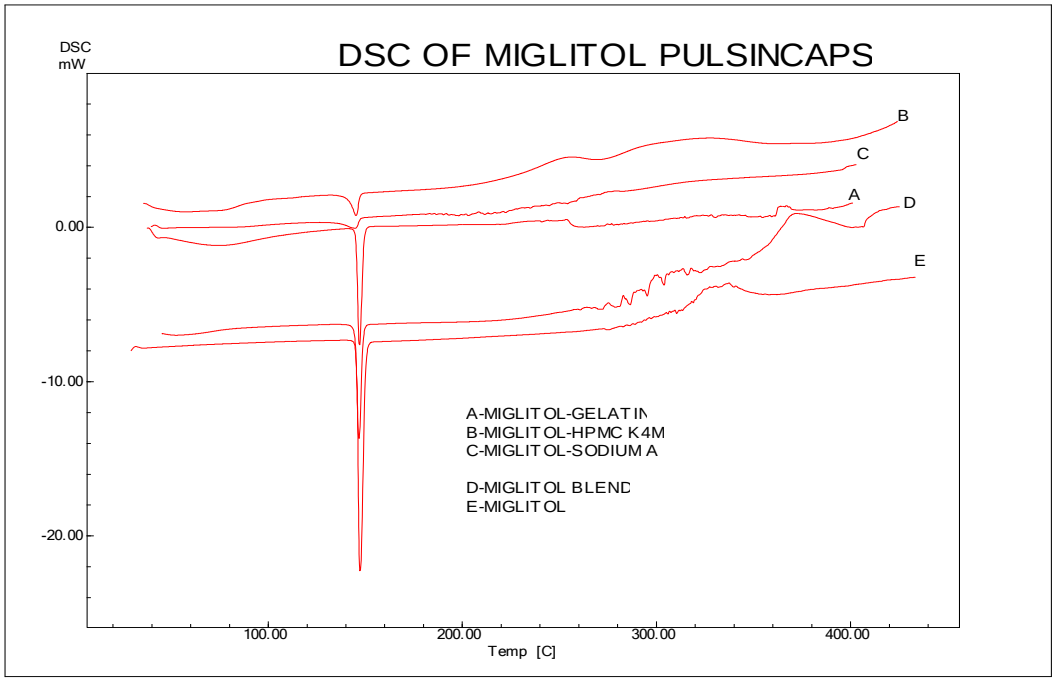

Fig.7.55

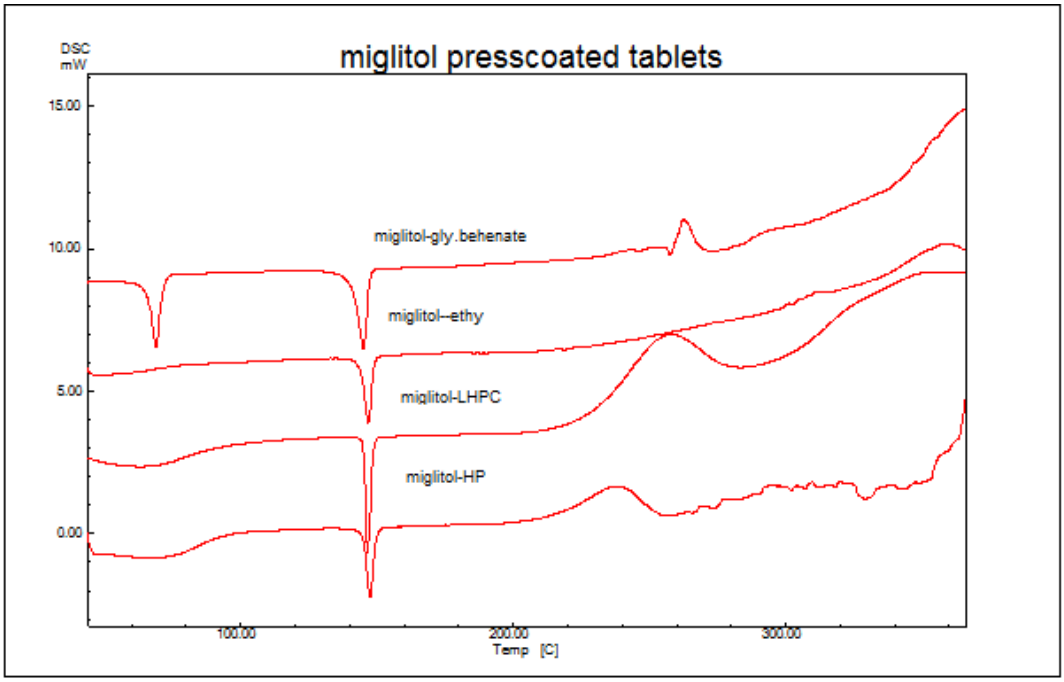
miglitol presscoated tablets
DSC
mW
15.00
10.00
5.00
0.00
miglitol-gly.behenate
miglitol--ethy
miglitol-LHPC
miglitol-HP
100.00
200.00
300.00
Temp [C]

Fig.7.56

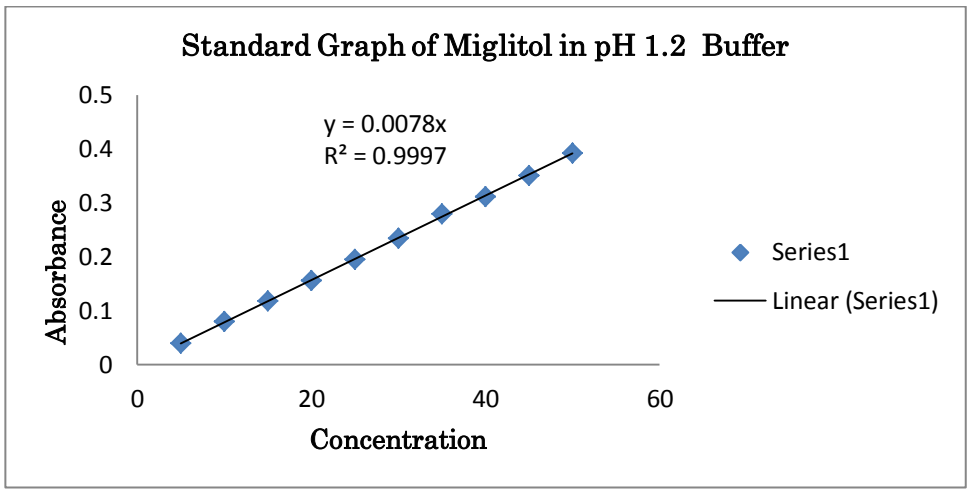

Fig.7.57. Standard graph of Miglitol in pH 1.2 buffer

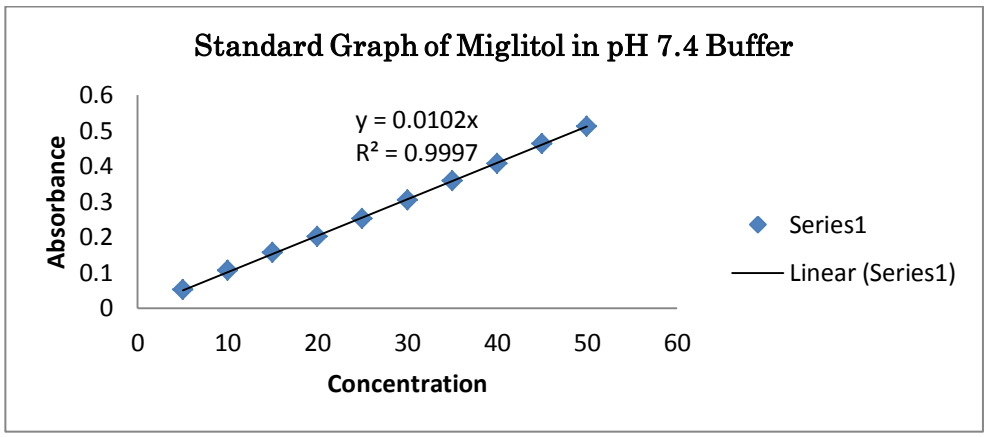

Fig.7.58. Standard graph of Miglitol in pH 7.4 buffer

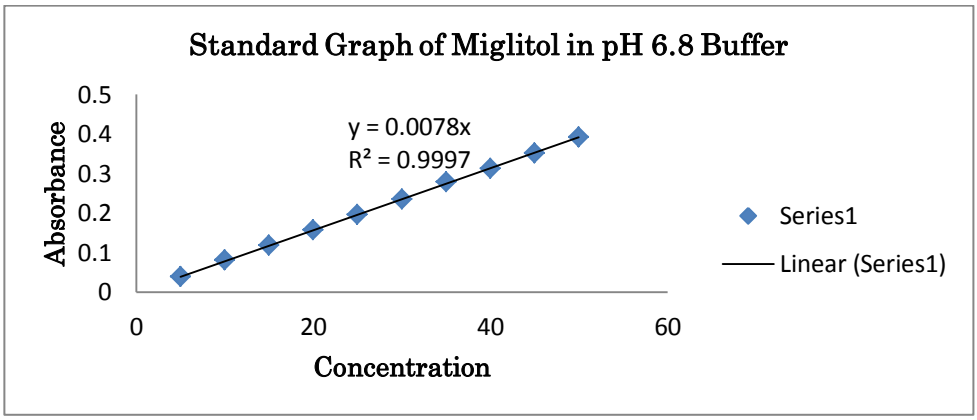

Fig.7.59. Standard graph of Miglitol in pH 6.8 buffer

2. MIGLITOL PULSINCAPS (MPC1-MPC9)

2.1. Post compression parameters of Miglitol immediate release tablets

Post compression parameters of Miglitol immediate release tablets results indicated that there was no significant change in the thickness, average weight, content uniformity and drug content. The results were found to be within the limits for the prepared Miglitol immediate release tablets.

The immediate release miglitol tablets in MCT1 were prepared without super disintegrant and the formulations MCT2, MCT3 and MCT4 were prepared with 2, 4, and 6 mg / tab concentration of sodium starch glycollate respectively. The results of hardness and disintegration time for these formulations were found to be more than the limits. Hence the formulation containing super disintegrant in a concentration of 8 and 10 mg/tab (MCT5 and MCT6) were prepared .The hardness of tablets of MCT6 (containing sodium starch glycollate in a concentration of 10 mg/tab) was not enough (1.5±0.04 kg/cm^2) when compared to the hardness of tablets of MCT5 (containing sodium starch glycollate in a concentration of 8 mg/tab) and the friability percentage also found to be more with the trial MCT6. The reasons for the poor hardness and friability of the formulation MCT6 was due to more concentration of super disintegrant.[224, 225]

The results were given in **table 7.7**.

Table 7.7. Post compression parameters of Miglitol immediate release tablets

Trials	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Average weight (mg)	Disintegration time (min)	Content uniformity (%)	Drug content (%)
MCT1	2.12 ± 0.01	5.0±0.12	0.15 ± 0.05	100.42± 0.15	6.25 ±0.12	99.64±0.54	99.83± 0.63
MCT2	2.14 ± 0.02	4.5±0.15	0.19 ± 0.03	101.02± 0.23	5.12 ±0.18	99.36±0.42	99.76± 0.44
MCT3	2.16 ± 0.02	4.0±0.13	0.31 ± 0.05	100.17± 0.34	4.24 ±0.25	99.67±0.38	99.74± 0.56
MCT4	2.18 ± 0.03	3.5±0.17	0.59 ± 0.01	101.05± 0.18	3.19 ±0.32	99.65±0.51	99.69± 0.27
MCT5	2.08 ± 0.02	3.0±0.09	0.65 ± 0.01	100.08± 0.16	2.00 ±0.11	99.85±0.28	99.87± 0.25
MCT6	2.10 ± 0.03	1.5±0.04	1.12 ± 0.01	100.78± 0.24	1.40 ±0.14	99.54±0.49	99.72± 0.37

n = 3; Mean ± S.E.M.

2.2. Effect of super disintegrant on *in vitro* drug release of Miglitol immediate release tablets

- Three different types of dissolution medium (pH 1.2, pH 7.4 and pH 6.8) were chosen to carry out the *in vitro* dissolution studies.

- The different concentrations of super disintegrant sodium starch glycollate exhibited significant increase in the *in vitro* drug release profile of prepared Miglitol immediate release tablets. The formulations without super disintegrant (MCT1) and formulation containing lesser concentrations of super disintegrant (MCT2-MCT4) exhibited poor dissolution drug release profile when compared to MCT5 and MCT6.

- The *in vitro* drug release was desirable with the formulations containing 8 mg/tab and 10 mg/tab concentration of sodium starch glycollate (MCT5 and MCT6). The formulation **MCT5** gave desired drug release profile of 99.83± 0.22, 99.87± 0.18 and 99.84± 0.15 in dissolution medium pH 1.2, pH 7.4 and pH 6.8 respectively.

- From the above study, it was found that the desirable hardness and *in vitro* drug release was obtained with the formulation **MCT5**.

- Hence the formulation **MCT5** containing super disintegrant in a concentration of 8 mg/tab was selected as an optimized batch and was chosen for the formulation of Miglitol pulsincaps and press coated tablets as a core tablet.

- The hardness and *in vitro* drug release of the formulation were depended upon the concentration of super disintegrant used in the formulation. These super disintegrants accelerate the disintegration of tablets by means of their ability to absorb large amount of water when exposed to aqueous environment[224, 225,226].

  The results were given in **table 7.8 to 7.10** and **fig. 7.60 to 7.65**

Table.7.8. Effect of super disintegrant on *in vitro* drug release of Miglitol immediate release tablets in buffer pH 1.2

Time in mts	Cumulative % drug release in buffer pH 1.2					
	Trials					
	MCT1	MCT2	MCT3	MCT4	MCT5	MCT6
0	0	0	0	0	0	0
15	18.56± 0.13	24.43± 0.42	29.72± 0.13	37.93± 0.18	46.75± 0.07	46.79± 0.12
30	36.72± 0.24	48.24± 0.33	49.72± 0.24	55.76± 0.27	74.83± 0.12	75.04± 0.17
45	54.32± 0.17	70.47± 0.35	72.32± 0.27	79.27± 0.25	96.15± 0.18	96.85± 0.05
60	72.73± 0.43	78.67± 0.41	81.44± 0.32	85.61± 0.19	99.85± 0.05	99.85± 0.19
90	82.83± 0.27	85.34± 0.14	87.45± 0.18	91.74± 0.15	99.84± 0.13	99.83± 0.22
120	88.56± 0.18	92.85± 0.18	94.73± 0.16	97.45± 0.12	99.83± 0.22	99.82± 0.18

n = 3; Mean ± SE.M.

Table.7.9. Effect of super disintegrant on *in vitro* drug release of Miglitol immediate release tablets in buffer pH 7.4

Time in mts	Cumulative % drug release in buffer pH 7.4					
	Trials					
	MCT1	MCT2	MCT3	MCT4	MCT5	MCT6
0	0	0	0	0	0	0
15	19.46± 0.29	25.52± 0.23	30.49± 0.22	38.32± 0.16	47.13± 0.04	47.55± 0.13
30	37.74± 0.15	49.31± 0.14	50.51± 0.27	56.53± 0.23	75.38± 0.16	75.73± 0.12
45	56.83± 0.21	71.43± 0.18	73.47± 0.45	80.42± 0.21	96.73± 0.28	96.36± 0.24
60	73.43± 0.26	79.75± 0.23	82.58± 0.42	86.53± 0.28	99.88± 0.12	99.88± 0.25
90	84.17± 0.45	85.88± 0.25	88.33± 0.32	92.48± 0.29	99.82± 0.17	99.78± 0.24
120	91.13± 0.63	93.54± 0.28	95.23± 0.24	97.88± 0.13	99.87± 0.18	99.76± 0.14

n = 3; Mean ± S.E.M.

Table.7.10. Effect of super disintegrant on *in vitro* drug release of Miglitol immediate release tablets in buffer pH 6.8

Time in mts	Cumulative % drug release in buffer pH 6.8					
	Trials					
	MCT1	MCT2	MCT3	MCT4	MCT5	MCT6
0	0	0	0	0	0	0
15	17.83± 0.13	24.26± 0.12	29.13± 0.28	37.25± 0.15	47.52± 0.19	46.43± 0.24
30	35.37± 0.24	47.69± 0.34	48.88± 0.42	54.82± 0.24	74.14± 0.09	74.65± 0.23
45	53.65± 0.52	70.24± 0.45	71.79± 0.31	78.82± 0.33	95.24± 0.14	96.64± 0.18
60	71.82± 0.42	77.67± 0.52	81.23± 0.36	85.51± 0.45	99.85± 0.22	99.74± 0.21
90	81.29± 0.11	84.12± 0.57	86.94± 0.25	91.15± 0.35	99.86± 0.18	99.75± 0.16
120	90.45± 0.24	92.76± 0.27	94.11± 0.18	97.14± 0.12	99.84± 0.15	99.74± 0.07

n = 3; Mean ± S.E.M.

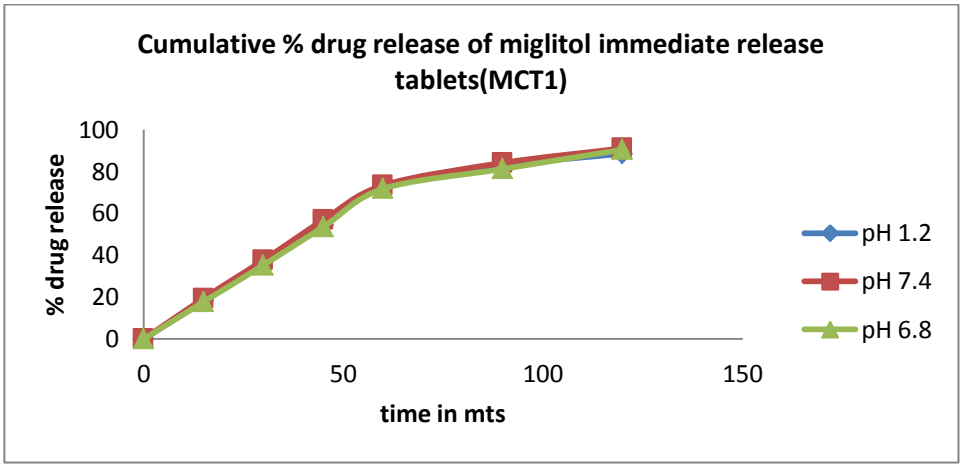

Fig. 7.60. Cumulative % drug release of Miglitol immediate release tablets (MCT1)

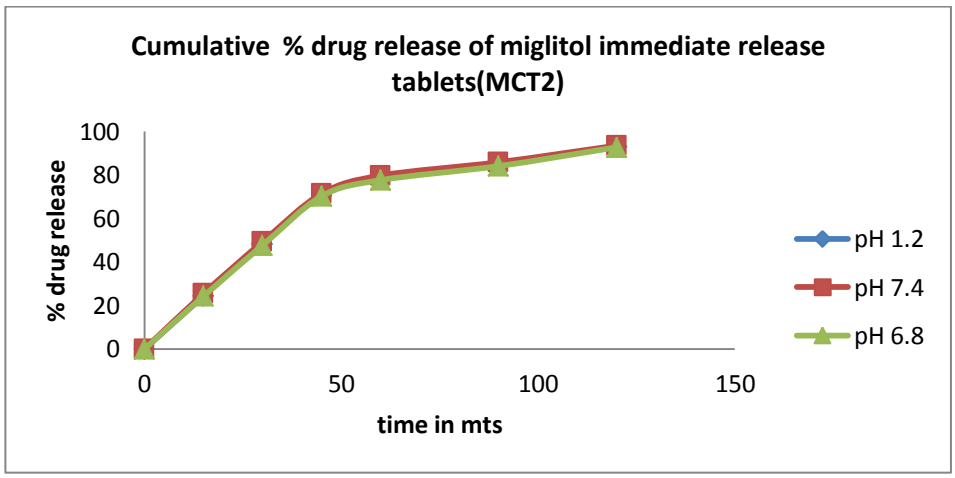

Fig. 7.61. Cumulative % drug release of Miglitol immediate release tablets (MCT2)

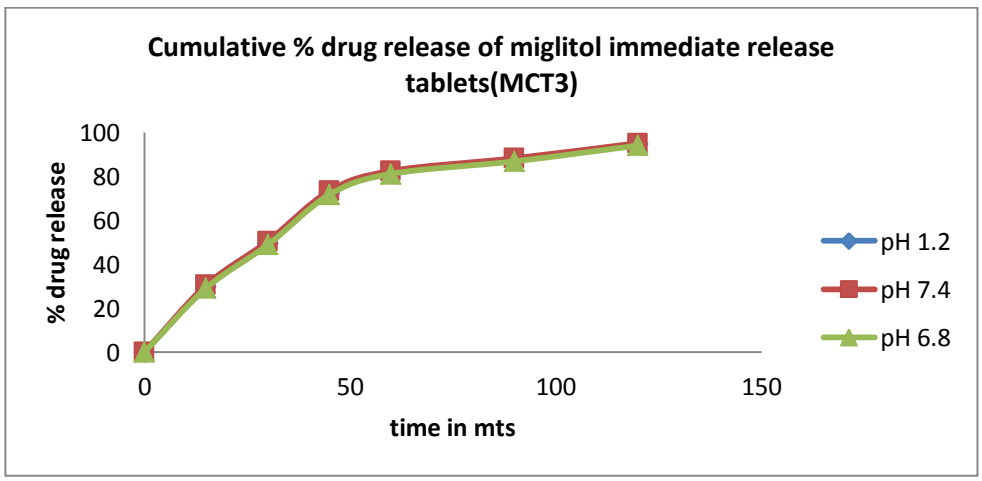

Fig. 7.62. Cumulative % drug release of Miglitol immediate release tablets (MCT3)

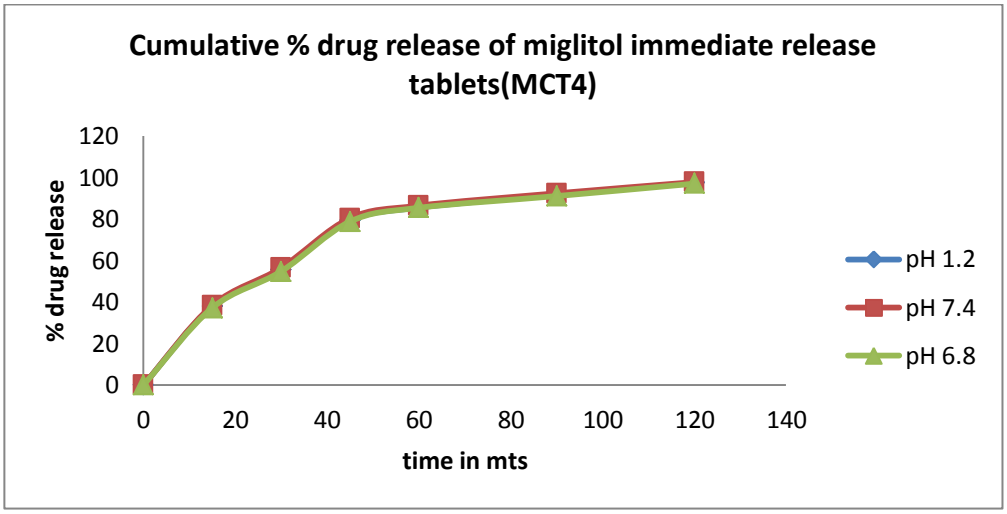

Fig. 7.63. Cumulative % drug release of Miglitol immediate release tablets (MCT4)

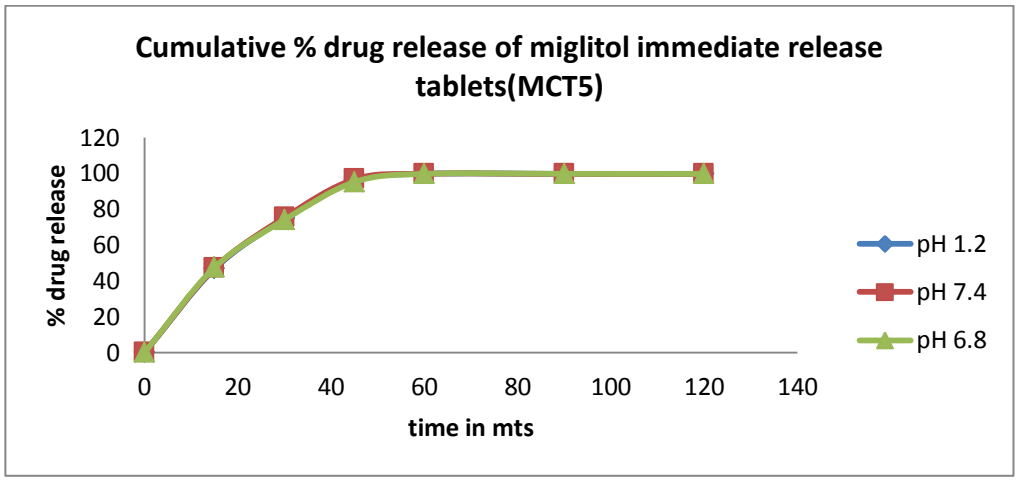

Fig. 7.64. Cumulative % drug release of Miglitol immediate release tablets (MCT5)

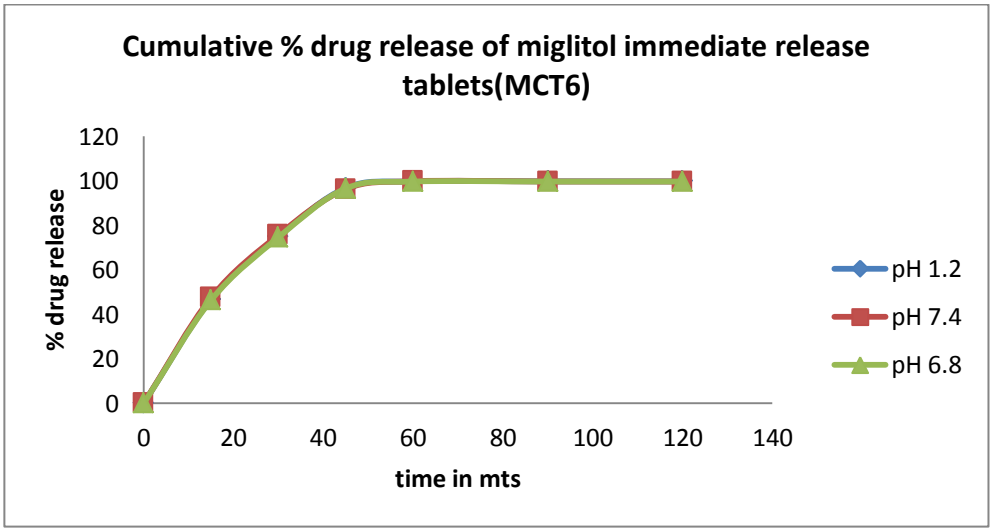

Fig. 7.65. Cumulative % drug release of Miglitol immediate release tablets (MCT6)

2.3. Average weight, content uniformity and drug content results of Miglitol Pulsincaps (MPC1-MPC15)

There were no significant changes in the average weight, content uniformity and drug content of the prepared Miglitol pulsincaps in the all formulatons (MPC1-MPC15). The average weight, content uniformity, drug content results for the prepared Miglitol pulsincaps were found to be within the limits. The content uniformity and drug content results for all the formulations were nearly 100% which indicated that there was no drug loss by manufacturing process or by additives used in the preparation. **(Table.7.11)**

Table 7.11. Results of average weight, content uniformity and drug content of Miglitol pulsincaps

Trials	Average weight (mg)	Content uniformity (%)	Drug content (%)
MPC1	420.56± 0.16	99.82± 0.12	99.82± 0.14
MPC 2	460.27± 0.26	99.73± 0.17	99.76± 0.17
MPC 3	500.78± 0.14	99.76± 0.45	99.83± 0.13
MPC 4	540.25± 0.18	99.65± 0.37	99.81± 0.15
MPC 5	581.14± 0.23	99.64± 0.29	99.84± 0.23
MPC 6	421.33± 0.27	99.63± 0.38	99.79± 0.19
MPC 7	461.09± 0.09	99.47± 0.53	99.72± 0.22
MPC 8	501.13± 0.32	99.71± 0.21	99.84± 0.23
MPC 9	541.03± 0.33	99.81± 0.19	99.85± 0.32
MPC10	580.78± 0.34	99.55± 0.32	99.87± 0.21
MPC11	422.02± 0.11	99.88± 0.27	99.80± 0.24
MPC12	460.84± 0.42	99.92± 0.34	99.85± 0.32
MPC13	500.85± 0.19	99.77± 0.14	99.75± 0.29
MPC14	540.32± 0.05	99.59± 0.11	99.89± 0.09
MPC15	580.55± 0.15	99.81± 0.19	99.77± 0.27

n = 3; Mean ± S.E.M.

2.4. Effect of hydrogel plug of various hydrophilic polymers on *in vitro* drug release profile and lag time of Miglitol pulsincaps (MPC1-MPC9)

- Three different dissolution mediums were chosen to carry out the *in vitro* dissolution studies. From the results obtained it was found that the drug release was not affected by the pH of the medium.

- All the prepared pulsincaps (MPC1-MPC15) showed desirable *in vitro* drug release profile in the first 2 hrs of study (pH 1.2 buffer). The cumulative percentage drug release of all the formulations in the pH 1.2 buffer were nearly 100% (first pulse)

- The formulation prepared with gelatin as hydrogel plug in various concentrations such as 30, 40, 50, 60 and 70 mg (MPC1-MPC5) exhibited maximum of 1hr lag time with the concentration of 70 mg. In this formulation, the second pulse of drug was started to release at 4^{th} hr which was not desirable.

- The formulation prepared with sodium alginate as hydrogel plug (MPC11-MPC15) exhibited maximum of 3 hrs lag time (MPC15) with the concentration of 70 mg and the second pulse of drug started to release at 6^{th} hr which was not found to be a desirable lag time.

- The formulations (MPC1-MPC5) and (MPC11-MPC15) prepared with gelatin and sodium alginate as hydrogel plug absorbed the dissolution medium rapidly, swelled and released the drug within a shorter lag time.

- Hence the formulations (MPC1-MPC5) and (MPC11-MPC15) were considered to be not satisfactory for pulsatile drug release of Miglitol due to its poor lag time.

- The formulations prepared with HPMC K4M (MPC6-MPC10) as hydrogel plug showed minimum lag time of 1hr (MPC6) and maximum of 4 hrs 30 mts (MPC10) with the concentration of 30 mg and 70 mg respectively.

- *In vitro* drug release studies of Miglitol pulsincaps prepared with HPMC K4M **(MPC9)** as hydrogel plug in a concentration of 60mg showed the maximum drug release of 99.76% (first pulse), 99.81% (Second pulse) , 99.92% (Third Pulse) with the desirable lag time 4 hours. Hence the formulation **MPC 9** was selected as an optimized batch and was chosen for stability studies.

- During dissolution study it was found that, the cap of the pulsincap dissolved in buffer solutions and the first dose of the drug was released initially and rapidly. Then the exposed hydrogel plug absorbed the surrounding fluid gradually, swelled and released the second and third doses of drug depending upon the nature of hydrogel plug and its concentration of used in the preparation. After few hours the hydrogel plug was wetted completely and it becomes soft mass. Then this wet soft mass was ejected out from the body of the capsule and released the second pulse of the drug immediately. The same mechanism was followed for the release of third pulse of the drug after a lag time of 4 hrs and released the Miglitol immediately.[223,227,228,229,230]

- The different hydrophilic polymer such as gelatin, HPMC K4M, sodium alginate in different concentration exhibited significant changes in the lag time were observed during the *in vitro* drug release studies of Miglitol pulsincaps.[231,232,233,234]

  The results were given in **table 7.12 to 7.14** and **fig.7.66 to 7.69**

Table 7.12. Effect of gelatin hydrogel plug on i*n vitro* drug release of Miglitol pulsincaps (MPC1-MPC5)

Time	Cumulative percentage drug release				
In buffer pH1.2					
	MPC1	**MPC2**	**MPC3**	**MPC4**	**MPC5**
0	0	0	0	0	0
15 mts	43.46± 0.12	43.38± 0.32	43.29± 0.07	42.87± 0.06	43.17± 0.61
30mts	75.14± 0.34	74.93± 0.09	75.33± 0.53	75.09± 0.45	74.93± 0.57
45mts	92.44± 0.27	91.74± 0.26	90.61± 0.43	91.96± 0.64	91.74± 0.28
60mts	99.82± 0.13	99.72± 0.76	98.83± 0.29	99.81± 0.31	99.72± 0.51
90mts	99.85± 0.18	99.85± 0.37	99.82± 0.13	99.82± 0.13	99.85± 0.71
120mts	99.84± 0.28	99.86± 0.39	99.82± 0.13	99.82± 0.13	99.86± 0.49
In buffer pH 7.4					
3hr	35.78± 0.12	15.25± 0.09	5.25± 0.19	0	0
4hr	99.81± 0.31	90.39± 0.27	85.56± 0.24	45.72± 0.32	25.72± 0.29
5hr	99.81± 0.31	99.80± 0.54	99.79± 0.28	90.58± 0.38	85.76± 0.17
In buffer pH 6.8					
6hr	-	-	-	99.82± 0.26	99.75± 0.12

n = 3; Mean ± S.E.M.

Table 7.13. Effect of Hydrogel plug of HPMC K4M on i*n vitro* drug release of Miglitol pulsincaps (MPC 6-MPC 10)

Time	Cumulative percentage drug release				
In buffer pH1.2					
	MPC6	**MPC7**	**MPC8**	**MPC9**	**MPC10**
0	0	0	0	0	0
15 mts	43.45± 0.26	43.54± 0.36	42.87± 0.33	43.72± 0.07	43.25± 0.04
30mts	74.34± 0.17	75.87± 0.44	74.48± 0.21	75.37± 0.11	75.46± 0.13
45mts	90.83± 0.42	92.82± 0.29	92.58± 0.49	92.15± 0.25	92.48± 0.18
60mts	98.79± 0.08	99.65± 0.27	99.72± 0.53	99.76±0.27	99.76± 0.27
90mts	99.87± 0.24	99.85± 0.09	99.82± 0.22	99.76±0.23	99.81± 0.29
120mts	99.88± 0.26	99.84± 0.37	99.83± 0.28	99.76±0.27	99.80± 0.36
In buffer pH 7.4					
3hr	0	0	0	0	0
4hr	10.25± 0.42	0	0	0	0
5hr	68.55± 0.39	12.46± 0.28	0	0	0
In buffer pH 6.8					
6hr	95.87± 0.36	70.89± 0.29	30.46± 0.32	0	0
6hr 15 mts	99.79± 0.18	92.78± 0.24	65.28± 0.15	48.87± 0.08	0
6hr 30 mts	-	99.83± 0.28	76.85± 0.16	75.55± 0.32	0
6hr 45 mts	-	-	90.38± 0.26	93.46± 0.29	15.78± 0.11
7hr	-	-	99.85± 0.09	99.74±0.35	58.89± 0.26
7hr 30 mts	-	-	-	99.78± 0.52	91.76± 0.15
8hr	-	-	-	99.81±0.29	99.79± 0.07
9hr	-	-	-	0	0
10hr	-	-	-	0	0
11hr	-	-	-	0	0
12hr	-	-	-	0	0
12hr 15 mts	-	-	-	47.47± 0.15	0
12hr 30mts	-	-	-	76.64± 0.28	0
12hr 45mts	-	-	-	94.18± 0.09	16.34± 0.18
13 hr	-	-	-	99.82±0.54	60.76± 0.08
13 hr 30mts	-	-	-	99.92± 0.14	92.85± 0.41
14 hr	-	-	-	99.92±0.42	99.84± 0.37

n = 3; Mean ± S.E.M.

Table 7.14. Effect of hydrogel plug of sodium alginate on *in vitro* drug release of Miglitol pulsincaps (MPC11-MPC15)

Time	Cumulative percentage drug release				
In buffer pH1.2					
	MPC11	**MPC12**	**MPC13**	**MPC14**	**MPC15**
0	0	0	0	0	0
15 mts	42.94± 0.13	43.08± 0.29	42.68± 0.28	43.56± 0.19	43.39± 0.22
30mts	75.32± 0.27	74.61± 0.17	75.24± 0.19	75.57± 0.42	75.12± 0.08
45mts	92.76± 0.38	91.79± 0.38	92.36± 0.08	92.39± 0.51	92.37± 0.25
60mts	99.85± 0.09	99.74± 0.31	99.67± 0.09	99.79± 0.34	99.72± 0.25
90mts	99.82± 0.27	99.83± 0.25	99.80± 0.41	99.82± 0.27	99.83± 0.25
120mts	99.82± 0.27	99.81± 0.23	99.79± 0.34	99.81± 0.23	99.82± 0.27
In buffer pH 7.4					
3hr	30.54± 0.08	15.25± 0.32	0	0	0
4hr	85.76± 0.15	66.84± 0.26	31.45± 0.17	0	0
5hr	99.80± 0.19	82.64± 0.14	86.74± 0.22	34.86± 0.13	0
In buffer pH 6.8					
6hr		99.85± 0.15	99.84± 0.18	88.53± 0.21	35.84± 0.18
6hr 15 mts				99.78± 0.32	86.79± 0.15
6hr 30 mts					99.82± 0.27

n = 3; Mean ± S.E.M.

CUMULATIVE % DRUG RELEASE OF MIGLITOL PULSINCAPS

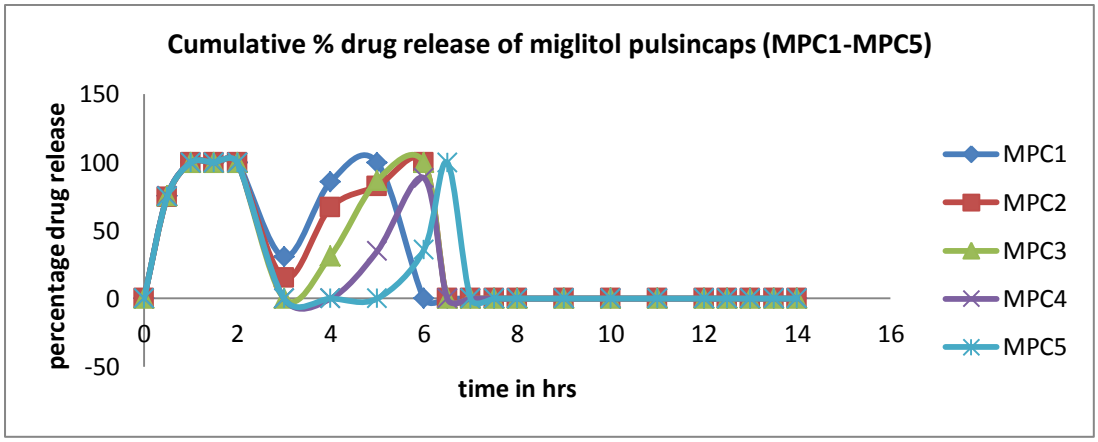

Fig.7.66. Cumulative % drug release of Miglitol pulsincaps (MPC1-MPC5)

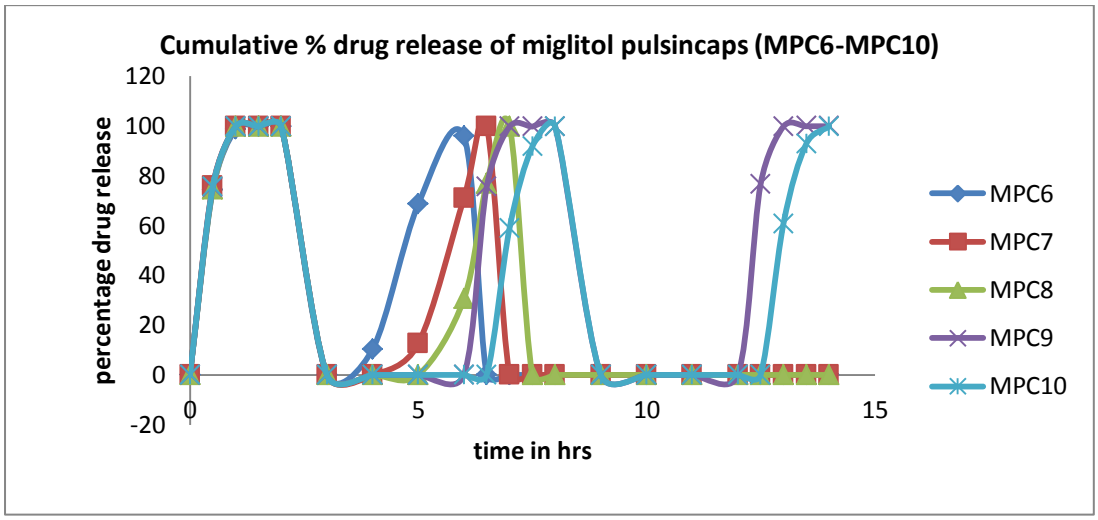

Fig.7.67. Cumulative % drug release of Miglitol pulsincaps (MPC6-MPC10)

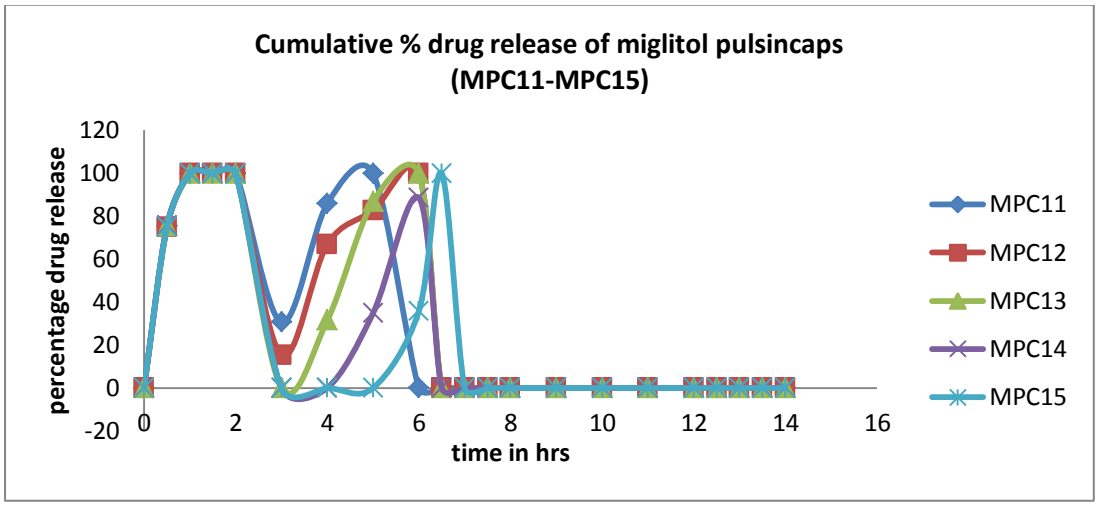

Fig.7.68. Cumulative % drug release of Miglitol pulsincaps (MPC11-MPC15)

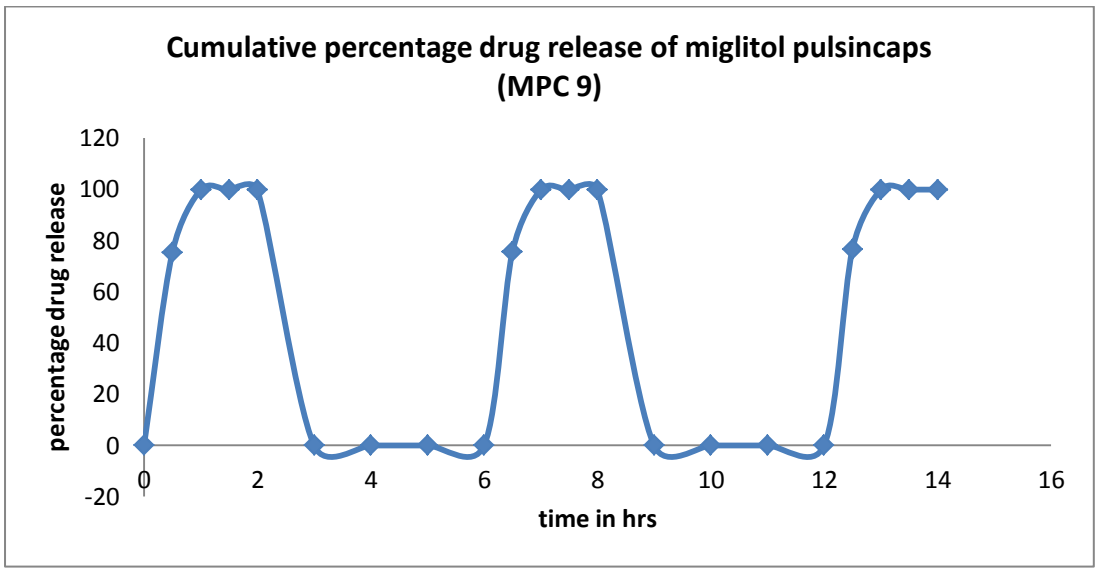

Fig.7.69 Cumulative % drug release of Miglitol pulsincaps (MPC 9)

3. MIGLITOL PRESS COATED TABLETS (MPT1-MPT26)

3.1. Post compression parameters of Miglitol press coated tablets

- The optimized formula **MCT5** used in the preparation of Miglitol immediate release tablets were selected for the preparation of core tablets in the formulation of press coated tablet of Miglitol. The pre and post compression results of **MCT 5** were found to be stable. The results were given in **table 7.6- 7.10**

- The post compression parameters such as hardness, friability, weight variation and drug content results for the prepared press coated tablets of Miglitol were found to be within the limits. There was no significant change in the hardness, friability; weight variation and drug content for all the formulations (MPT1-MPT26) were observed. The drug content for all the formulations were nearly 100% which indicated that there was no drug loss by manufacturing process or by excipients used in the formulations.

The results were given in **table 7.15** and **7.16**

Table 7.15. Post compression parameters of Miglitol press coated tablets (MPT1-MPT15)

Trials	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Average weight(mg)	Drug content (%)
MPT1	6.5± 0.17	0.58± 0.02	8.5± 0.05	653.12± 0.17	99.92± 0.25
MPT2	6.5± 0.17	0.72± 0.12	8.5± 0.05	650.16± 0.41	99.92± 0.25
MPT3	7.0± 0.08	0.87± 0.11	8.5± 0.05	651.34± 0.12	99.95± 0.87
MPT4	6.5± 0.17	0.27± 0.13	8.5± 0.05	653.34± 0.19	99.88± 0.49
MPT5	6.5± 0.17	0.97± 0.09	8.5± 0.05	650.82± 0.25	99.93± 1.02
MPT6	7.0± 0.08	0.45± 0.15	8.5± 0.05	650.41± 0.08	99.87± 0.16
MPT7	7.0± 0.08	0.57± 0.07	8.6± 0.12	650.49± 0.16	99.91± 0.58
MPT8	6.5± 0.17	0.64± 0.22	8.5± 0.05	652.31± 0.22	99.87± 0.17
MPT9	6.5± 0.17	0.39± 0.14	8.5± 0.05	651.29± 0.25	99.94± 0.76
MPT10	7.0± 0.08	0.91± 0.17	8.5± 0.05	652.92± 0.27	99.87± 0.17
MPT11	6.5± 0.17	0.42± 0.17	8.5± 0.05	650.05± 0.16	99.94± 0.76
MPT12	6.5± 0.17	0.38± 0.06	8.5± 0.05	650.29± 0.24	99.95± 0.87
MPT13	7.0± 0.08	0.77± 0.02	8.6± 0.12	652.08± 0.26	99.87± 0.16
MPT14	6.5± 0.17	0.85± 0.10	8.5± 0.05	653.06± 0.04	99.85± 0.53
MPT15	7.0± 0.08	0.83± 0.19	8.5± 0.05	651.19± 0.28	99.90± 0.67

n = 3; Mean ± S.E.M.

Table 7.16. Post compression parameters of Miglitol press coated tablets (MPT16-MPT26)

Trials	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Average weight (mg)	Drug content (%)
MPT16	7.0± 0.08	0.54± 0.08	8.6± 0.12	652.86± 0.10	99.88± 0.49
MPT17	6.5± 0.17	0.64± 0.10	8.5± 0.05	653.34± 0.12	99.89± 0.75
MPT18	7.0± 0.08	0.76± 0.03	8.5± 0.05	651.49± 0.15	99.92± 0.25
MPT19	6.5± 0.17	0.85± 0.10	8.5± 0.05	652.72± 0.23	99.85± 0.53
MPT20	6.5± 0.17	0.93± 0.12	8.5± 0.05	650.82± 0.09	99.94± 0.76
MPT21	7.0± 0.08	0.78± 0.11	8.6± 0.12	653.07± 0.28	99.87± 0.16
MPT22	6.5± 0.17	0.81± 0.07	8.5± 0.05	651.19± 0.07	99.90± 0.67
MPT23	6.5± 0.17	0.91± 0.13	8.5± 0.05	652.08± 0.31	99.91± 0.58
MPT24	6.5± 0.17	0.82± 0.05	8.5± 0.05	651.89± 0.05	99.93± 1.02
MPT25	7.0± 0.08	0.74± 0.02	8.6± 0.12	651.27± 0.19	99.87± 0.16
MPT26	6.5± 0.17	0.69± 0.09	8.5± 0.05	652.05± 0.25	99.92± 0.25

n = 3; Mean ± S.E.M.

3.2. Effect of barrier layers on *in vitro* drug release and lag time of Miglitol press coated tablets (MPT1-MPT24)

- Three different dissolution mediums were chosen to carry out the *in vitro* dissolution studies.[223] From the results obtained it was found that the drug release was not affected by the pH of the medium.

- The effect of same amount of four different hydrophilic and hydrophobic polymers and combination of these polymers used as a barrier layer exhibited significant role in the determination of lag time were observed.[233,234,235]

- The barrier layer prepared with single and combination of hydrophobic polymer (Glyceryl behenate or Ethyl cellulose) alone showed maximum lag time of more than 20 hrs (MPT1, MPT2 and MPT5).

- The barrier layer prepared with the hydrophilic polymers (HPMC or L-HPC) alone showed least lag time of 45 mts and 1hr 15 mts (MPT4 and MPT3) and released the drug immediately due to the hydration of the hydrophilic barrier layer by the dissolution medium.

- The combination of hydrophobic and hydrophilic polymer showed differences in lag time depending upon the ratios of hydrophobic and hydrophilic polymers used in the preparation of barrier layer. The hydrophobic polymer retards the hydration of hydrophilic polymer. Because of this dissolution medium did not penetrate outer barrier layer easily but the barrier layer eroded slowly.[236,237,239]

- The erosion rate of the hydrophilic polymer by the dissolution medium depends upon the concentration of hydrophilic and hydrophobic polymer used in the formulation which was responsible the lag time of the prepared press coated tablets.

- Here the L-HPC and HPMC are the responsible for the erosion of barrier layer and Ethyl cellulose and Glyceryl behenate are the responsible for the retardation of penetration of dissolution medium.[239,240]

- The hydrophobic nature of the glyceryl behenate and Ethyl cellulose retards the release of drug from the core tablet by preventing the penetration of dissolution medium into the core tablet through barrier layers.[239]

- The *in vitro* drug release studies of formulations MPT11-MPT18 showed maximum lag time of 9 hr 45 mts and minimum lag time of 8 hr 15 mts which were not found to be not desirable.

- The formulations of MPT19-MPT26 exhibited maximum lag time of 5hr 45 mts and minimum lag time of 4 hrs. The maximum drug was obtained after these lag time of all formulations due to the lesser concentration of hydrophobic polymer and higher concentration of hydrophilic polymer used in the formulation.

- The formulation **MPT24** prepared with barrier layer containing **Glyceryl behenate 25 mg** and **L-HPC175 mg** gave desired drug release profile after the lag time of 4 hrs. The *in vitro* dissolution study of **MPT24** showed the maximum drug release (99.85% for first pulse, 99.43% for second pulse and 99.76% for third pulse) and desirable lag time 4hrs. Hence the formulation **MPT24** was selected as an optimized batch and was chosen for stability studies.

- Based on the results obtained with the dissolution study, it was found that the lag time was decreased when the concentration of HPMC or L-HPC is increased and the increased lag time of was obtained when the concentration of Glyceryl behenate or Ethyl cellulose was increased.[241,242,243,244,245]

- During the dissolution it was observed that when the press coated tablets contacts with dissolution medium, the immediate release layer (first pulse) dissolves and released the drug immediately. Then the dissolution medium gradually reaches the barrier layers which are responsible for the lag time, eroding and rupturing the barrier layer, results in the rapid releasing of drug from the press coated tablets which depends upon the concentration, hydrophobicity and hydrophilicity of the polymers used in the formation of barrier layer.[246,247,248,249,250]

The results were given in **table 7.17** to **7.21** and **fig.7.70 to 7.76**

Table 7.17. Effect of barrier layers on *in vitro* drug release and lag time of Miglitol press coated tablets (MPT1-MPT5)

Time	Cumulative percentage drug release				
In buffer pH1.2					
	MPT1	**MPT2**	**MPT3**	**MPT4**	**MPT5**
0	0	0	0	0	0
15 mts	46.52± 0.10	47.13± 0.22	47.49± 0.31	46.98± 0.34	47.54± 0.51
30mts	75.72± 0.12	76.34± 0.18	77.43± 0.23	75.76± 0.42	77.31± 0.49
45mts	96.49± 0.15	97.25± 0.08	97.64± 0.11	97.81± 0.28	98.16± 0.36
60mts	99.82± 0.09	99.79± 0.26	99.84± 0.17	99.80± 0.07	99.85± 0.25
90mts	99.83± 0.13	99.79± 0.26	99.82± 0.09	99.79± 0.26	99.85± 0.25
120mts	99.82± 0.09	99.78± 0.08	99.83± 0.13	99.80± 0.07	99.86± 0.35
In buffer pH 7.4					
3hr	No release up to 22 hrs	No release up to 22 hrs 45mts	0	46.58± 0.10	No release up to 21 hrs
3hr 15 mts	0	0	48.24± 0.55	75.82± 0.74	0
3hr 30 mts	0	0	76.71± 0.51	95.83± 0.64	0
3hr 45 mts	0	0	99.81± 0.47	99.81± 0.47	0
4hr	0	0	99.81± 0.47	99.82± 0.09	0
4hr 45 mts	0	0	99.81± 0.47	0	0
5hr	0	0	99.81± 0.47	45.87± 0.83	0
In buffer pH 6.8					
5hr 15mts	0	0	47.82± 0.76	74.97± 0.57	0
5hr 30mts	0	0	99.82± 0.09	95.74± 0.88	0
5hr 45mts	0	0	99.82± 0.09	99.82± 0.09	0

n = 3; Mean ± S.E.M.

Table 7.18. Effect of barrier layers on *in vitro* drug release and lag time of Miglitol press coated tablets (MPT6-MPT10)

Time	Cumulative percentage drug release				
In buffer pH1.2					
	MPT6	**MPT7**	**MPT 8**	**MPT 9**	**MPT 10**
0	0	0	0	0	0
15 mts	46.75± 0.23	46.63± 0.56	47.05± 0.97	47.16± 0.44	46.65± 0.48
30mts	75.87± 0.42	76.34± 0.49	76.98± 0.19	75.59± 0.56	75.79± 0.66
45mts	96.35± 0.33	95.46± 0.81	96.45± 0.78	96.48± 0.61	97.14± 0.57
60mts	99.71± 0.13	99.58± 0.37	99.72± 0.31	99.65± 0.69	99.54± 1.06
90mts	99.79± 0.25	99.81± 0.53	99.82± 0.47	99.85± 0.71	99.84± 0.10
120mts	99.79± 0.25	99.81± 0.53	99.82± 0.47	99.85± 0.71	99.84± 0.10
In buffer pH 7.4					
3hr	No release up to 15hrs	No release up to 14hrs 30mts	No release up to 15hrs 15mts	No release up to 15hrs 45mts	0
3hr 45mts	0	0	0	0	0
4hr	0	0	0	0	47.12± 0.34
4hr 15mts	0	0	0	0	76.27± 0.60
4hr 30mts	0	0	0	0	95.83± 0.26
4hr 45 mts	0	0	0	0	99.82± 0.47
5hr	0	0	0	0	99.82± 0.47
In buffer pH 6.8					
6hr	0	0	0	0	0
6hr 45 mts	0	0	0	0	0
7hr	0	0	0	0	47.25± 0.45
7hr 30 mts	0	0	0	0	95.89± 0.72
8hr	0	0	0	0	99.79± 0.25

n = 3; Mean ± S.E.M.

Table 7.19. Effect of barrier layers on *in vitro* drug release and lag time of Miglitol press coated tablets (MPT 11-MPT 18)

Time	Cumulative percentage drug release							
	In buffer pH1.2 (2hrs)							
	Trials							
	MPT11	**MPT12**	**MPT13**	**MPT14**	**MPT15**	**MPT16**	**MPT17**	**MPT18**
0mt	0	0	0	0	0	0	0	0
15mts	47.23± 0.25	46.98± 0.22	47.41± 0.49	46.86± 0.51	47.03± 0.28	45.63± 0.38	45.72± 0.35	47.47± 1.21
30mts	75.15± 0.19	75.40± 0.24	76.33± 0.28	75.65± 0.43	76.42± 1.03	74.97± 0.49	75.02± 0.39	76.49± 0.88
45mts	96.58± 0.76	96.77± 0.14	97.02± 0.36	96.91± 0.39	96.76± 0.90	95.89± 0.63	95.77± 0.30	97.35± 0.47
60mts	99.84± 0.13	99.81± 0.36	99.65± 0.72	99.63± 0.23	99.74± 0.53	99.68± 0.44	99.80± 0.50	99.12± 0.78
90mts	99.83± 0.16	99.80± 0.41	99.85± 0.54	99.83± 0.16	99.84± 0.13	99.78± 0.29	99.79± 1.12	99.80± 0.93
120 mts	99.84± 0.13	99.81± 0.36	99.85± 0.54	99.83± 0.16	99.84± 0.13	99.78± 0.29	99.80± 0.93	99.82± 0.21
In buffer pH 7.4 (3hrs)								
3hr	No release up to 9hr45mts	No release up to 8hr15mts	No release up to 9hr15mts	No release up to 8hr15mts	No release up to 9hr	No release up to 8hr30mts	No release up to 9hr15mts	No release up to 8hr45mts
4hr	0	0	0	0	0	0	0	0
5hr	0	0	0	0	0	0	0	0
In buffer pH 6.8 (subsequent hrs)								
6hr	0	0	0	0	0	0	0	0

n = 3; Mean ± S.E.M.

Table 7.20. Effect of barrier layers on *in vitro* drug release and lag time of Miglitol press coated tablets (MPT19-MPT26)

Time	Cumulative percentage drug release							
	In buffer pH1.2 (2hrs)							
	Trials							
	MPT19	**MPT20**	**MPT21**	**MPT22**	**MPT23**	**MPT24**	**MPT25**	**MPT26**
0mt	0	0	0	0	0	0	0	0
15mts	44.74± 0.10	45.63± 0.16	44.89± 0.49	45.07± 0.09	44.99± 1.15	46.48± 0.47	45.87± 0.08	46.03± 0.30
30mts	73.86± 0.34	74.02± 0.23	73.94± 1.09	76.12± 0.19	73.37± 0.91	74.76± 0.06	75.34± 1.21	76.19± 0.56
45mts	94.56± 0.45	95.38± 0.44	94.67± 0.88	96.55± 0.15	94.84± 0.78	96.83± 0.50	96.31± 0.95	95.88± 0.41
60mts	98.49± 0.76	99.07± 0.39	98.73± 0.35	98.44± 0.86	97.56± 0.42	99.74± 0.20	98.64± 0.05	97.84± 1.32
90mts	99.79± 0.45	99.80± 0.132	99.78± 0.64	99.81± 0.77	99.77± 0.87	99.83± 0.18	99.79± 0.45	99.81± 0.77
120mts	99.81± 0.37	99.83± 0.67	99.80± 0.59	99.82± 0.19	99.79± 0.45	99.85± 0.07	99.81± 0.77	99.83± 0.67
In buffer pH 7.4 (3hrs)								
3hr	0	0	0	0	0	0	0	0
4hr	0	0	0	0	0	0	0	0
5hr	0	0	0	0	0	0	0	0
In buffer pH 6.8 (subsequent hrs)								
6hr	0	0	0	0	0	0	0	0
6hr 15mts	0	0	0	0	0	45.12± 0.27	0	0
6hr 30mts	0	0	0	0	46.07± 0.49	75.34± 0.10	0	0
6hr 45mts	0	0	0	0	74.97± 0.27	96.58± 0.11	0	44.23± 0.57
7hrs	0	0	0	0	95.39± 0.94	95.83± 0.26	45.09± 0.28	74.27± 0.55
7hr 30mts	0	74.88± 0.20	0	46.75± 0.55	99.75± 0.21	99.41± 0.39	94.93± 0.29	99.60± 1.22

8hrs	46.45± 0.17	94.93± 0.29	74.67± 0.30	95.86± 0.47	99.83± 0.67	99.43± 0.60	97.81± 0.68	99.77± 0.87
9hrs	99.74± 0.42	99.85± 0.07	99.81± 0.77	99.79± 0.45	0	0	99.85± 0.07	99.81± 0.77
9hr30mts	99.80± 0.59	0	99.83± 0.67	0	0	0	0	0
10hrs	0	0	0	0	0	0	0	0
11hrs	0	0	0	0	0	0	0	0
12hrs	0	0	0	0	0	0	0	0
12hrs 15mts	0	0	0	0	0	47.52± 0.80	0	0
12hr 30mts	0	0	0	0	0	76.65± 0.10	0	0
12hr 45mts	0	0	0	0	45.84± 0.26	94.63± 0.08	0	0
13hr	0	0	0	0	74.86± 1.10	99.67± 0.38	0	0
13hr 30mts	0	0	0	0	99.69± 1.08	99.76± 0.33	0	75.48± 0.57
14hr	0	0	0	0	99.82± 0.19	99.76± 0.33	43.89± 0.68	99.58± 0.10
15hr	0	96.15± 0.29	0	77.87± 0.30	99.81± 0.77	-	98.43± 1.01	99.81± 0.77
16hr	75.86± 1.21	99.82± 0.19	95.12± 0.57	99.78± 0.64	-	-	99.84± 0.53	-
16hr 30mts	95.13± 0.91	-	99.76± 0.33	99.81± 0.77	-	-	-	-
17hr	99.68± 0.89	-	99.82± 0.19	-	-	-	-	-
17hr 30mts	99.81± 0.77	-	-	-	-	-	-	-

n = 3; Mean ± S.E.M.

Table 7.21. Effect of barrier layers on Lag time of Miglitol press coated tablets (MPT1-MPT24)

S.No	Trials	Lag time	S.No	Trials	Lag time
1	**MPT1**	22hrs	14	**MPT14**	8hr.15mts
2	**MPT2**	22hrs.45mts	15	**MPT15**	9hrs
3	**MPT3**	1hr 15mts	16	**MPT16**	8hr.30mts
4	**MPT4**	45mts	17	**MPT17**	9hrs.15mts
5	**MPT5**	21hrs	18	**MPT18**	8hrs.45mts
6	**MPT6**	15hrs	19	**MPT19**	5hrs.45mts
7	**MPT7**	14hrs.30mts	20	**MPT20**	5hrs
8	**MPT8**	15hrs.15mts	21	**MPT21**	5hrs.30mts
9	**MPT9**	14hrs.45mts	22	**MPT22**	5hrs.15mts
10	**MPT10**	1hr.45mts	23	**MPT23**	4hrs.15mts
11	**MPT11**	9hr.45mts	24	**MPT24**	**4hrs**
12	**MPT12**	8hr.15mts	25	**MPT25**	4hrs.45mts
13	**MPT13**	9hr.15mts	26	**MPT26**	4hrs.30mts

EFFECT OF BARRIER LAYER ON CUMULATIVE % DRUG RELEASE OF MIGLITOL PRESS COATED TABLETS

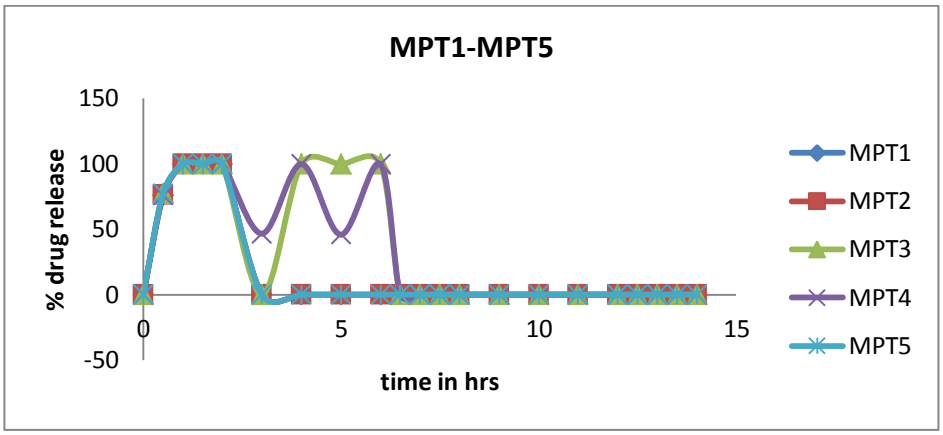

Fig.7.70 .Cumulative % drug release of Miglitol press coated tablets(MPT1-MPT5)

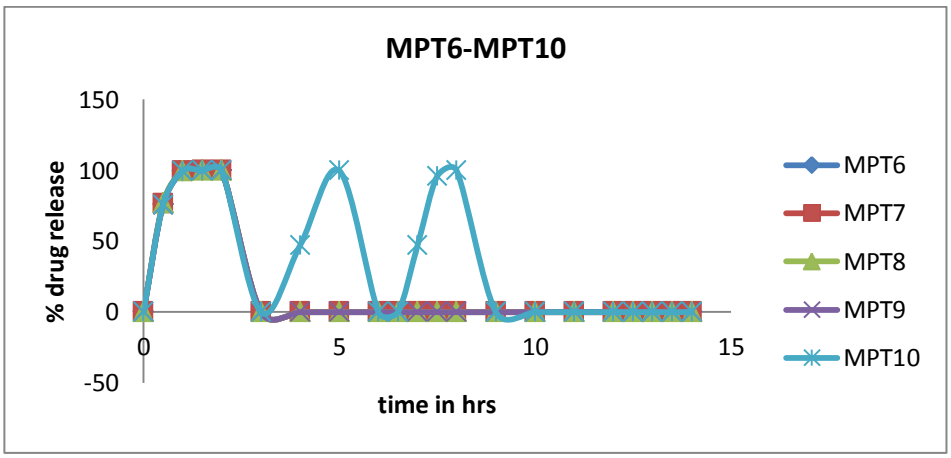

Fig.7.71. Cumulative % drug release of Miglitol press coated tablets(MPT6-MPT10)

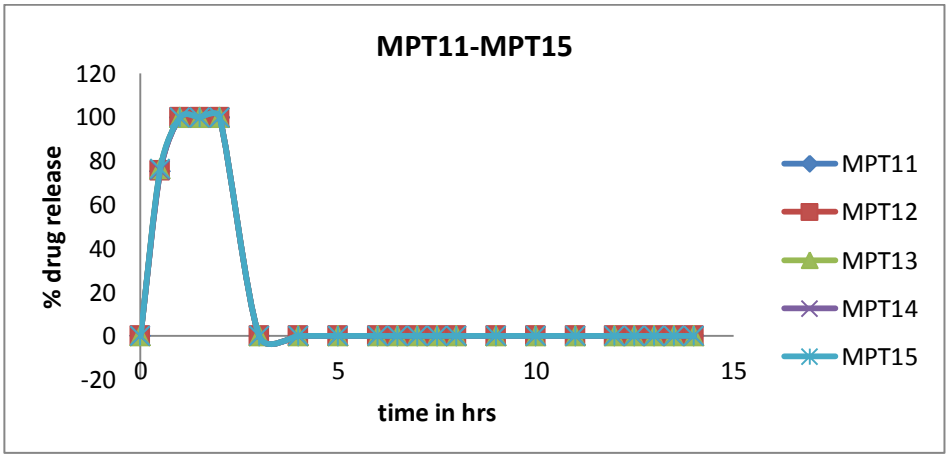

Fig.7.72. Cumulative % drug release of Miglitol press coated tablets(MPT11-MPT15)

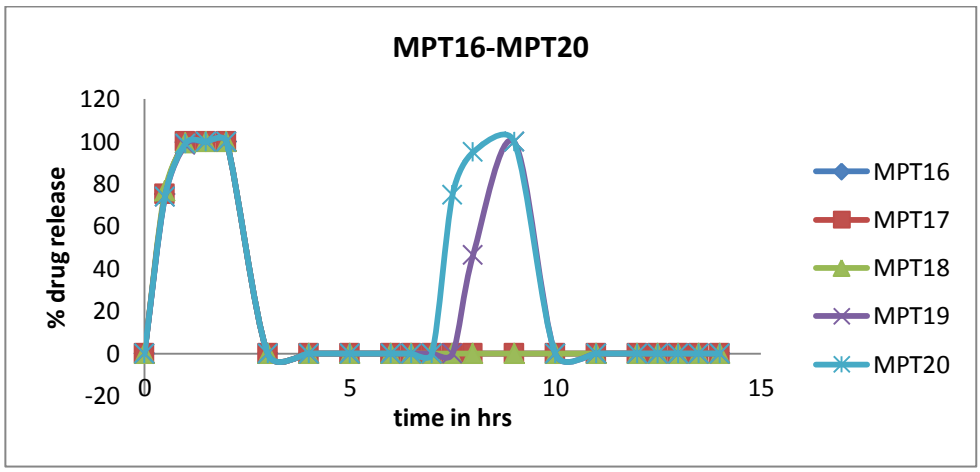

Fig.7.73. Cumulative % drug release of Miglitol press coated tablets(MPT16-MPT20)

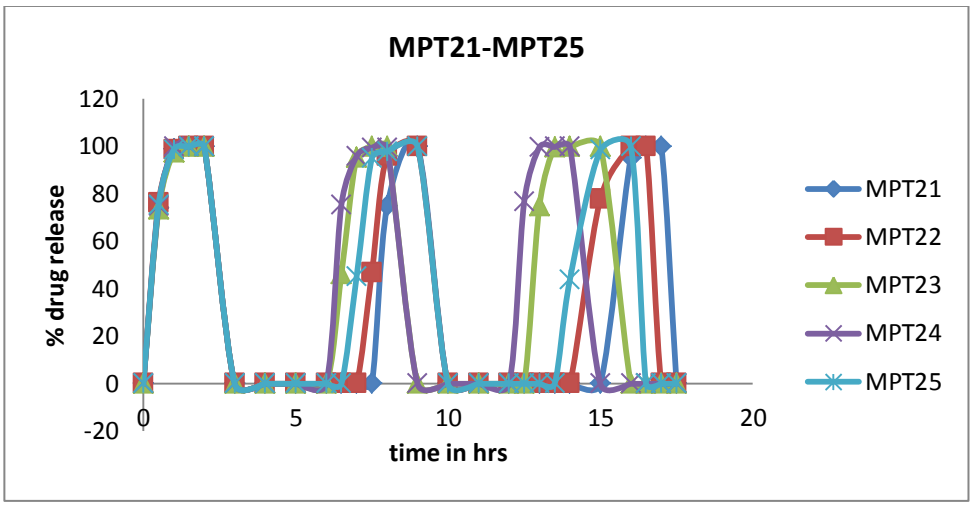

Fig.7.74. Cumulative % drug release of Miglitol press coated tablets (MPT21-MPT25)

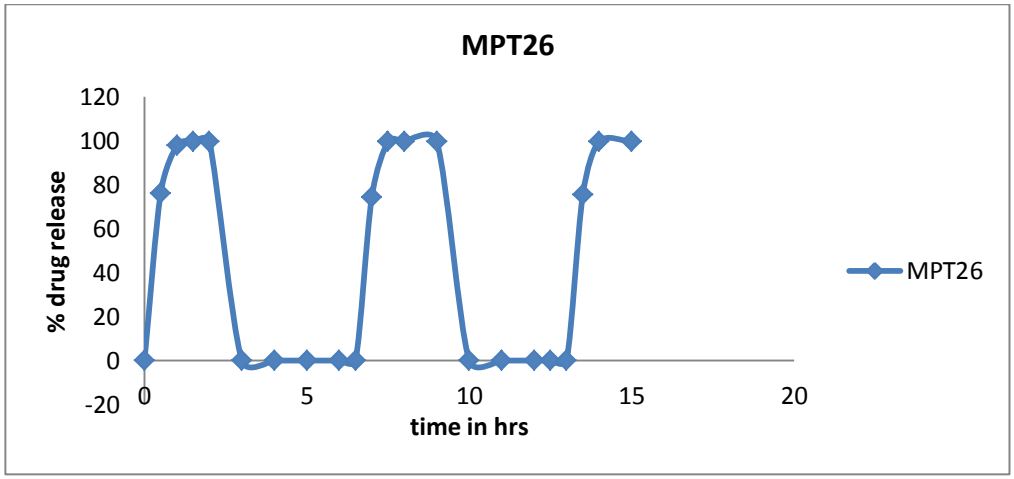

Fig.7.75. Cumulative % drug release of Miglitol press coated tablets (MPT26)

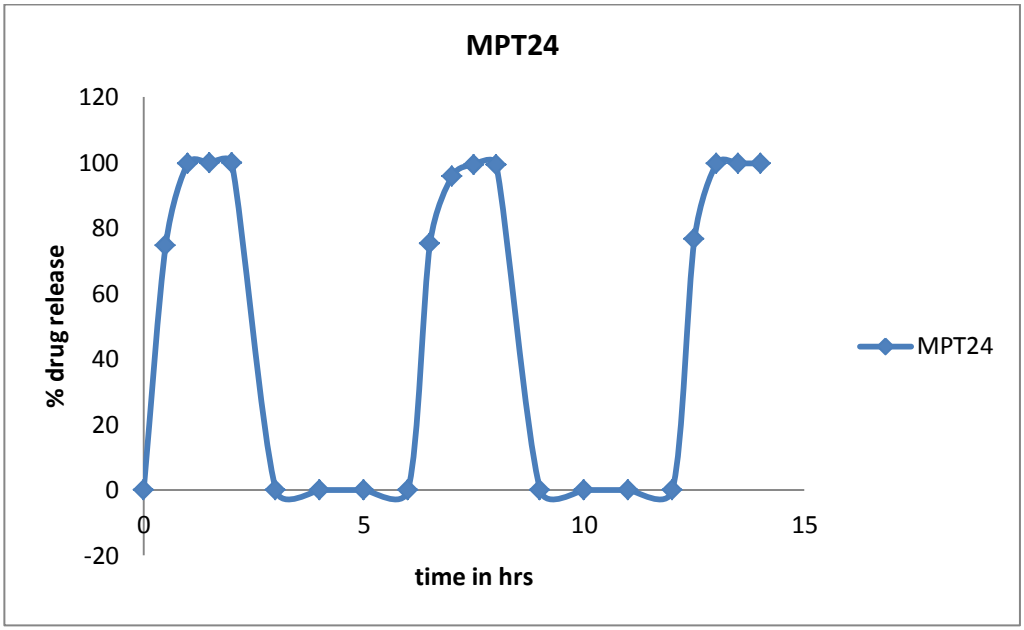

Fig.7.76. Cumulative % drug release of Miglitol press coated tablets(MPT24)

4. PERFORMANCE EVALUATION OF OPTIMIZED MIGLITOL PULSINCAPS AND MIGLITOL PRESS COATED TABLETS

4.1. Pharmacokinetic analysis[172,212,213,215]

- Based on the data from the HPLC analysis the mean plasma concentrations and pharmacokinetic parameters were calculated. The mean concentration of Miglitol pure after one-week treatment was increased slightly after half an hour of administration compared to day 1 concentration in plasma, but it was not statistically significant ($P>0.05$). On administration of Miglitol pulsincaps and press coated tablets in rabbits for 7 days showed that there was a significant enhancement in the plasma concentration after 0.5h of last dose.

- The increase in $AUC_{0-12,}$ and C_{max} of Miglitol pulsincap on day1 & 7 were 1072±42.12 to 1210±36.34 ng. h. ml-1 and 388.2±33.42 to 596.70±48.50 ng/ ml ($P<0.05$) respectively. The pharmacokinetic study of Miglitol press coated tablets on 7 days treatment showed alteration in C_{max}, AUC0-t, $AUC_{0-\infty}$ and $t_{1/2}$ were observed but it was not statistically significant. All the other parameters were decreased after 7 days of treatment. The changes in AUC_{0-t}, $t_{1/2}$ and C_{max} on day 1 and 7 for press coated tablets were 1084.37±76.18 $ng.h.ml^{-1}$ to 1682.30±91.06 $ng.h.ml^{-1}$($P<0.01$), 2.68±0.48 to 4.42±0.37h ($P<0.05$) and 429.98±37.61 to 587.8±43.80 ng/ml ($P<0.05$) respectively. Pharmacokinetic changes in all the formulations analyzed were almost similar as standard marketed drug.

- All the parameters altered in both the formulations treated groups were found to be within biological limits. No major changes were observed when compared to standard formulations. Hence it can be summarized that the pharmacokinetic changes among the tested groups were comparable with that of standard pure and standard marketed formulations. No remarkable deviations have been identified in both kinetic and dynamic parameters in the animal models used in this present investigation.

4.2. Pharmacodynamic study[251,252,253,254,255]

- Diabetes mellitus is a serious complex chronic condition that is a major source of ill health worldwide. This metabolic disorder is characterized by hyperglycemia and disturbances of carbohydrate, protein, and fat metabolisms, secondary to an absolute or relative lack of the hormone insulin. NIDDM has also been associated with an increased risk for premature arteriosclerosis due to increase in triglycerides and low density lipoprotein levels. About 70-80% of deaths in diabetic patients are due to vascular disease. An ideal treatment for diabetes would be a drug that not only controls the glycemic level but also prevents the development of arteriosclerosis and other complications of diabetes. Long before the use of insulin became common, indigenous remedies were used for the treatment of diabetes mellitus and hyperlipidemia.

- The undesirable side effects and contraindications of synthetic drugs, and the fact that they are not suitable for use during pregnancy, have made scientists look towards alternative hypoglycemic agents[256]. Besides hyperglycemia, several other factors including dislipidemia or hyperlipidemia are involved in the development of micro and macrovascular complications of diabetes that are the major causes of morbidity and death. According to WHO projections, the prevalence of diabetes is likely to increase by 35%. Currently, there are over 150 million diabetic patients worldwide and this is likely to increase to 300 million or more by the year 2025. Statistical projection about India suggests that the number of diabetics will rise from 15 million in 1995 to 57 million in the year 2025, the highest number of diabetics in the world. Reasons for this rise include increase in sedentary lifestyle, consumption of energy-rich diet, obesity, higher life span, etc[258,259,260].

- Miglitol pure produced 186.20±10.15 reduction in blood glucose towards normal ($p < 0.01$) at the dose of 0.5mg/kg of body weight during 10 days of treatment onwards. Miglitol pulsincap and press coated formulations produced a significant ($p<0.01$) reduction in blood glucose at the range of

45.52-67.14% compared to control. It was observed that the Miglitol pulsincap treatment gradually increases the efficiency during 8hrs in sugar control capability, the antihyperglycemic action of Miglitol pulsincap was peak after 6-8hrs of treatment compared to Miglitol pure. The percent reduction in blood glucose in the diabetic condition compared to the normal state was highly significant ($P<0.01$). Since our results showed that Miglitol pulsincap reduced blood glucose levels in hyperglycemic animals better than the Miglitol pure.

- The total cholestrol and trigliceride levels were also normalized significantly in both the formulations ($P<0.01$) when compared to diabetic control group. But no statistically significant difference among the treated group was observed. Miglitol (1,5-dideoxy-1,5-[2-hydroxy ethyl] iminol)-D-glucitol is an α–glucicosidase inhibitor used as an anti hyperglycemic agent in the treatment of non-insulin dependent diabetes mellitus. Miglitol delays the digestion of ingested carbohydrate, there by resulting in a smaller blood glucose concentration.

- The anti hyperglycemic action of Miglitol results from a reversible inhibition of membrane bound intestinal α–glycosidase which hydrolyzes oligosaccharides and disaccharides to glucose and other monosaccharide in the brush border of small intestine. In diabetic patients the enzyme inhibition resulted in delayed glucose absorption and lowering of postprandial hyperglycemia[255,256]. Current consensus supports the use of AGI's as monotherapy or adjunct therapy for poorly controlled NIDDM. Pulsatile Drug Delivery systems are basically time-controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, gastro-intestinal motility, etc.

- Traditionally, drugs are released in an immediate or extended fashion. However, in recent years, pulsatile drug release systems are gaining growing interest. These systems are designed according to the circadian rhythm of the body. A pulsatile drug release, where the drug is released rapidly after a well

defined lag-time, could be advantageous for many drugs or therapies. Diseases wherein PDDS are promising include asthma, peptic ulcer, cardiovascular diseases, arthritis, and diabetes. This drug delivery system is programmed drug delivery system in harmonization with body clock.

- The pulse has to be designed in such a way that a complete and rapid dug release is achieved after the lag time. Therefore Pulsatile drug delivery is one such systems that, by delivering drug at the right time, right place and in right amounts, holds good promises of benefit to the patients suffering from diabetes.

The results were given in **table 7.22** to **7.26** and **fig.7.77** to **fig.7.79**

Table 7.22: Absolute Recovery of Miglitol Pure, Pulsincap, Press coated and Miglitol marketed tablet

Miglitol Concentration (μg / ml)	Absolute Recovery (%)							
	Miglitol Pure		Pulsincap		Press coated tablet		Marketed Miglitol Tablet	
	Mean ± S.D	Range (min - max)	Mean ± S.D	Range (min-max)	Mean ± S.D	Range (min-max)	Mean ± S.D	Range (min - max)
5	86.19 ± 3.48	83.5 – 87.4	85.1 ± 2.88	82.4 – 89.6	85.1 ± 2.88	82.4 – 89.6	84.12 ± 3.42	85.1 – 85.1
10	90.06 ± 3.92	88.16 – 91.8	88.3 ± 2.27	86.7 – 93.2	88.3 ± 2.27	86.7 – 93.2	90.04 ± 3.28	84.12 – 89.4
15	84.15 ± 4.11	80.22 –85.3	86.6 ± 2.68	88.5 – 92.1	86.6 ± 2.68	88.5 – 92.1	84.21 ± 4.11	80.10 –82.0
20	88.22 ± 3.87	86.19 – 91.5	95.9 ± 2.46	90.2 – 99.3	95.9 ± 2.46	90.2 – 99.3	86.25 ± 3.62	82.10 – 90.1
25	89.87 ± 3.80	85.72 – 92.4	97.4 ± 2.63	94.4 - 100.2	97.4 ± 2.63	94.4 - 100.2	89.10 ± 3.71	84.55 – 91.3
50	90.23 ± 2.99	88.43 – 91.00	99.2 ± 2.48	99.1-102	99.2 ± 2.48	99.1-102	90.28 ± 2.45	88.55 – 90.04

Table 7.23. Mean changes in concentration (µg/ml) of Miglitol Pure, Pulsincap, Press coated and Marketed Miglitol Tablet for 7 days treatment in rabbits.

Time (hr)	Miglitol Pure once daily		Pulsincap once daily		Press coated tablet once daily		Marketed Miglitol Tablet	
	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
0	0.00±0.00	0.00±0.00	0.00±0.00	2.54±0.21	0.00±0.00	2.42±0.14	0.00±0.00	0.10±0.01
0.5	8.82±1.16	9.34±1.10	6.96±0.79	11.36±1.08	6.98±0.82	11.07±1.00	8.16±1.05	9.19±1.18
1	36.41±2.49	37.85±2.36	32.34±2.28	43.22±3.28	32.19±2.35	43.10±3.22	36.34±2.23	37.56±2.35
2	38.78±3.76	39.10±4.75	38.45±3.65	46.46±3.27	38.44±3.72	46.37±3.18	38.68±3.65	39.09±4.64
4	29.60±3.51	32.20±2.45	26.38±2.76	37.21±2.68	26.21±2.89	37.18±2.71	29.41±3.32	32.14±2.39
6	21.48±3.00	23.88±2.98	18.09±2.08	31.40±2.41	18.00±2.17	31.46±2.48	21.27±2.86	23.76±2.85
8	10.26±1.43	12.69±1.46	13.21±1.96	24.20±2.09	13.86±2.00	24.28±2.15	10.06±1.37	12.54±1.32
24	7.25±1.00	8.53±1.13	6.16±1.23	13.58±1.49	6.10±1.12	13.66±1.54	6.88±1.02	8.09±1.08

Values are expressed as Mean ± S.E.M.; (n=6); (*P<0.05); [a]Comparison made between treatment groups on day1 and 7.

Table 7.24. Pharmacokinetic changes of Miglitol Pure, Pulsincap, Press coated and Marketed Miglitol Tablet for 7days treatment in rabbits

Pharmacokinetic Parameters	Miglitol Pure once daily		Pulsincap once daily		Press coated tablet once daily		Marketted Miglitol Tablet	
	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
C_{max} (ng/ml)	468.4±56.11	522.79±48.68^{ns}	388.2±33.42	596.70±48.50*	429.98±37.61	587.8±43.80^{ns}	452.80±45.18	498.96±50.00^{ns}
T_{max} (h)	0.5±0.1	0.6±0.1^{ns}	0.6±0.12	0.6±0.12^{ns}	0.5±0.1	0.5±0.1^{ns}	0.6±0.1	0.6±0.2^{ns}
$AUC_{(0-t)}$ (ng h/ml)	968.12±36.56	1134.51±85.34^{ns}	1072±42.12	1210±36.34^{ns}	1084.37±76.18	1682.30±91.06**	1088±48.23	1021±56.21^{ns}
$AUC_{(0-\infty)}$ (ng.h/ml)	893.28±41.21	225.23±98.63**	228±61.17	123±36.22^{ns}	202.56±63.49	189.74±64.26^{ns}	198.45±53.92	108.23±48.31^{ns}
$T_{½}$ (h)	2.36±0.54	2.47±0.68^{ns}	3.11±0.42	2.0±0.12^{ns}	2.68±0.48	4.42±0.37*	2.66±0.24	2.00±0.12^{ns}
Cl/f (L/h)	6.84±0.26	2.83±0.29**	5.49±0.8	3.2±1.02*	5.41±0.24	2.66±0.62**	5.10±0.35	5.35±0.40^{ns}
Vd/f (L/kg)	9.86±2.10	10.2±2.00^{ns}	16.25±2.86	12.8±1.22^{ns}	10.7±2.06	14.82±2.11^{ns}	13.44±1.56	8.12±1.00^{ns}

Values are expressed as Mean ± S.E.M.; (n=6); *P<0.05; **P<0.01; Comparison made between day1 and 7.

Table 7.25. Effect of Miglitol Pure, Pulsincap, Press coated and Marketed Miglitol Tablet on Glucose concentration in alloxan-induced diabetic rabbits during 14 days oral administration

Treatment	Glucose concentration (mg/dl) measured at regular intervals (Days)			
	Day 1	Day 5	Day 10	Day 14
Normal	74.64±2.40	71.36±3.00	74.34 ± 8.10	78.13±3.12
Diabetic Control	225.17±16.64[a**]	257.10±12.2[a**]	283.10 ±10.10[a**]	312.10±14.62[a**]
Miglitol Pure	221.05±13.09[b*]	186.20±10.15[b**]	124.28 ± 11.67[b**]	109.17±12.48[b]
Press coated Tablet	230.15±12.69[b*]	162.45± 12.00[b**]	112.10 ± 12.53[b**]	102.56±12.33[b**]
Marketted Miglitol Tablet	251.96±12.65[b*]	120.10±13.12[b**]	98.5 ± 10.11[b**]	101.12±14.12[b**]
Miglitol Pulsincap	235.42±12.40[b*]	182.34±13.00[b**]	154.22 ± 12.14[b**]	168.20 ±12.10[b**]

n=6; Values are expressed as Mean ±S.E.M;

[a]Comparison made between normal and diabetic control

[b]Comparison made between diabetic control and test group

[*]P<0.05; [**]P<0.01

Table 7.26. Effect of Miglitol Pure, Pulsincap, Press coated and Marketed Miglitol Tablet on Total Cholesterol and Triglyceride levels in alloxan-induced diabetic rabbits during 14 days oral administration.

Treatment and dose	Parameters (mg/dl)	
	Total Cholesterol	**Triglycerides**
Normal	84.14 ± 2.2	86.2 ± 2.96
Diabetic Control	115.2 ± 3.0[a**]	120.1 ± 4.24[a**]
Miglitol Pure	91.28 ± 3.5[b**]	68.2 ± 2.17[b**]
Press coated Tablet	106.12 ± 2.1[b**]	74.6 ± 2.35[b**]
Marketted Miglitol Tablet	84.0 ± 4.2[b**]	82.3 ± 3.22[b**]
Miglitol Pulsincap	78.10 ± 4.5[b**]	91.0 ± 4.12[b**]

n=6; Values are expressed as Mean ±S.E.M;

[a]Comparison made between normal and diabetic control

[b]Comparison made between diabetic control and test group

[*]P<0.05; [**]P<0.01

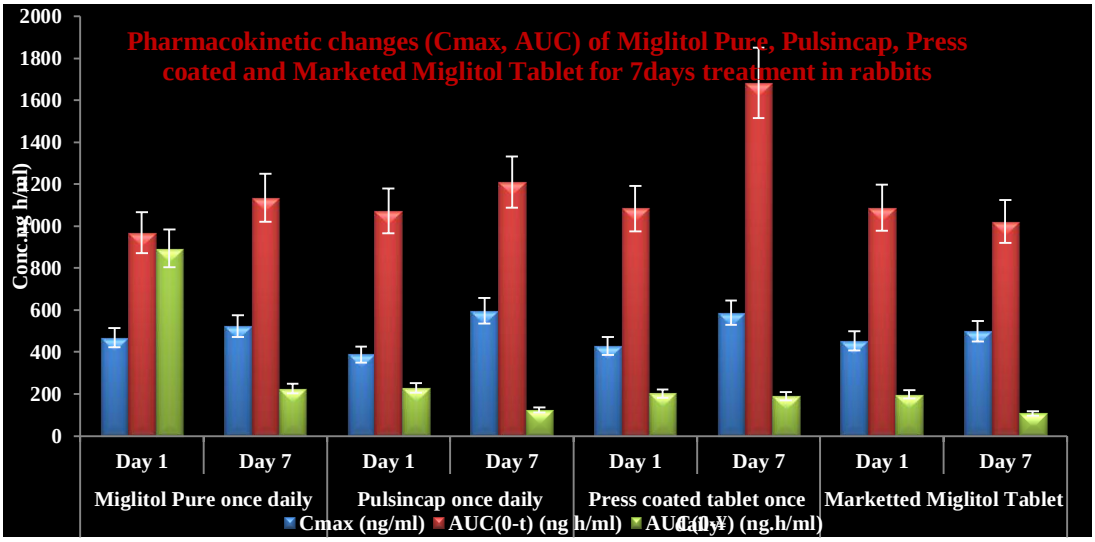

Fig.7.77. Pharmacokinetic changes (C_{max}, AUC) of Miglitol Pure, Miglitol pulsincaps, Miglitol press coated tablets and Miglitol marketed tablets for 7 days treatment in rabbits.

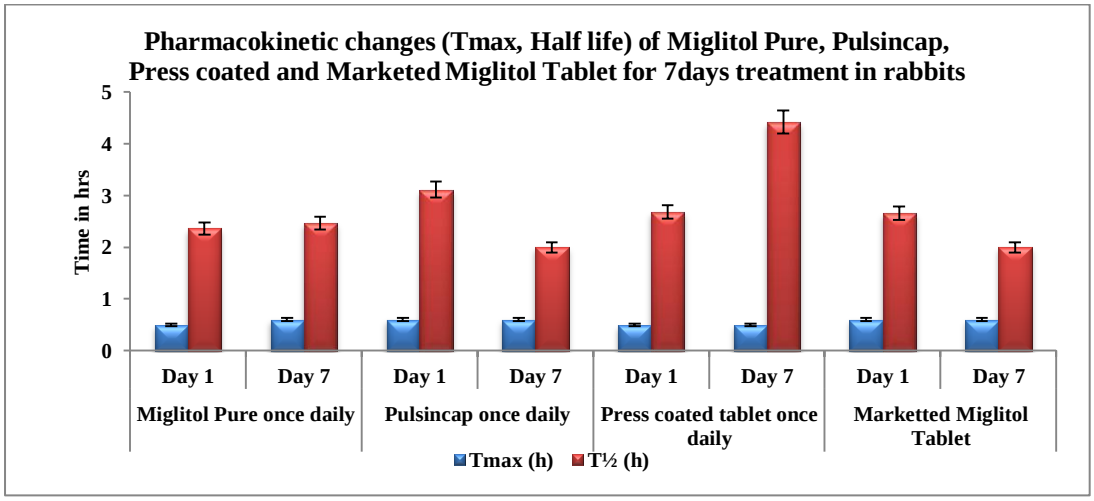

Fig.7.78. Pharmacokinetic changes (T_{max}, Half life) of Miglitol Pure, Miglitol pulsincaps, Miglitol press coated tablets and Miglitol marketed tablets for 7 days treatment in rabbits.

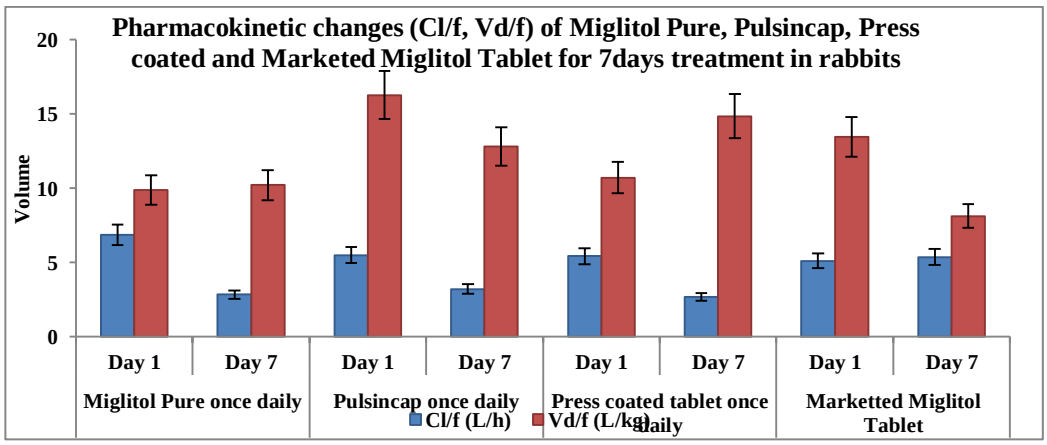

Fig.7.79. Pharmacokinetic changes (Cl/f, Vd/f) of Miglitol Pure, Miglitol pulsincaps, Miglitol press coated tablets and Miglitol marketed tablets for 7 days treatment in rabbits.

5. STABILITY EVALUATION OF OPTIMIZED MIGLITOL PULSINCAPS (MPC9) AND MIGLITOL PRESS COATED TABLETS (MPT24)

5.1. Stability studies of Miglitol Pulsincaps (MPC9)

The stability study result of Miglitol pulsincaps (MPC9) indicates that there were no significant changes in the physicochemical properties of the formulation and the drug concentration. During the stability the following were observed

- No significant changes in the physical and chemical characteristics were observed.
- No significant variations in the *in vitro* dissolution drug release and lag time were observed.
- From this stability study, it was also inferred that the formulated Miglitol pulsincaps (MPC 9) were stable.

The stability study results for Miglitol pulsincaps (MPC9) were given in **table 7.27** to **7.32**

Table 7.27. Stability study results of average weight, content uniformity and drug content of Miglitol pulsincaps MPC9 at temperature 40^0C /75% RH

Parameters	Months				
	Initial	1	2	3	6
Average weight (mg)	541.03± 0.33	541.27 ± 0.36	541.46± 0.27	541.19± 0.31	541.05± 0.24
Content uniformity (%)	99.81± 0.19	99.84±0.15	99.82± 0.23	99.84± 0.15	99.83± 0.34
Drug content (%)	99.85± 0.32	99.82 ± 0.34	99.83± 0.12	99.81± 0.29	99.79± 0.26

n = 3; Mean ± S.E.M.

Table 7.28. Stability study results of average weight, content uniformity and drug content of Miglitol pulsincaps MPC9 at temperature 30^0C /65% RH

Parameters	Months				
	Initial	3	6	9	12
Average weight (mg)	541.03± 0.33	540.97± 0.31	541.09± 0.09	540.88± 0.27	540.92± 0.41
Content uniformity (%)	99.81± 0.19	99.87± 0.31	99.83± 0.36	99.85± 0.42	99.84± 0.28
Drug content (%)	99.85± 0.32	99.88± 0.41	99.84± 0.33	99.85± 0.27	99.83± 0.24

n = 3; Mean ± S.E.M.

Table 7.29. Stability study results of average weight, content uniformity and drug content of Miglitol pulsincaps MPC9 at temperature 25^0C / 60% RH

Parameters	Months				
	Initial	3	6	9	12
Average weight (mg)	541.03± 0.33	540.93± 0.18	541.07± 0.34	541.02± 0.45	540.88± 0.33
Content uniformity (%)	99.81± 0.19	99.85± 0.24	99.83± 0.34	99.85± 0.29	99.87± 0.43
Drug content(%)	99.85± 0.32	99.81± 0.29	99.84± 0.14	99.81± 0.23	99.84± 0.19

n = 3; Mean ± S.E.M.

Table 7.30. Stability studies on *In vitro* drug release profile of Miglitol Pulsincaps (MPC9) at temperature 40^0C /75% RH

Time (hrs)	Cumulative percentage drug release				
	Months				
	pH 1.2				
	Initial	1	2	3	6
0	0	0	0	0	0
1	99.76±0.23	99.57±0.23	99.68±0.21	99.82±0.63	99.71±0.43
2	99.76±0.27	99.88±0.13	99.87±0.17	99.99±0.34	99.79±0.25
pH 7.4					
3	0	0	0	0	0
4	0	0	0	0	0
5	0	0	0	0	0
pH 6.8					
6	0	0	0	0	0
7	99.74±0.35	99.71±0.18	99.71±0.08	99.64±0.03	99.65±0.29
8	99.81±0.29	99.78±0.21	99.87±0.39	99.81±0.37	99.82±0.11
9	0	0	0	0	0
10	0	0	0	0	0
11	0	0	0	0	0
12	0	0	0	0	0
13	99.82±0.54	99.48±0.08	99.66±0.38	99.72±0.27	99.56±0.34
14	99.92±0.42	99.91±0.12	99.93±0.24	99.91±0.12	99.89±0.53

n = 3; Mean ± S.E.M.

Table 7.31. Stability studies on *In vitro* drug release profile of Miglitol Pulsincaps (MPC 9) at temperature 30^0C / 65% RH

Time (hrs)	Cumulative percentage drug release				
	Months				
	pH 1.2				
	Initial	3	6	9	12
0	0	0	0	0	0
1	99.76±0.23	99.72±0.28	99.68±0.32	99.72±0.34	99.78±0.29
2	99.76±0.27	99.74±0.29	99.76±0.23	99.83±0.27	99.81±0.35
pH 7.4					
3	0	0	0	0	0
4	0	0	0	0	0
5	0	0	0	0	0
pH 6.8					
6	0	0	0	0	0
7	99.74±0.35	99.65±0.28	99.76±0.41	99.75±0.23	99.72±0.32
8	99.81±0.29	99.76±0.34	99.77±0.43	99.76±0.37	99.82±0.26
9	0	0	0	0	0
10	0	0	0	0	0
11	0	0	0	0	0
12	0	0	0	0	0
13	99.82±0.54	99.63±0.32	99.69±0.28	99.71±0.36	99.67±0.44
14	99.92±0.42	99.78±0.37	99.87±0.32	99.85±0.41	99.86±0.18

n = 3; Mean ± S.E.M.

Table 7.32. Stability studies on *In vitro* drug release profile of Miglitol Pulsincaps (MPC 9) at temperature 25^0C / 60% RH

Time (hrs)	Cumulative percentage drug release				
	Months				
	pH 1.2				
	Initial	3	6	9	12
0	0	0	0	0	0
1	99.76±0.23	99.67±0.28	99.72±0.42	99.45±0.54	99.72±0.32
2	99.76±0.27	99.83±0.17	99.83±0.32	99.88±0.21	99.87±0.29
pH 7.4					
3	0	0	0	0	0
4	0	0	0	0	0
5	0	0	0	0	0
pH 6.8					
6	0	0	0	0	0
7	99.74±0.35	99.65±0.43	99.69±0.27	99.63±0.45	99.71±0.23
8	99.81±0.29	99.82±0.26	99.85±0.28	99.84±0.42	99.83±0.16
9	0	0	0	0	0
10	0	0	0	0	0
11	0	0	0	0	0
12	0	0	0	0	0
13	99.82±0.54	99.65±0.23	99.69±0.21	99.68±0.34	99.70±0.38
14	99.92±0.42	99.87±0.25	99.90±0.38	99.92±0.54	99.89±0.45

n = 3; Mean ± S.E.M.

5.2. Stability studies of Miglitol Press coated tablets (MPT24)

During the stability the following were observed

- No significant changes in the physical and chemical characteristics were observed.
- No significant variations in the *in vitro* dissolution drug release and lag time were observed.
- From this stability study, it was also inferred that the formulated Miglitol press coated tablets (MPT 24) were stable.

The stability study results for Miglitol press coated tablets (MPT24) were given in **table 7.33** to **7.38**

Table 7.33. Stability study results of hardness, friability, average weight and drug content of MPT24 at temperature 40^0C /RH 75%

Parameters	Months				
	Initial	**1**	**2**	**3**	**6**
Average weight(mg)	651.89± 0.05	652.17± 0.32	651.76± 0.41	651.58± 0.37	651.39± 0.18
Hardness (Kg/Cm^2)	6.5±0.17	6.5±0.13	7±0.25	6.5±0.13	6.5±0.13
Friability (%)	0.82±0.05	0.65±0.23	0.73±0.31	0.91±0.07	0.75±0.26
Thickness (mm)	8.50± 0.05	8.52± 0.14	8.55± 0.21	8.56± 0.08	8.54± 0.07
Drug content	99.93± 1.02	99.88± 0.18	99.85± 0.28	99.87± 0.35	99.84± 0.21

n = 3; Mean ± S.E.M.

Table 7.34. Stability study results of hardness, friability, average weight and drug content of MPT24 at temperature 30^0C /RH 65%

Parameters	Months				
	Initial	**3**	**6**	**9**	**12**
Average weight (mg)	651.89± 0.05	651.09± 0.23	650.98± 0.27	651.43± 0.36	651.57± 0.42
Hardness (Kg/Cm^2)	6.5±0.17	6.5±0.14	7±0.08	6.5±0.13	6.5±0.13
Friability (%)	0.82±0.05	0.92±0.43	0.76±0.23	0.87±0.12	0.73±0.26
Thickness (mm)	8.50± 0.07	8.51± 0.12	8.53± 0.08	8.52± 0.07	8.54± 0.13
Drug content (%)	99.93± 1.02	99.86± 0.14	99.89± 0.26	99.86± 0.32	99.91± 0.23

n = 3; Mean ± S.E.M.

Table 7.35. Stability study results of hardness, friability, average weight and drug content of MPT24 at temperature 25^0C /RH 60%

Parameters	Months				
	Initial	**3**	**6**	**9**	**12**
Average weight (mg)	651.89± 0.05	651.76± 0.32	651.38± 0.49	651.38± 0.27	651.37± 0.42
Hardness (Kg/Cm^2)	6.5±0.17	7±0.09	6.5±0.09	7±0.04	6.5±0.12
Friability (%)	0.82±0.05	0.71±0.17	0.80±0.22	0.83±0.23	0.78±0.29
Thickness (mm)	8.50± 0.05	8.56± 0.24	8.55± 0.19	8.54± 0.14	8.54± 0.13
Drug content (%)	99.93± 1.02	99.90± 0.28	99.83± 0.13	99.87± 0.16	99.88± 0.21

n = 3; Mean ± S.E.M.

Table 7.36. Stability studies on *in vitro* drug release profile of Miglitol press coated tablets (MPT 24) at temperature 40^0C /RH 75%

Time (hrs)	Cumulative percentage drug release				
	Months				
	pH 1.2				
	Initial	1	2	3	6
0	0	0	0	0	0
1	99.74±0.20	99.58±0.21	99.65±0.33	99.59±0.52	99.71±0.55
2	99.85±0.07	99.83±0.32	99.88±0.29	99.82±0.39	99.84±0.27
pH 7.4					
3	0	0	0	0	0
4	0	0	0	0	0
5	0	0	0	0	0
pH 6.8					
6	0	0	0	0	0
7	95.83±0.26	95.57±0.09	95.72±0.38	95.54±0.03	95.63±0.72
8	99.43±0.60	99.84±0.32	99.84±0.27	99.86±0.05	99.82±0.39
9	0	0	0	0	0
10	0	0	0	0	0
11	0	0	0	0	0
12	0	0	0	0	0
13	99.67±0.38	99.67±0.76	99.66±0.37	99.58±0.21	99.54±0.03
14	99.76±0.33	99.81±0.44	99.80±0.19	99.83±0.32	99.83±0.32

n = 3; Mean ± S.E.M.

Table 7.37. Stability studies on *in vitro* drug release profile of Miglitol press coated tablets (MPT 24) at temperature 30^0C /RH 65%

Time (hrs)	Cumulative percentage drug release				
	Months				
	pH 1.2				
	Initial	3	6	9	12
0	0	0	0	0	0
1	99.74±0.20	99.66±0.18	99.61±0.09	99.69±0.26	99.55±0.21
2	99.85±0.07	99.89±0.71	99.80±0.19	99.84±0.08	99.82±0.07
pH 7.4					
3	0	0	0	0	0
4	0	0	0	0	0
5	0	0	0	0	0
pH 6.8					
6	0	0	0	0	0
7	95.83±0.26	95.63±0.69	95.59±0.48	95.56±0.21	95.65±0.07
8	99.43±0.60	99.81±0.44	99.87±0.35	99.87±0.16	99.87±0.16
9	0	0	0	0	0
10	0	0	0	0	0
11	0	0	0	0	0
12	0	0	0	0	0
13	99.67±0.38	99.61±0.41	99.71±0.23	99.62±0.37	99.67±0.65
14	99.76±0.33	99.82±0.56	99.81±0.44	99.80±0.61	99.87±0.42

n = 3; Mean ± S.E.M.

Table 7.38. Stability studies on *in vitro* drug release profile of Miglitol press coated tablets (MPT 24) at temperature 25^0C /RH 60%

Time (hrs)	Cumulative percentage drug release				
	Months				
	pH 1.2				
	Initial	3	6	9	12
0	0	0	0	0	0
1	99.74±0.20	99.65±0.37	99.64±0.22	99.55±0.45	99.64±0.34
2	99.85±0.07	99.82±0.31	99.75±0.26	99.84±0.12	99.79±0.19
pH 7.4					
3	0	0	0	0	0
4	0	0	0	0	0
5	0	0	0	0	0
pH 6.8					
6	0	0	0	0	0
7	95.83±0.26	95.67±0.36	95.75±0.28	95.67±0.54	95.69±0.31
8	99.43±0.60	99.86±0.32	99.89±0.51	99.88±0.13	99.81±0.29
9	0	0	0	0	0
10	0	0	0	0	0
11	0	0	0	0	0
12	0	0	0	0	0
13	99.67±0.38	99.74±0.53	99.71±0.08	99.61±0.12	99.67±0.32
14	99.76±0.33	99.81±0.32	99.79±0.25	99.81±0.31	99.80±0.10

n = 3; Mean ± S.E.M.

6. COMPARISON OF *IN VITRO* DRUG RELEASE PROFILE OF OPTIMIZED MIGLITOL PULSINCAPS (MPC9) AND MIGLITOL PRESS COATED TABLETS (MPT24) WITH MARKETED MIGLITOL TABLETS.

The evaluation of optimized Miglitol pulsincaps (MPC9) and Miglitol press coated tablets (MPT24) were carried out for its *in vitro* drug release profile and compared with the *in vitro* drug release profile of marketed conventional Miglitol tablets.

- Studies *of in vitro* drug release of Miglitol pulsincaps (MPC9) exhibited the maximum drug release 99.77±0.09% for first pulse, 99.82±0.19% for Second pulse and 99.91±0.11% for third Pulse. The lag time after each drug release was found to be 4 hrs.

- The *in vitro* dissolution study of Miglitol press coated tablets (MPT24) exhibited the maximum drug release 99.84± 0.07% for first pulse, 99.42± 0.34 % a for second pulse and 99.74± 0.16 % for third pulse with the lag time of 4 hrs after each drug release.

- During this study it was observed that the maximum percentage drug release for the first pulse was obtained in the first 2 hrs of study and after that there was no drug release up to 4 hrs i.e. (3-6 hrs). The second pulse starts to release after 6^{th} hr and releases the maximum drug at the end of 8^{th} hr. Again there was no drug release up to 4 hrs i.e. (9-12 hrs). The third pulse of the drug starts to release after 12 hrs and releases the maximum percentage of drug at the end of 14 hrs. The second and third pulses of the drugs were released after 4 hrs of lag time which confirms the timed release of the formulated Miglitol pulsincaps and press coated tablets.

- The *in vitro* drug release for the Miglitol marketed conventional tablets were carried out in buffer solution pH 1.2. The cumulative percentage drug release at different time intervals such as 15, 30, 45, 60, 90 and 120 mts were 38.55±0.18, 68.97±0.25, 89.76±0.19, 97.85±0.55, 99.17±0.27 and 99.20±0,46 % respectively. The cumulative percentage drug release at different time intervals for Miglitol conventional marketed tablets were compared with

cumulative percentage drug release of formulated Miglitol pulsincaps (MPC 9) and press coated tablets (MPT24). It was found that there was no drug release after 2 hrs due to complete disintegration and dissolution of conventional Miglitol tablets where as in the formulated Miglitol pulsincaps (MPC9) and press coated tablets (MPT24) which encompasses three pulses of drug in a single unit and releases the drug at different time intervals.

- The results of comparative dissolution studies of Miglitol pulsincaps (MPC 9) and press coated tablets (MPT24) with marketed Miglitol tablets indicates that the optimized formulations of Miglitol pulsincaps (MPC9) and press coated tablets (MPT24) were found to have three pulses of drug release with desirable lag time. It may be suitable for the management of postmeal hyperglycemia as in diabetics when compared to the marketed conventional Miglitol tablets which contains only single dose of drug. The results were given in **table 7.39** and **fig.7.80**

Table 7.39. Comparison of *in vitro* drug release profile of optimized Miglitol pulsincaps (MPC9) and press coated tablets (MPT24) with marketed Miglitol tablets.

Time	Cumulative percentage drug release		
	In Buffer pH 1.2		
	MPC9	MPT24	Marketed tablets
0	0	0	0
15mts	43.75± 0.23	47.09± 0.26	38.55±0.18
30mts	75.36± 0.14	74.75± 0.14	68.97±0.25
45mts	92.23± 0.26	96.79± 0.18	89.76±0.19
60mts	99.67±0.09	99.72± 0.22	97.85±0.55
90mts	99.71±0.15	99.81± 0.27	99.17±0.27
120mts	99.77±0.09	99.84± 0.07	99.20±0,46
In Buffer pH 7.4			
3hr	0	0	0
4hr	0	0	0
5hr	0	0	0
In Buffer pH 6.8			
6hr	0	0	0
6hr 15 mts	48.76± 0.12	45.43± 0.12	0
6hr 30 mts	75.61± 0.23	75.51± 0.17	0
6hr 45 mts	93.52± 0.16	96.63± 0.22	0
7hr	99.77±0.26	95.88± 0.13	0
7hr 30 mts	99.79± 0.28	99.40± 0.21	0
8hr	99.82±0.19	99.42± 0.34	0
9hr	0	0	0
10hr	0	0	0
11hr	0	0	0
12hr	0	0	0
12hr 15 mts	47.65± 0.24	47.36± 0.34	0
12hr 30 mts	76.75± 0.17	76.73± 0.22	0
12hr 45 mts	94.22± 0.13	94.87± 0.26	0
13 hr	99.79±0.28	99.71± 0.21	0
13 hr 30 mts	99.89± 0.24	99.73± 0.11	0
14 hr	99.91±0.11	99.74± 0.16	0

n = 3; Mean ± S.E.M.

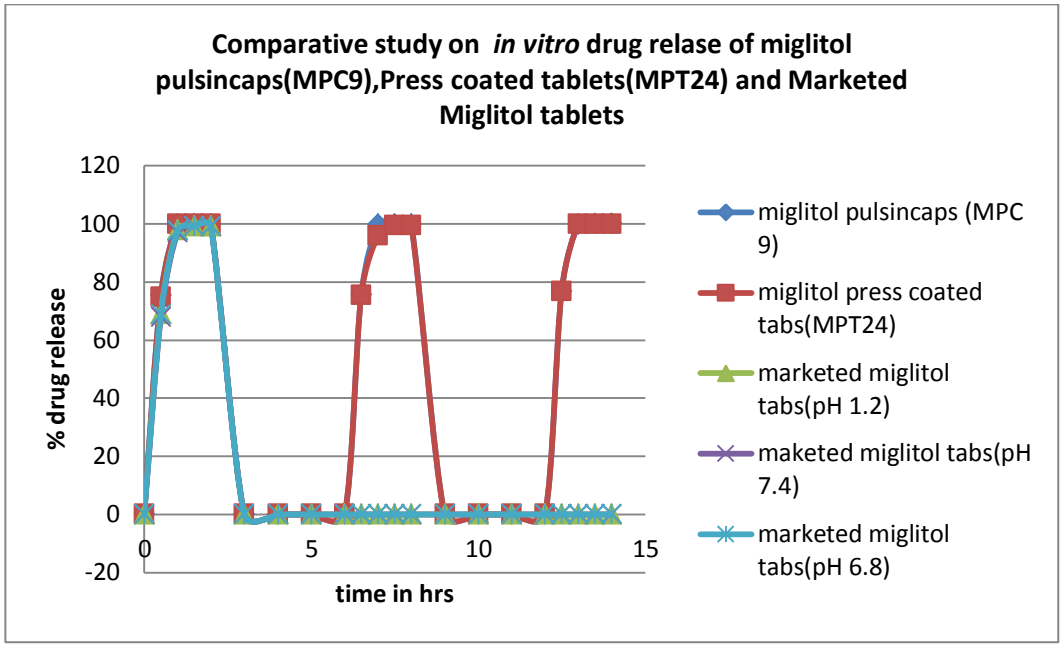

Fig.7.80.comparison of *in vitro* drug release profile of Miglitol pulsincaps(MPC 9),Miglitol press coated tablets (MPT 24) and marketed Miglitol tablets

8. SUMMARY AND CONCLUSION

Pulsatile drug delivery system are recently introduced system to deliver the drugs at the specific site of action at the right time and in the required concentration, which are designed according to the circadian rhythm of the body and it is most suitable, convenient, safe, economic and highly efficient method to deliver the drug.

Miglitol is a drug commonly used in the management of Type 2 diabetes mellitus which belongs to the category of alpha-glucosidase enzyme inhibitor. Miglitol delay the absorption of carbohydrates from the gastrointestinal tract, thereby limiting postmeal plasma glucose excursions. As the chronological behavior of diabetes mellitus confirms increased blood glucose level after meal (postmeal hyperglycaemia) which is associated with increased risk of retinopathy, carotid intima-media thickness (IMT), oxidative stress, inflammation and endothelial dysfunction, decreased myocardial blood volume and myocardial blood flow, increased risk of cancer, impaired cognitive function in elderly people with Type 2 diabetes. The biological half life of Miglitol is 2 hrs. Hence, by conventional dosage form it needs to be administered three times a day. These conditions demand the development of pulsatile drug delivery system for Miglitol to prevent the complications caused by postmeal hyperglycemia by delivering the drug Miglitol immediately after a meal. The development of pulsatile drug delivery systems for the anti diabetic drug Miglitol encompasses three pulses of drug in a unit dosage forms. Thus the main aim and objective of this work is to enhance the therapeutic efficacy of Miglitol by timed release, minimize complications due to postmeal hyperglycemia, reduce dosing frequency and achieve better patient compliance.

To achieve the above goals two pulsatile drug delivery systems are designed:

1. Pulsincaps
2. Press coated tablets

The prepared dosage forms were optimized and evaluated *in vitro* and *in vivo*. The preformulation studies were carried out for the drug and excipients to develop the

final formulation. Drug excipient compatibility studies suggested that there was no interaction between Miglitol and other excipients used in the formulation of Miglitol pulsincaps and press coated tablets.

Miglitol pulsincaps were formulated using, body of the capsules with modified solubility; Miglitol immediate release tablets and hydrogel plug of various hydrophilic polymers in different concentrations. The results of the *in vitro* release studies showed that the formulation MPC9 was found to ideal for pulsatile release. The maximum *in vitro* drug release of 99.76% (first pulse), 99.81% (Second pulse), 99.92% (Third Pulse) and the desirable lag time 4 hours was obtained for the Miglitol pulsincaps prepared with 60 mg of HPMCK4 M as hydrogel plug **(MPC9)**.

Miglitol press coated tablets (MPT1-MPT24) were prepared with varying proportions of hydrophilic polymers (HPMC and L-HPC) and hydrophobic polymers (Glyceryl behenate and Ethylcellulose) alone and in combinations as barrier layer to achieve desired lag time. The ideal concentrations of hydrophilic and hydrophobic polymers were selected based on the results of the *in vitro* drug release studies and lag time. The *in vitro* dissolution study results showed the maximum drug release (99.85% for first pulse, 99.43% for second pulse and 99.76% for third pulse) with a lag time of 4hrs for the Miglitol press coated tablets prepared using glyceryl behenate 25 mg and L-HPC175 mg **(MPT24)** as barrier layer.

The selected formulations of Miglitol pulsincaps and press coated tablets (MPC9 and MPT24) were subjected for pharmacokinetic and pharmacodynamic studies using male albino rabbits.

Pharmacokinetic changes in all the formulations analyzed were almost similar as standard marketed drug. All the parameters altered in both the formulations treated groups were found to be within biological limits. No major changes were observed when compared to standard formulations. Hence it can be summarized that the pharmacokinetic changes among the tested groups were comparable with that of standard pure and standard marketed formulations. No remarkable deviations have been identified in both kinetic and dynamic parameters in the animal models used in

this present investigation. The results of these studies revealed that the *in vivo* release of Miglitol pulsincap and press coated formulations correlated with release pattern of standard marketed Miglitol tablets. The extended $T_{max,}$ and C_{max} confirms the delayed release of formulation.

The optimized formulation of Miglitol pulsincap (MPC9) and press coated tablets (MPT24) were subjected to stability studies as per ICH guidelines. No significant changes in the physical and chemical characteristics were observed during the stability studies of Miglitol pulsincap (MPC9) and Miglitol press coated tablets (MPT24).

The optimized Miglitol pulsincaps(MPC9) and Miglitol press coated tablets were evaluated for its *in vitro* drug release profile and compared with the *in vitro* drug release profile of marketed conventional Miglitol tablets. Studies *of in vitro* drug release of Miglitol pulsincaps (MPC9) exhibited the maximum drug release 99.77±0.09% for first pulse, 99.82±0.19% for Second pulse and 99.91±0.11% for third Pulse. The lag time after each drug release was found to be 4hrs.The *in vitro* dissolution study of Miglitol press coated tablets (MPT24) exhibited the maximum drug release 99.84± 0.07% for first pulse, 99.42± 0.34 % for second pulse and 99.74± 0.16 % for third pulse with the lag time of 4hrs after each drug release. The *in vitro* drug release for the Miglitol marketed conventional tablets were carried out in buffer solution pH1.2. The cumulative percentage drug release at different time intervals such as 15, 30, 45, 60, 90 and 120 mts were 38.55±0.18, 68.97±0.25, 89.76±0.19, 97.85±0.55, 99.17±0.27 and 99.20±0,46 respectively.

CONCLUSION

The present study was made to develop the pulsatile drug delivery of Miglitol. Pulsincap and press coated tablets for the timed release of Miglitol were formulated and evaluated. Miglitol pulsincap prepared with different concentrations of hydrogel plug of gelatin, HPMC K4M and sodium alginate were optimized by conducting various trials. Press coated tablets of Miglitol were prepared with different ratios of glyceryl behenate, ethyl cellulose, HPMC and L-HPC that were optimized. The

optimization procedure aided in the preparation of pulsincap and press coated tablets of Miglitol with lag time up to 4 hrs. The *in vitro* dissolution studies revealed that the formulated pulsincap and press coated tablets of Miglitol released the desired concentration of the drug at pre-determined time points. The animal studies confirmed that the pharmacokinetic and Pharmacodynamic parameters of Miglitol press coated tablets and pulsincap formulations were comparable to standard Miglitol marketed tablets. The stability studies on the selected formulation of Miglitol pulsincap and press coated tablets were found to be stable. Comparative studies on *in vitro* drug release profile of Miglitol pulsincap and press coated tablets were found to have three pulses of drug release with desirable lag time when compared to the marketed conventional Miglitol tablets which contains only single dose of drug. Hence it may be concluded that the newly formulated pulsatile drug delivery systems of Miglitol produce effective control of the increased blood glucose level after intake of meals by allowing the drug to release after a lag time (after meals).

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