Chapter 1

Introduction

1.1 DIABETES

Diabetes mellitus (or diabetes) is one of the chronic, lifelong metabolic disorders that affect individuals, families and society at large. It is caused due to disturbances in carbohydrate, fat and protein metabolisms and also due to the defects in insulin secretion, insulin action or both. The disease condition may lead to short and long term complications like retinopathy, peripheral neuropathy, coronary heart disease, stroke and peripheral vascular diseases affecting normal life of people. Since last twenty years, there has been an increase in the number of diabetes patients in many parts of the world and considered as one of the important health issues worldwide to be addressed to immediately. The death rate is increased, in case of diabetes patients, mainly due to diabetes related complications developed because of poor treatment methods to the patients. The global prevalence of diabetes in 1998 was estimated to be 143 million people by the year 2030 and the prevalence is expected to increase by 366 million people based on the data published (Wild et al., 2004). A survey report shown in Table 1 represents the country having highest number of diabetic patients (Gupta et al., 2013).

Schematic diagram-1 Prevalence of diabetes (web source) in the world
Table 1 Survey report on diabetes from 2000 to 2030: Countries with highest numbers of diabetes patient

<table>
<thead>
<tr>
<th>Ranking</th>
<th>Country</th>
<th>Diabetic patient (millions)</th>
<th>Year 2000</th>
<th>Country</th>
<th>Diabetic patient (millions)</th>
<th>Year 2030</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>India</td>
<td>31.7</td>
<td></td>
<td>India</td>
<td>79.4</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>China</td>
<td>20.8</td>
<td></td>
<td>China</td>
<td>42.3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>U.S.</td>
<td>17.7</td>
<td></td>
<td>U.S.</td>
<td>30.3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Indonesia</td>
<td>8.4</td>
<td></td>
<td>Indonesia</td>
<td>21.3</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Japan</td>
<td>6.8</td>
<td></td>
<td>Japan</td>
<td>13.9</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Pakistan</td>
<td>5.2</td>
<td></td>
<td>Pakistan</td>
<td>11.3</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Russian Federation</td>
<td>4.6</td>
<td></td>
<td>Russian Federation</td>
<td>11.1</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Brazil</td>
<td>4.6</td>
<td></td>
<td>Brazil</td>
<td>8.9</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Italy</td>
<td>4.3</td>
<td></td>
<td>Italy</td>
<td>7.8</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Bangladesh</td>
<td>3.2</td>
<td></td>
<td>Bangladesh</td>
<td>6.7</td>
<td></td>
</tr>
</tbody>
</table>

Increased number of patients necessitates more research on diabetes for a better treatment procedure. The development of further complications due to type 2 diabetes conditions creates more significance and attention to this field of research.

1.1.1 CURRENT STATUS OF DIABETES IN INDIA

Complications of diabetes is a major cause leading to morbidity and mortality in India and type 2 diabetes is thus considered as one of the major growing epidemics (Sadikot et al., 2004; Yoon et al., 2006; Anjana et al., 2011; Shetty et al., 2012) currently facing an uncertain future imposing potential burden to the country. As per the Indian scenario, the prevalence of diabetes in 2013 was 9.1% vs. 8.3% worldwide which is slightly higher in India (International Diabetes Federation, 2014). A report says that 60% of death in 2012 is due to non-communicable diseases say cardiovascular disease, respiratory disease, diabetes, cancer etc (World Health Organization, India, 2014; Noncommunicable Diseases, 2014).

Prevalence of type 2 diabetes in India mainly depends on regional and socioeconomic condition like rural areas showing low prevalence 3.1% but urban areas shows high prevalence 7.3% (Mohan et al., 2008). A similar distribution is found in Indian sub-continent countries such as Bangladesh, Nepal, Bhutan and Sri Lanka (Wild et al., 2004). The study conducted by Indian council of medical research (ICMR) revealed that population is affected by diabetes in various states of India like Chandigarh 0.12
million, Jharkhand 0.96 million, Maharashtra 9.2 million and Tamil Nadu 4.8 million (Anjana et al., 2011) but the National urban survey conducted study in metropolitan cities of India and found Kolkata 11.7% (Eastern India), Kashmir 6.1%, New Delhi 11.6% (Northern India), Mumbai 9.3% (West India), Chennai 13.5%, Hyderabad 16.6%, Bangalore 12.4% (South India) (Zara et al., 2000; Ramachandran et al., 2001). The prevalence of disease is more in southern part of the country as compared to north and eastern parts of India (Gupta and Misra, 2007).

The reports on economic and social condition of India reveal that India is being considered the diabetes capital of the world (Guariguata et al., 2013) and necessary steps should have to be taken for the treatment. It has been reported that the expenses required for the complete treatment of type 2 diabetes in India is USD 2.2 billion (Ramachandran, 2007).

1.1.2 DIFFERENCE BETWEEN NORMAL PROCESS AND INSULIN RESISTANCE PROCESS

In normal process, insulin is necessary for glucose to produce energy and move through the blood stream to the body cells and the liver. In case of diabetic condition, insulin is unable to break glucose into energy and the excess glucose remains in the blood stream resulting in higher than normal blood glucose levels as explained in the schematic representation below.

It represents the differences between normal process and insulin resistance process (diabetes condition). The blue dots represent glucose and yellow dots represent insulin present in the body. In normal process glucose move from the blood stream and absorbed in body cell but in case of insulin resistance glucose remains in the blood stream and increase the blood glucose level leading to diabetes condition.

Type 1 diabetes can be treated with insulin injection but for the type 2 diabetes treatment mainly depends upon oral antidiabetic drugs (say Glipizide, glimepiride, glyburide, sexagliptin, sitagliptin, metformin, pioglitazone, miglitol etc.)
1.1.3 CLASSIFICATION OF DIABETES

Mainly classified into four clinical classes

(A) Type 1 diabetes (Insulin dependent diabetes mellitus- IDDM)
(B) Type 2 diabetes (Non insulin dependent diabetes mellitus- NIDDM)
(C) Gestational diabetes mellitus
(D) Other specific types of diabetes

(A) TYPE 1 DIABETES MELLITUS (IDDM)

Type 1 diabetes mellitus is an autoimmune-mediated destruction of pancreatic islet β-cells treated mainly by administering subcutaneous insulin injection (Norris et al., 2001). It can be developed at any stage of life but mostly prevalent in children and young age people due to the insufficient insulin secretion from pancreas. It is also known as juvenile onset or insulin dependent diabetes. Due to the insufficient amount of insulin in the body, fat is utilised as a source of energy instead of glucose. This leads to deposition of ketones in the body which can cause death in later stage (Tripathi, 2003).

Schematic diagram-2 Difference between normal process and insulin resistance process (web source)
(B) TYPE 2 DIABETES MELLITUS (NIDDM)

Type 2 diabetes mellitus results from insufficient secretion or insufficient utilization of insulin treated by various therapeutic medications, in addition to diet and exercise (Norris et al., 2001). Most of the affected patients can be categorized as adults, overweight and blood relatives (especially first degree) of the patient (Shojania et al., 2006). The report says that out of 90-95% of North Americans affected by type 2 diabetes, 20% patients are over the age of 65. This ratio in other parts of the world varies significantly depending on environmental and life style of the people. Diabetes at later stage can increase the risk of health issues like blindness, kidney problem, irregular function of lower limbs, nerve damage and cardiac disorder (DCCT Research group, 1993). It can be controlled and managed by medication or by pharmacological strategies (Deakin et al., 2005; Minet et al., 2010) but cannot be cured.

(C) GESTATIONAL DIABETES MELLITUS

This is developed in pregnant women having high blood sugar levels. During the 24 to 26 weeks of pregnancy, the placenta release many hormones, one of these hormones may block the action of insulin in the mothers body. This insulin resistance leads to high blood sugar level causing over weight of the baby. If untreated, these changes can produce serious and harmful effects on both mother and child. The women who are obese and having family history of diabetes and if they are under severe stress there are more chances of developing gestational diabetes (Mahendra et al., 2006; Michael, 2006).

(D) OTHER TYPES OF DIABETES

Due to some other reasons, say, genetic defect in β-cell function, insufficient insulin secretion and action, disease of the pancreas and excess intake of medication may also lead to diabetic condition.

1.1.4 TREATMENT OF TYPE 2 DIABETES MELLITUS

The treatment of type 2 diabetes, more or less directly depends upon oral antidiabetic drugs. In the last few years, research has been carried out in order to find new
alternatives to the existing drugs with less side effects or modification of release pattern of the conventional drug to create a new era in the field of advanced treatment. In the beginning, during 1940, sulfonamide was introduced as an antidiabetic drug and was found to be associated with a lot of side effects. This was modified and accepted, in 1957, as sulfonylurea tolbutamide. Further, during 1970, second generation sulfonylureas have been introduced with greater potency for the treatment of diabetes. Recently, new classes of drugs are introduced such as α-glucosidase inhibitors, meglitinides and thiazolidinediones (Mishra et al., 1993; Chakrabarti et al., 2002).

1.1.5 CLASSIFICATION OF TYPE 2 ANTIDIABETIC DRUGS

<table>
<thead>
<tr>
<th>Medications</th>
<th>Action</th>
<th>Advantages</th>
<th>Possible side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meglitinides (Repaglinide,Nateglinide)</td>
<td>Stimulate the release of insulin</td>
<td>Work quickly</td>
<td>Severely low blood sugar, weight gain; nausea; back pain; headache</td>
</tr>
<tr>
<td>Sulfonylureas (Glipizide,Glimepiride, Glyburide )</td>
<td>Stimulate the release of insulin</td>
<td>Work quickly</td>
<td>Hypoglycemia; weight gain; nausea; skin rash</td>
</tr>
<tr>
<td>Dipeptidy peptidase-4 (DPP-4) inhibitors (Saxagliptin,Sitagliptin, Linagliptin )</td>
<td>Stimulate the release of insulin; inhibit the release of glucose from the liver</td>
<td>Don't cause weight gain</td>
<td>Upper respiratory tract infection; sore throat; headache; inflammation of the pancreas</td>
</tr>
<tr>
<td>Biguanides (Metformin )</td>
<td>Inhibit the release of glucose from the liver; improve sensitivity to insulin</td>
<td>May promote modest weight loss</td>
<td>Nausea; diarrhea</td>
</tr>
<tr>
<td>Thiazolidinediones (Rosiglitazone, Pioglitazone)</td>
<td>Improve sensitivity to insulin; inhibit the release of glucose from the liver</td>
<td>May slightly increase high-density lipoprotein</td>
<td>Heart failure; heart attack; stroke; liver disease</td>
</tr>
<tr>
<td>Alpha- glucosidase inhibitors (Acarbose, Miglitol )</td>
<td>Slow the breakdown of starches and some sugars</td>
<td>Don't cause weight gain</td>
<td>Stomach pain, gas, diarrhea</td>
</tr>
</tbody>
</table>
1.1.6 A FEW TYPE 2 ANTIDIABETIC DRUGS AND THEIR CHARACTERISTICS

1.1.6.1 BIGUANIDES (METFORMIN)

Metformin is used as monotherapy or in combination with sulfonylureas, thiazolidinediones or with insulin. It is taken with food to minimize adverse gastrointestinal (GI) effect. It is available as immediate release and sustained release formulations or combined with other antidiabetic drugs. Metformin lowers basal and postprandial plasma glucose level by decreasing hepatic gluconeogenesis production. It decreases initial absorption of glucose and improve insulin sensitivity and utilization. It does not produce hypoglycemia.

1.1.6.2 SULFONYLUREAS (GLIPIZIDE, GLIMEPIRIDE AND GLYBURIDE)

Sulfonylureas stimulate the release of insulin from pancreatic beta cells and have the capacity to control hyperglycemia. It also enhances peripheral sensitivity by insulin receptor binding. Sulfonylureas are adjuncts to diet and the most common side effect is hypoglycemia. The first generation sulfonylureas are acetohexamide, chlorpropamide, tolazamide and tolbutamide but in the second generation drugs like glypizide, glyburide and glimepiride are structurally modified. The use of sulfonylureas as an oral agent is a chief cause of cardiovascular death in patient, glyburide was associated with highest mortality (7.5%) as compared to glimepiride (2.7%). Glipizide is rapidly and completely absorbed through oral administration and it shows 100% bioavailability in a single oral dose for type 2 diabetes patients. Plasma drug concentrations gradually increase and the maximum concentration can be achieved within 6 to 12 h of its consumption. Glimepiride gastrointestinal absorption is complete with no interference of meals. Absorption of glimepiride was obtained within 1h and is distributed throughout the body and metabolized.

1.1.6.3 MEGLITINIDE DERIVATIVES (REPAGLINIDE AND NATEGLINIDE)

Meglitinides are short acting insulin stimulating and more expensive as compared to sulfonylureas. Meglitinides is unable to lower the glycemic condition then advised to add with metformin or thiazolidinedione. It can be used as a substitution for sulfonylureas
which produce allergic conditions for patients. Meglitinides have a similar risk of hypoglycemia, weight gain, nausea and back pain.

1.1.6.4 ALPHA-GLUCOSIDASE INHIBITORS (ACARBOSE AND MIGLITOL)

These drugs delay sugar absorption by slowing the breakdown process of starch and some sugars and help to prevent postprandial glucose absorption. Alpha-glucosidase inhibitors delay absorption of carbohydrates and reduce gastrointestinal intolerance.

1.1.6.5 THIAZOLIDINEDIONES (ROSIGLITAZONE AND PIOGLITAZONE)

Thiazolidinediones act to improve insulin sensitivity and inhibit the release of glucose from liver. In presence of insulin, these drugs show good results and to achieve a maximum effect it requires 12-16 weeks. These drugs can be used as monotherapy or in combination with sulfonylurea, metformin, meglitinide, dipeptidy peptidase-4 inhibitors (DPP-4) or with insulin. These drugs slow the progress in an early stage of diabetes. The chances of bladder cancer is increased if the patient using pioglitazone more than 2 years in a highest cumulative doses. The report suggested that the patient treated with rosiglitazone has increased chances of myocardial infarction.

1.1.6.6 DIPEPTIDY PEPTIDASE-4 INHIBITORS (DPP-4) (SAXAGLIPTIN, SITAGLIPTIN AND LINGAGLIPTIN)

DPP-4 inhibitors are a class of drugs that prolongs the release of glucose from the liver and stimulate the release of insulin. These drugs can be used as a monotherapy or in combination with metformin or thiazolidinediones. The report says that an adverse GI effect was lower with sitagliptin than with metformin. Upper respiratory tract infections have been increased by the use of DPP-4 inhibitors as compared to other antidiabetic drugs.

1.2 SUSTAINED RELEASE DRUG DELIVERY SYSTEM

Conventional dosage forms produce wide range of fluctuations in drug concentration in the blood stream and tissues with concurrent toxic effects and poor efficiency of drug action. In addition, repetitive dosing and unpredictable drug absorption led to the research
of other alternative modes of drug delivery and action. The design of sustained drug delivery systems paved way to overcome the setbacks associated with conventional dosage forms. So, controlled release dosage form releases one or more drug continuously in a predetermined pattern over a fixed period of time, either systematically or to a specific target organ. It provides a better control of plasma drug levels, less frequency, lesser side effects, increased potency and consistent delivery at the desired site (Manckar et al., 1999).

1.2.1 TERMINOLOGIES USED

Modified release delivery system may be divided conveniently into four categories:

(A) Delayed release
(B) Sustained release
  ✓ Controlled release
  ✓ Extended release
(C) Site specific targeting
(D) Receptor targeting

(A) Delayed release:

These systems are those that use repetitive intermittent dosage of a drug from one or more immediate release unit incorporated into single dosage form. Examples of delayed release system include repeated action tablets and capsules and enteric coated tablets where timed release achieved by the barrier coating.

(B) Sustained release:

These systems include any drug delivery system that achieves slow release of drug over an extended period of time.
  ✓ Controlled release:
These systems also provide a slow release of drug over an extended period and the system is successful in maintaining constant drug levels in the target tissue or cells.
✓ Extended release:
Pharmaceutical dosage form that release the drug slower than the normal manner at predetermined rate and necessarily reduce the dosage frequency.

(C) Site specific targeting:
These systems refer to targeting of a drug directly to a specific part of the body. In this case the target is adjacent to or in the diseased organ or tissue.

(D) Receptor targeting:
These systems refer to a targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue (Manckar et al., 1999). Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and also considered to be controlled drug delivery systems.

1.3 POLYMERS USED IN SUSTAINED RELEASE DRUG DELIVERY SYSTEM

Recently, more attention has been focused on the manner in which the drugs are delivered. Mainly drugs are being incorporated into solid polymer matrices to achieve sustained and targeted release systems.

Polymers had officially been introduced to the world of pharmacy as polyethylene and other plastics in the 20th revision of the United State of Pharmacopeia (U.S.P). Polymers have been proved advantageous as all aspects of drug development and the treatment procedures since many years. It is playing an important role as a drug carrier. An ideal polymer should process the following characteristics.

1.3.1 IDEAL POLYMER CHARACTERISTICS

It should be:
✓ Inert and compatible with the environment.
✓ Non toxic.
✓ Easily administered.
✓ Easy and inexpensive to fabricate.
✓ Good mechanical strength.
The polymer must be soluble and easy to synthesize. It must have a finite molecular weight and narrow distribution.

It should facilitate drug interaction with polymer linkage, favouring drug absorption and release.

The polymer should be compatible with the biological environment being, nontoxic, non antigenic and non provocative in all aspects.

It should be biodegradable and eliminated from the system once its intended role is completed.

1.3.2 CLASSIFICATION OF POLYMER

It is broadly classified as:

- Natural polymers: These include nucleic acids, proteins, polysaccharides and complexes of protein and polysaccharide.
- Synthetic polymers: These include polyesters, polyurethanes, polyamide, polycarbonates, polysiloxanes, polyolefins and polyvinyl compounds.
  Polymers can also be classified on the basis of their interaction with water, into
- Non biodegradable polymer: These are inert in the environment of use, are eliminated or excreted intact from the site of administration and serve as a rate limiting barrier to the transport and release of the drug from the device.
  Example: polyethylene vinyl acetate, polydimethyl siloxane, polyurethane, ethyl cellulose, cellulose acetate, polyethylene, polyvinyl chloride.
- Hydrogels: These swell but do not dissolve when brought in contact with water. They are inert removed intact from the site of administration and function by forming a rate limiting barrier to the transport and release of drugs.
  Examples: polyvinyl alcohol, cross-linked polyvinyl pyrrolidone, polyacrylamide and dextran.
- Soluble polymers: These are moderate molecular weight and cross-linked polymers that dissolve in water. These materials can be used alone or in combination with hydrophobic polymers to provide devices that slowly erode over time.
Example: polyethylene glycol, uncross-linked polyvinyl alcohol, hydroxyl propyl methyl cellulose.

- Biodegradable polymers: these slowly disappear from the site of administration. However this disappearance occurs in response to a chemical reaction such as hydrolysis.
  Example: polylactic acid, polyglycolic acid, polycaprolactone.

1.4 MODES OF DRUG DELIVERY SYSTEM

Different forms of pharmaceutical dosage forms (tablets, capsules, pills, creams, ointments, aerosols, injectables, emulsions, buccal film and suppositories as carriers) have been used for the last three decades for the treatment of acute or chronic diseases. In many therapies, sustained release preparations are considered desirable due to its significant progress in terms of clinical efficacy and patient compliance. It is chosen as an important area of research in the field of pharmaceutical and health care sectors. The drug release from the formulation is mainly controlled by the type, grade and concentration of polymers intended to achieve greater availability of drug over extended period of time. Thus, polymeric matrices serve as a good drug carrier and release the drug in a sustained manner at the desired site of action. The goal in designing sustained and controlled delivery is to reduce the frequency of dosage and to increase the effectiveness of the drug by localizing its site of action.

1.4.1 TABLET

A tablet is a pharmaceutical solid dosage form made up of a mixture of active substances and excipients in powder form and compressed as a solid dosage. Tablets are simple and convenient to use. The excipients used as diluents, binders, granulating agents and lubricants to instil favourable characteristics such as surface morphology, hardness, friability, thickness, drug content, disintegration time and dissolution profile. The compressed tablet is the most popular solid dosage form, about two-third of all prescriptions are dispensed with it. They are usually taken orally, but also administered sublingually, buccally, rectally, intravaginally etc. These are mostly labeled with symbols, letters and numbers which can easily be identified.
Process development and new techniques in the field of tablet formulations provide special characteristics; say, sustained release, immediate release, controlled release, enteric coated release. In direct compression method the physical mixture of ingredients are directly compressed and requires particle size distribution and free flowing ability of the ingredients. It is usually necessary to granulate before compression followed by wet-granulation and dry-granulation methods. The presence of moisture content may influence the chemical and physical stability of the final tablet. So, granules and powders are normally mixed with glidants or lubricants before the compression of tablet in order to improve the flow property of powder and prevent adhesion to the walls of punching machine. Magnesium stearates, if added in excess, reduce the mechanical resistance of tablets providing favourable disintegration and disintegration time. In the manufacture, packaging, storage and distribution of tablets, suitable measures have to be taken to ensure their microbiological quality. The packaging needs to be adequate to protect the tablets from light, moisture and damage during transportation. The polymers used in tablet preparation control the release of active drug and also acts as a coating to make the tablet palatable.

1.4.1.1 DIFFERENT TYPES OF TABLETS USED IN DRUG DELIVERY SYSTEM

Tablets are modified as per the necessity of patient and diseases.

1.4.1.1.1 IMMEDIATE RELEASE (IR) TABLETS

IR tablets are designed for occasional and for temporary pain because they work fast but don’t last. The patient uses these short acting medications for immediate treatment like headache, pain relief, cardiovascular disease etc. IR medications are the wrong choice for a constant pain or chronic diseases (Cancer, diabetes, heart problem etc.).

1.4.1.1.2 DISPERSIBLE OR EFFERVESCENT TABLETS

These tablets are designed to added with water just before to swallowing. They are very large and contain more amount of sodium. The increased size and sodium intake is a restriction for patient to take many of them.
1.4.1.1.3 SUB-LINGUAL TABLETS

Sub-lingual tablets designed to be dissolved under the tongue, and rapidly absorbed with saliva and directly reach to the blood stream for a quick effect. These types of tablets are very useful in case of angina pain and other general pain. Patient can take this tablet without water but sufficient saliva is required.

1.4.1.1.4 BUCCAL TABLETS

Buccal tablets are intended to be placed on the gum or in the cheek for a complete absorption. Patient keeps this tablet for longer period of time to release at prolong manner as compared to sublingual tablets. This route is used for anti-nausea drugs or nicotine replacement purpose.

1.4.1.1.5 MELT TABLETS

Melt tablets are placed on the tongue and are designed to dissolve directly in oral cavity. Saliva is needed to swallow the tablet without administration of water. This concept is useful for the patients who are unable to swallow the tablet with water.

1.4.1.1.6 ORO-DISPERSIBLE TABLETS

Oro-dispersible tablets are similar to melt tablets which are designed to disperse in the mouth and to be washed down with saliva. As like sub-lingual, buccal and melts, oro-dispersible tablets require sufficient amount of saliva for a better effect.

1.4.1.1.7 SUSTAINED RELEASE (SR) TABLETS

In order to control the pain or chronic diseases the right tool is sustained release medications. These types of tablets designed in a manner to prolong the release rate of active drug for a better result. This can be a better suggestion for long term disease treatment.
1.4.2 MICROSPHERE

Microspheres are advantageous over conventional dosage forms by enhancing drug stability, improve solubility, reduce toxicity and prolong therapeutic bioavailability. They are homogenous, spherical particle made of polymers (Natural polymers and synthetic polymers) with size ranging from 1 to 1000 µm. The commercially available microspheres are polymer microspheres, glass microspheres and ceramic microspheres. Microspheres protect the unstable drug in unfavorable conditions. Polymer microspheres act as a drug carrier to prolong the drug release pattern by providing localization of active substance at the required site of action (Jeyanthi et al., 1996; Remington, 2000). It gains special attention in drug delivery system due to its minute size and larger surface area which favors good absorption property of drug in localized site. They facilitate accurate delivery of small quantity of active drug and control the toxicity by reducing the concentration. An ideal microsphere should possess following characteristics. It should have:

✓ Longer duration of action.
✓ Control the release rate of potent drug and increase its therapeutic efficacy.
✓ Protection of drug against the unfavorable condition (Moisture, light).
✓ Biocompatibility.
✓ Reduced toxicity.
✓ Taste and odor masking
✓ Water solubility.

1.4.3 NANOPARTICLE

In the last 35yrs, the growth of nanotechnology has opened several new vistas in medical science, especially in the field of drug delivery for the treatment of chronic diseases. This technology is used in the pharmaceutical industry to design an effective therapeutic drug with minimum side effects. The diameter size of nanoparticle lies between 1 to 100nm. The importance of nanoparticle increases due to its wide variety of a scientific interest in biomedical, optical and electronic fields. Nanoparticle shows larger surface area which make the particle very reactive and can easily enter cell membranes and start its
biological action (Ying, 2001). It is a system that delivers drugs to the desired parts of
the body for the therapeutic activity by ensuring that they are released when needed. This
system helps to carry the drug safely to the site of the action and cure the disease. It can
be used in modification of bone implants due to its durability and compatibility with
human tissue. The major trend in further development of nanoparticles is to make them
more efficient by controlling them through signals and used as multifunctional purposes.
Researchers developed nanosponges that absorb toxins and remove them from blood
stream.

1.4.4 LIPOSOMES

Liposome is an artificially developed a stable microscopic spherical vesicles. It is
composed of phospholipids and amphipathic lipids. The properties vary significantly due
to the lipid composition, size, surface charge and its preparation method. Liposomes are
mainly divided into three different classes based on their size and number of bilayers.

1) Small unilamellar vesicles with single lipid layer ranging from 25-50nm.
2) Large unilamellar vesicles of heterogeneous group with single lipid layer.
3) Multilamellar vesicles consist of several layers separated by a layer of a aqueous
solution.

Lipid bilayers of liposomes are similar in structure and found in living cell membranes
which can carry lipophilic substances such as drugs and nutrients. The effect of
liposomes depends on the composition of lipid bilayer and its permeability and fluidity.
The significance of liposomes is as a vehicle for pharmaceutical drugs, antibodies for
targeted delivery of anticancer agents. The limitation of liposomes is due to poor
stability, inability to deliver to the right site and inability to release drug in right site.
Liposome surfaces can be readily modified by polyethylene glycol to enhance their
circulation time in bloodstream. It can be further developed by conjugated to antibodies
or liganda to improve targeted drug therapy. As therapeutic vehicle liposomes has shown
some drawbacks like toxicity and its biochemical behavior in drug delivery system.
1.4.5 HYDROGELS

A hydrogel is a network of hydrophilic polymer chains or it may be a colloidal gel in which is the dispersion medium. Hydrogels are very spongy and possess a degree of flexibility as similar to natural tissue due to its water content nature. Hydrogel first introduced in 1894 as an absorbent and it is commonly used as

- Scaffolds in tissue engineering to repair the tissue.
- Hydrogel coated wells have been used as cell culture.
- Sensitive hydrogels can able to change pH and temperature.
- Sustained release drug delivery system.
- Provides absorption, desloughing and debriding of necrotic and fibrotic tissue.
- Biosensors.
- Disposable diapers and sanitary napkins.
- Contact lenses (silicon hydrogels, polyacrylamides, polymacon)
- Hydrogels composed of crosslinked polymers used in EEG and ECG medical electrodes.
- Water gel explosive
- Rectal drug delivery
- Breast implants, glue, dressing for healing of burn, reservoir in drug delivery
1.5 LITERATURE SURVEY ON SUSTAINED RELEASE DRUG DELIVERY SYSTEM

Park et al. (2008), prepared polymer matrix between chitosan and Carbopol by interpolymer complex (IPC) using a precipitation method in an acidic solution as a carrier for theophylline drug. A theophylline tablet was prepared using the IPC as a matrix material to achieve an extended release drug delivery system. They found that the drug release profile from this tablet was similar as HPMC tablet and showed a pH-independent release profile. The kinetic study for drug release from the IPC tablet was found to be diffusional release at pH 6.8 and relaxational release at pH 1.2. The pH dependency of Carbopol was reduced due to the formation of a complex with chitosan, and appeared as a pH independent extended-release matrix tablet.

The extended release matrix tablet of nicorandil was prepared (Abdelbary et al., 2008) by using Chitosan (CH), hyaluronate sodium (HA), pectin (PE) or alginate sodium (AL) by interpolymer complexes. Nicorandil matrix tablets were combined with Imwitor 900 K (Hydrophobic waxy retardant polymer) in different ratio to form sustained-release drug delivery system. Dissolution study revealed that formula F11 (CH:AL, 20:80) IPC:Imwitor 900 K, 3:1) could extend drug release >8 h.

ZK 811 752, a potent drug was selected (Kranz et al., 2005) to overcome the pH dependent solubility nature of the drug. Three different polymers were used as matrix forming agent, say polyvinylacetate/polyvinylpyrrolidone, ethylcellulose and hydroxypropyl methylcellulose. To solve the problem of pH-dependent solubility different organic acids were added to the drug–polymer ratio. Successfully an extended release pH-independent matrix tablet of ZK 811 752 drug has been developed.

Tiwari et al. (2003) studied the effect of concentration of hydrophilic (Hydroxypropyl methylcellulose [HPMC]) and hydrophobic (Hydrogenated castor oil and Ethyl cellulose) polymers on the release rate of tramadol drug. Dissolution study revealed that hydrophobic matrix tablets followed a good sustained release pattern (>20h) as compared with hydrophilic matrix tablets (>14h) whereas combination effect of these two polymers
failed to prolong the release pattern more than 12h. As a coating substance composition of ethyl cellulose with lactose and HPMC proved to be useful in control the drug release.

Solid lipid ketoprofen micropellets (SLKM) at different drug/beeswax ratios [(1:1) and (1:2)] were prepared by emulsion congealing technique and then compressed into tablets (Uner et al., 2005) to obtained a controlled drug delivery system. The results of the in vitro release studies showed that ketoprofen was released in a slower and lesser extent due to the beeswax which could be a suitable polymer for preparing SLKM and its tablets.

The miscibility study of hydroxypropyl methylcellulose (HPMC)/polyvinyl alcohol (PVA) blend in water was studied (Fadnis et al., 2008) at two different temperatures (30 and 50°C). Interaction parameters μ and α values revealed that HPMC/PVA blend is miscible when the HPMC content is more than 60% in the blend at 30 and 50°C.

Nanaki et al. (2012) used chitosan (CS), 2-hydroxyethyl starch (HES) polymers for miscibility study and found that all the compositions were miscible. Individual polymers and their blends were used to prepare solid dispersion formulations of ropinirole drug. Results revealed that drug released immediately within 15–30 min from HES while the release was slower from CS matrix. But the release rates showed a sustained profile from the blends containing high amounts of CS.

Nayak et al. (2014) formulated novel mucoadhesive beads containing metformin HCl made of low methoxy pectin- -tamarind seed polysaccharide (TSP) polymer-blend was developed through ionotropic-gelation technique. Calcium pectinate-TSP mucoadhesive beads containing metformin HCl displayed high drug encapsulation, good mucoadhesivity with the biological membrane, suitable controlled in vitro drug release pattern and also significant hypoglycaemic activity.

Newly developed ionically gelled calcium pectinate- fenugreek seed mucilage (FSM) mucoadhesive beads containing metformin HCl displayed high drug encapsulation, good
mucoadhesivity, suitable controlled drug release pattern and also significant hypoglycemic activity observed through oral administration followed by in vivo study. Nayak et al. (2013) observed that this type of mucoadhesive beads can be used for other drugs demanding sustained release in controlled manner over a longer period to improve their bioavailability and therapeutic efficacy.

Gupta and Jabrail were prepared microspheres for controlled delivery of centchroman drug at different degree of cross-linking, using chitosan with different degree of deacetylation. They confirmed that degree of deacetylation and cross-linking has controlled the loading and release profile of centchroman from prepared microspheres.

Snima et al. (2012) developed metformin loaded O-carboxymethyl chitosan (O-CMC) nanoparticles (NPs) by ionic-gelation method to reduce its solubility in aqueous medium. The developed nanoformulation showed burst drug release followed by slow and sustained release of the drug at neutral pH and it may increase the drug retention time in blood. Hence by the application of this nanoformulation, bioavailability of metformin can be increased without losing its anticancer property for efficient treatment of pancreatic cancer as well as type-2 diabetes.

Based on the report, Gandhi et al. (2014) developed Eudragit RLPO based nanoparticles of acyclovir to increase its efficacy and overcome its oral bioavailability. The in vitro drug release in phosphate buffer, pH 7.4 of these prepared acyclovir loaded nanoparticles showed sustained drug release over a period of 24 h. These obtained results showed that acyclovir loaded Eudragit RLPO nanoparticles could be effective in sustaining drug release for a prolonged period of time.

Wadher et al. (2011) reported the significance of combinations of hydrophobic polymer (ethyl cellulose) in the presence of hydrophilic polymer (Eudragit RSPO and RLPO) towards controlling the drug release rate of metformin as compared to individual hydrophilic polymers
Different grades of HPMC (like HPMC K4M, HPMC K15M, and HPMC K100M) have been used for controlled drug release of metformin as reported (Bagyalakshmi et al., 2011).

The above literature survey focuses on the significance of polymeric matrices in controlling the drug release pattern thereby improving the treatment procedure. In view of this we have chosen the antidiabetic drug “metformin” blended into polymeric matrices of various forms such as tablet, microsphere, nanoparticle etc. Hence the drug profile of metformin is discussed below. The aim of our study is to design and formulation of metformin loaded drug carriers of various forms to manipulate the drug release pattern and making it a sustained release form.
1.6 DRUG PROFILE OF METFORMIN HYDROCHLORIDE

Metformin hydrochloride (Met) is an orally active drug for treating type 2 noninsulin-dependent diabetes mellitus (NIDDM). It possesses biguanide group (Frier and Fisher, 2002), in its structure and is categorized as BCS class III drug showing 40%-60% bioavailability and has shorter half life (Ching-Ling et al., 2004; Corti et al., 2007).

This drug is chosen based on the following characteristics.

- It reduces glucose production by the liver and also decreasing intestinal absorption of glucose.
- Unlike sulfonylureas, metformin does not cause hypoglycemia.
- It promotes modest weight loss, less side effects, short half life and highly water soluble (Biopharmaceutical classification system (BCS) Class III) drug.

Due to its short half life and high water solubility, it is a big challenge to control the release pattern and make it sustainable.

- Chemical name – N,N-dimethyl imido dicarbonimidic diamide
- Formula – C₄H₁₁N₅
- Mol. mass – 129.164 g/mol
- Structure –

![Chemical Structure of Metformin](image)

- Half life – 1.5 – 5hr
- Molecular weight - 129.164 g/mol (free)
  165.63 g/mol (HCl)
- Appearance – Metformin hydrochloride is a white to off-white crystalline compound
- Tablets: 500 mg, 850 mg, 1000 mg and 1250 mg.
- Melting point – 223-226 °C
- Water, ethanol, ethyl alcohol - soluble
- Storage - In room temperature between 20-25°C (68-77°F).
1.6.1 PHARMACOKINETICS

Metformin has an oral bioavailability of 50–60% under fasting conditions, and is absorbed slowly. Peak plasma concentrations ($C_{\text{max}}$) are reached within one to three hours of taking immediate-release metformin and four to eight hours with extended-release formulations. The plasma protein binding of metformin is negligible, as reflected by its very high apparent volume of distribution (300–1000 L after a single dose). Steady state is usually reached in one or two days. Metformin is undetectable in blood plasma within 24 hours of a single oral dose. Metformin is not metabolized. It is cleared from the body by tubular secretion and excreted unchanged in the urine.

1.6.2 MECHANISM OF ACTION

Metformin is an oral medication that lowers blood glucose and is used for treating type 2 diabetes. Insulin is a hormone produced by the pancreas that controls glucose levels in blood by reducing the amount of glucose made by the liver and by increasing the removal of glucose from the blood by muscle and fat tissues. As a result, blood glucose levels fall. Metformin plays an important role for the utilization of insulin by liver, muscle, fat, and other tissues. These actions lower the level of sugar in the blood.

Unlike glucose-lowering drugs of the sulfonylurea class, for example glyburide or glipizide, metformin does not increase the concentration of insulin in the blood and, therefore, does not cause excessively low blood glucose levels (hypoglycemia) when used alone. In scientific studies, metformin reduced the complications of diabetes such as heart disease, blindness and kidney disease and was approved by the FDA in December 1994.

Literature survey report focuses the importance of metformin and its development in different forms (Tablet, microsphere, nanoparticles, hydrogels, buccal film etc.) towards achieving a novel treatment in the field of diabetes listed in Table 2.
Table 2 Literature review on metformin hydrochloride

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Polymers used</th>
<th>Formulation type/method</th>
<th>Drug/release pattern</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Calcium pectinate-fenugreek seed mucilage (FSM)</td>
<td>Bead / Ionotropic-gelation technique</td>
<td>Metformin /Controlled release (10h)</td>
<td>Nayak et al., (2013) Int. J. Bio. Macromol. 54 , 144–3154</td>
</tr>
<tr>
<td>3</td>
<td>O- Carboxy methyl, Chitosan</td>
<td>Nanoparticle / Ionic gelation method</td>
<td>Metformin /Sustained release (70h)</td>
<td>Snima et al., (2012), Carbohydr. Polym. 89, 1003-1007</td>
</tr>
</tbody>
</table>

1.6.3 CALIBRATION CURVE OF METFORMIN HYDROCHLORIDE

Metformin has been subjected to preformulation study using different concentrations (2,4,6,8,10,12 µg/ml) of metformin standard solutions. The absorbances were measured at 232nm by UV-Visible spectrophotometer. A standard plot of absorbance vs. concentration was drawn at both the pH (pH-2 and pH-6.8) shown in figure 1.

![Figure 1 Calibration curve of metformin at pH-2 and pH-6.8](image_url)
Further, in our study, we have chosen chitosan and hydroxypropyl methylcellulose (HPMC K4M and HPMC K100M), refined bleached shellac and white beeswax for tablet formulation, eudragit and chitosan for microsphere and eudragit and hydroxypropyl methylcellulose (HPMC K100M) for the preparation of nanoparticle. The characteristics of the chosen polymers are given below.

1.7 POLYMERS PROFILE

A good selection of polymer is useful for controlling the drug release rate without disturbing its therapeutic efficacy. Here are the few polymers which are commonly used for pharmaceutical applications.

1.7.1 CHITOSAN

Chitosan (CH), origin from chitin, as a natural amino functionalized polysaccharides, is a copolymer of β-[1 → 4]-linked 2-acetamido-2-deoxy-d-glucopyranose and 2-amino-2-2-deoxy-d-glucopyranose (Berger et al., 2004). It is useful in medical and pharmaceutical applications (Muzzarelli, 1977) due to its favorable characteristics such as, biocompatibility, biodegradability, mucoadhesiveness, hydrophilicity, non-toxicity and antimicrobial activity. It is also useful in wastewater treatment by chelating heavy metals or radioactive isotopes, separation membranes, drug delivery system, food packaging material and wound healing. Therefore, it is considered as a valuable material for biomedical and pharmaceutical industries (Yang et al., 2010; Patale and Patravale, 2011; Quinones et al., 2011). The application of chitosan in the field of drug delivery systems has received special attention due to the presence of repetitive amino and hydroxyl functional groups. It is soluble in dilute acidic solutions, and can be modified during blending with other polymers. (Fukuda et al., 2006; Sokker et al., 2009; Sahoo et al., 2010).

- Chemical name – Poly- β-(1, 4) -2-amino-2-deoxy-D-glucose.
- Molecular weight – Low molecular weight,
- Viscosity– 20-300 cps
- Density– 1.35-1.40 g/cm3
Glass transition temperature – 203°C

Structure –

Appearance – powder or flakes (Chitosan occurs as odourless, white or creamy-white).

Solubility – completely soluble in dilute acidic solution, sparingly soluble in water, practically insoluble in ethanol (95%)

Storage – Stored in tightly closed container in a cool, dry place and it should be stored at room temperature. It is a stable material at room temperature.

1.7.2 HYDROXYPROPYL METHYLCYLLOLOSE

Hydroxypropyl methyl cellulose (HPMC) is one of the cellulose ether, a hydrophilic polymer widely used in oral and topical pharmaceutical formulation. HPMC is generally used as tablet binder, in film coating and in extended release matrix tablets. It is used as a suspending and thickening agent in ophthalmic preparation for eye-drops or artificial tear solution. Also plays an important role in formulation of topical gels, ointments as emulsifier and stability agent in cosmetics and food products. It is one such hydrophilic polymer that controls drug release by its rapid hydration, gelation, cross linking properties and swelling nature (Ravikumar and Kumar, 2001; Mandal et al., 2007). The main advantage of HPMC matrix formulation is that it imparts steady rate of drug release irrespective of processing techniques involving several factors such as compaction pressure, drug particle size and incorporation of a lubricant (Ford et al., 1985).
Chemical name – Cellulose 2-hydroxy propyl methyl ether.

Molecular weight of different grades of HPMC:
- HPMC K4M, Mn= 86000, viscosity 4000 cps
- HPMC K100M, Mn= 150,000, viscosity 10,000 cps

Melting point:
- Browns at 190 – 200°C
- Chars at 225 – 230°C
- Glass transition temperature – 170 – 180°C

Structure –

Appearance – Odorless and tasteless, white or creamy white colour granular powder.

Solubility – completely soluble in water.

Storage – Stored in tightly closed container in a cool, dry place at room temperature.

1.7.3 SHELLAC

Shellac is a resin secreted by the female lac bug, on trees in the forests of India and Thailand. Shellac is a natural bioadhesive polymer and is chemically similar to synthetic polymers, and thus can be considered a natural form of plastic. When dissolved in alcohol (ethanol or methanol), it provides a coating of good durability and hardness. Liquid shellac used as a brush on colorant, food glaze, wood finish and tablet coating for controlled release.
Chemical name – It is an unsaturated polyester containing hydroxy aliphatic and sesquiterpenic acids and their esters containing free carboxyl, hydroxyl and aldehyde groups.

Refined bleached Shellac (Food grade) has been used

Melting point – 115 – 120°C

Structure –

Appearance – Flake like structure

Solubility – Insoluble in water, soluble in benzene (1 in 10), ethanol (1 in 2), ether (1 in 8) at 20°C.

Storage – Shellac should be stored in a well-closed container at temperatures below 27°C. After long periods of storage, shellac becomes less soluble in alcohol and darker in color.

1.7.4 BEESWAX

Beeswax is a natural wax mainly composed by a mixture of hydrocarbons, free fatty acids, monoesters, diesters, triesters, hydroxy monoesters, hydroxy polyesters, fatty acid polyesters and some unidentified compounds. Purified and bleached beeswax is used in the production of food, cosmetics and pharmaceuticals as soft gelatin capsules and tablet coatings (Hassan et al., 1995).

Chemical name – White beeswax

Melting point – 60 – 65°C

White beeswax has been used
✓ Appearance – White wax consists of tasteless, white or slightly yellow-colored sheets or fine granules with some translucence. Its odor is similar to that of yellow wax but is less intense.
✓ Solubility – soluble in chloroform, ether, fixed oils, volatile oils, and warm carbon disulfide; sparingly soluble in ethanol (95%), practically insoluble in water.
✓ Storage – White wax is stable when stored in a well-closed container, protected from light.

1.7.5 EUDRAGIT

Eudragit (RSPO, Mn=32000) a pH sensitive and mucoadhesive acrylic polymer acts as a matrix forming material. It is biocompatible, non-swelling polymers used widely in the preparation of sustained release drug delivery systems. It is a copolymer synthesized from acrylic and methacrylic acid esters. Among several polymers, methacrylic resins (Eudragit) are extensively used (Rodriguez et al., 1993), due to their high chemical stability, good compatibility.

✓ Chemical name – Poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride)
✓ Molecular weight – 32000 g/mole
✓ Glass transition temperature – 65°C
✓ Structure –

![Chemical Structure of Eudragit RSPO](image-url)
✓ Appearance – It is a solid substance in form of colourless, clear to cloudy granules with a faint amine-like odour.
✓ Solubility – completely soluble in acetone and alcohols.
✓ Storage – Dry powder forms are stable at temperatures less than 30°C. Above this temperature, powders tend to form clumps, although this does not affect the quality of the substance and the clumps can readily be broken up. Dry powders are stable for at least 3 years if stored in a tightly closed container at less than 30°C.

1.8 TECHNIQUES USED TO FORMULATE POLYMERIC MATRICES

1.8.1 INTERPOLYMER COMPLEX (IPC)

- In the complexes, the two individual polymer solutions mixed together and dried.
- Complexation possesses unique properties that are different from those of individual component.
- Interpolymer complexation is now the decisive factor useful in pharmaceutical preparation.

1.8.2 POLYMER BLEND

- The polymer blend strongly dependent on the differences between the interactions of the two polymers, which determine their degree of miscibility.
- Blending is a very interesting way of producing polymer materials with improved bulk properties.
- There is a great potential in utilizing these blends, especially in controlled release drug delivery systems.
1.9 SCOPE AND OBJECTIVES OF THE THESIS

Therapeutic techniques for treating diabetes are currently focused on development of alternatives to insulin, novel drugs without side effects, targeted drug delivery using drug carriers etc. Among these, our study is focused on designing different forms of polymeric drug carriers for the sustained release of antidiabetic drug metformin, primarily, aimed at achieving more predictable and increased bioavailability of the drug. The objective of oral sustained drug delivery system is to maintain therapeutic effective plasma drug concentration levels for a longer duration of time. This facilitates reduced dosing frequency and to minimum fluctuations in the plasma drug concentrations by delivering the drug in a controlled and reproducible manner. Thus the main objectives of our study include:

- To design of different forms of novel polymeric drug carriers like inter polymer complex based tablets and polymer blend based microsphere and microparticle.

- To incorporate the antidiabetic drug metformin to the polymeric matrices and evaluate physical parameters and compared with the standard limit of Indian pharmacopeia (IP).

- To carry out in vitro evaluation of sustained release metformin dosage forms at two different pH conditions (pH-2 and pH-6.8) followed by release kinetic study.

- To compare the effectiveness of different forms drug carriers based on their release patterns and also with marketed metformin tablet (Both Immediate release (IR) and sustained release (SR) tablets).