1.0 INTRODUCTION

1.1 INTRODUCTION TO DIABETES MELLITUS AND CURRENT INVESTIGATION

Diabetes mellitus is most common chronic disease in India and here it has achieved undesired title ‘centre for diabetes in world’ with millions populations and many more rising (Kaveeshwar & Cornwall, 2014). According to International Diabetes Federation (IDF, 2013) only in India 10 lacks 65 thousand people die with age 20-79 and about 30 lacks all around world in year 2013.

It is a condition characterized by metabolic disorder in which Patient is having high blood glucose intensity that may because insulin production is not enough, or because the body does not react properly to insulin, or both. Indian council of medical research (ICMR, section 1, 2005) define diabetes as metabolic cum vascular syndrome of multiple etiologies characterized by hyperglycemia with disturbances of carbohydrate protein and fat metabolism resulting from insulin secretion, insulin action or both (Nayak et al., 2008).

![Figure 1.1 Main Symptoms of Diabetes](image_url)
These kinds of Patients typically experience frequent urination i.e. polyuria, they might become all the time more thirsty i.e. polydipsia and hungry i.e. polyphagia. In some cases if diabetes remains untreated blurred vision, in critical condition permanent damage to eyes- retinopathy, nephropathy, cardiomyopathy, respiratory problems, neuropathy, and other complications have seen leading to economical burden on population (MNT Knowledge Center, 2013). The clinical symptom and progress of diabetes vary from countries to country and also vary between different ethnic groups within a nation. For example 24.4 million people in America, 10.9 in Russia, 61.5 million in India. As per the estimation of International Diabetes Federation world population affected by diabetes is 382 Million by 2013 will increase and will reach to 592 million in year 2035.

**Diagnosis**

The clinical diagnosis can be made by measuring available symptoms for hyperglycemia and glycosuria, although different organization gives their own limit for blood glucose level indicating diabetes. The Indian council of medical research (ICMR) indicates diabetes a person with diabetes when symptom of diabetes with casual plasma glucose of $\geq 200$ mg/dl, Fasting plasma glucose $\geq 126$ mg/dl and 2 h post 75g glucose $\geq 200$ mg/dl. The details are given in table 1.1 (ICMR, section 3, 2013). The ‘World Health Organization’ (WHO) criteria diagnose diabetes by fasting plasma glucose (FPG) i.e. post-prandial 2-h plasma glucose (PG) level of $\leq 11.1$ mmol/L (200mg/dL), or pre-prandial level of $\leq 7$ mmol/L (140mg/dL ) (Pushparaj, 2005; WHO factsheets, 2013).
Table 1.1 Glucose Tolerance and Diabetes Criteria for Diagnosis

<table>
<thead>
<tr>
<th>Normogycemia</th>
<th>Impaired Fasting Glucose (IFG) or Tolerance (IGT)</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG &lt;110 mg/dl</td>
<td>FPG ≥ 110 and &lt;126 mg/dl (IFG)</td>
<td>FPG ≥ 126 mg/dl</td>
</tr>
<tr>
<td>2h PG &lt;140 mg/dl</td>
<td>2h PG ≥ 110 and &lt;126 mg/dl (IGT)</td>
<td>2h PG ≥ 200 mg/dl</td>
</tr>
</tbody>
</table>

American Diabetes Association have given several diagnostic procedure for diabetes and if one is having classical symptoms of high glucose level with any one positive test than second test will not require for conformation. One can also determine ‘prediabetes’ with same tests. Prediabetes is a condition in that blood glucose levels are normal and high enough to be diagnosed as diabetes (American Diabetes Association, 2013).

A1C test: In the A1C test blood glucose for the past 2 to 3 months is measured. The patients do not need to be in conditions like fasting or drinking for being diagnosed and that is the advantage. In this test normal condition indicated by an A1C of less than 5.7%, Prediabetes 5.7% to 6.4% and Diabetes 6.5% or higher. It is also called as hemoglobin A1c, HbA1c, or glycohemoglobin test (American Diabetes Association, 2013).

Fasting Plasma Glucose (FPG): Fasting is a condition of not eating or drinking anything except water, and blood glucose is measured in this condition. Diabetes is normal if the level found less than 100 mg/dl, Prediabetes if 100 mg/dl to 125 mg/dl and positive if 126 mg/dl or higher (American Diabetes Association, 2013).

Oral Glucose Tolerance Test (OGTT): In OGTT blood glucose level is measured two times i.e. before and after dinking 100 g glucose in water (75 g if pragnant). If, blood glucose level ≤200 mg/dl Prediabetec if 140-199 mg/dl and normal if is <140 mg/dl, diagnosed as Diabetec when patient is tested after 2 h and (American Diabetes Association, 2013).
Diabetes Mellitus Classification

Diabetes mellitus embodies a various group of disorders. A global diabetes community of U.K. explains that there are various types of diabetes; they are mainly Type 1, Type 2 and other is Gestational Diabetes

**Type 1** diabetes mellitus is a form of diabetes that is most frequent in kids but can be diagnosed at any age. One can consider it as juvenile diabetes. This type is an autoimmune disease that destroys beta cells permanently in the pancreas; hence the body can no longer be able to produce insulin and thus type-1 diabetes also called as insulin-dependent diabetes mellitus (IDDM). People with type 1 diabetes as a result need regular insulin intake for management of the disease. In this type hyperglycemia followed by polyuria, polydipsia, and unexplained weight loss are common (The global diabetes community, 2013).

**Type 2** diabetes mellitus is nothing but hyperglycemia. It is a metabolic disorder that results in elevated blood glucose levels and it may be due to the body becomes unable to produce enough insulin or unsuccessful at using the insulin it has produced and thus type 2 diabetes also known as insulin resistance or non insulin dependent diabetes mellitus (NIDDM). This Type diabetes was formerly known as adult-onset diabetes due to its incidence mainly in people over 40. However, now it is becoming more common in children, teens and young adults and about 90% of diabetes cases are type 2 worldwide (The global diabetes community, 2013).

**Type III** Gestational Diabetes is a type of Diabetes mellitus and so called when first found during pregnancy. During pregnancy about 2-10 % women build up in to this condition. In Gestational Diabetes, the resistance of insulin because of changes in hormones is made by the placenta. Doctors say that as the growth demands of the foetus increases, an expectant woman's insulin needs increase by 2 to 3 times that of normal and thus it is very much essential to be screened for the incidence of gestational diabetes between 24-28 weeks of pregnancy.

**Type IV** Other different types:

A. Defect in genetic activity of insulin action
B. Defect in genetic activity of beta cell function due to mutations in various enzymes (earlier called MODY young diabetes)

C. En-do-cr-in-o-pathies (e.g. pheochromocytoma, syndrome, acromegaly)

D. Disease of pancreas (e.g. post pancreatectomy, pancreatic tumours)

E. local and systemic infections (e.g. cytomegalovirus, rubella a congenital, Coxsackievirus-B)

F. Drugs or induced chemically (e.g. b blockers, thyroid hormone, steroids, diuretic drugs, etc)

G. Syndromes other genetic causes (like Down syndrome)

H. Unusual performance of response immune carrier DM.

1.4 Diabetes Management

Diabetes can cause several metabolic disorders if it remains untreated and all this happened because of high level of blood sugar level may be due to either non production of insulin (type 1) or if produced insulin is not sufficient (type 2). Whatever the type of diabetes mellitus is, proper diabetes management is required to keep blood sugar in control.

Type 1 Diabetes Mellitus (T1DM) is seen in children and its management becomes even challenging task when children are unable to describe his/her condition. The management of T1DM is achieved by regular replacement of insulin, healthy diet and exercise. For the people having T1DM, it is a balancing act and they need to stick their schedules of insulin injections, food intake and regular checkups. Even small laps in schedule may lead to rise or fall in blood glucose level (Wherrett et al., 2013).
The treatment and management of Type 2 Diabetes Mellitus (T2DM) focus on regulation of blood glucose level too, but here the cause of same is different than T1DM. T2DM is mainly due to hyperglycemia and it occurs in body either by increased glucose production or in peripheral glucose-uptake is lowered or increased glucose absorption or insufficient insulin formation. One can control this situation in prediabetes stage and avoid developing into diabetes mellitus by controlled diet and physical exercise. In case if patients fail to control Prediabetes and develop diabetes, it can be control with the use of oral anti diabetic agents along with the diet control and exercise. These agents act on particular pathway to regulate blood glucose. Some of these classes of agents with their primary action are shown in figure 2. ICMR has issued a list of currently available oral anti diabetic agents according to their class in India (Table 1.2).
### Table 1.2 Types of oral antibiotic agent currently available in India

<table>
<thead>
<tr>
<th>No</th>
<th>Class</th>
<th>Mode of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sulfonyleureas (SU)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>a. First Generation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Chlorpropamide,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carbutamide,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tolbutamide)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>b. Second generation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Glibornuride Glipizide</td>
<td>Insulin Secretagogues: Binds to the $K_{ATP}$ channel and increase insulin secretion by $\beta$ cells of pancreas</td>
</tr>
<tr>
<td></td>
<td>Glisoxepide Gliquidone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glimepiride</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glyclopymide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gliclazide)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Non-Sulphonylurea Agents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a. Alpha glucosidase</td>
<td>Insulin Sensitizers: these agents are competitive inhibitors of alpha-glucosidase present in small intestine; there by carbohydrate digestion is being inhibited.</td>
</tr>
<tr>
<td></td>
<td>Inhibitors (Acarbose,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>voglibose)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>b. Megitinide analogs</td>
<td>Insulin Secretagogues: Binds weakly to the $K_{ATP}$ channel and increase insulin secretion by $\beta$ cells of pancreas</td>
</tr>
<tr>
<td></td>
<td>(Repaglinide, nateglinide)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>c. Thiazolidinediones</td>
<td>activat PPARs (peroxisome proliferator-activated receptors)</td>
</tr>
<tr>
<td></td>
<td>(Piglitazone,</td>
<td></td>
</tr>
</tbody>
</table>
Troglitazone, Rosiglitazone) Metabolize glucose and fat by higher production of certain protein.

d. Biguanides Insulin Sensitizers: Mechanism of action is unclear. It is considered to increase sensitivity to Insulin, reduce blood glucose level, decrease blood lipid concentration

I. Sulphonylureas (SU):

These are the oldest and widely used anti-diabetic agents which act by binding to sulphonylurea receptors on $\beta$ cells of pancreas and increase insulin secretion. These agents work efficiently for few months and thereafter function of $\beta$ cells decrease. About 5% patients every year stop responding sulphonylureas (Del et al., 2007; ICMR, section 7, 2013). Further SUs are associated with weight gain and a study in 2009 reported sulfonylureas increase risk of heart failure and higher risk of death compared to use of metformin (Boyles, 2009). In such condition combine therapy to focus on insulin-sensitizing required. sulphonylurea can combine with other class of agent like metformin and thiazolidinediones but except with another sulphonylurea or meglitinide, since they act similarly and no synergistic effect.

II. Non-Sulphonylureas

a. Alpha glucosidase inhibitors:

Alpha glucosidase inhibitors act by competitively inhibiting Alpha glucosidase enzyme which present in small intestine and necessary to hydrolyze disaccharides, mono-saccharides, and oligosaccharides. Example of such agent is acarbose, voglibose and it effectively decreases postprandial absorption of glucose (ICMR, section 7, 2013). These agents are helpful in pre-diabetics having impaired insulin sensitivity and for T2DM it is used in combination with other anti-diabetic agent but as alone it less effective than other anti-diabetic agent. There are many natural $\alpha$-glucosidase inhibitors available viz. Trigonella foenum-graceum (Fenugreek, methi), Eugenia jambolana (jamboos), Azadirachta Indica culinary mushroom, Bitter Gourd (Karela) and they are used as mono-therapy as in diet in south eastern country like India (Mukherjee and Sengupta, 2013).
b. Megitinide analogs (Glinides):

Megitinide or also called as glinides increase insulin secretion similar to sulfonylureas bind with weak affinity and faster dissociate from binding site hence act for shorter time. Although the researches show that Glinides act rapidly than sulfonylurea (Shigeto et al., 2007) and has no effect on insulin release in the absence of glucose like sulfonylurea (Repaglinide Apollo, 2012). Repaglinide and nateglinide stimulate insulin quickly in non-fasting condition and thus advise to take immediately before meal. Short and rapid onset of action makes glinides appropriate where meals are unpredictable or missed in our current lifestyles (Reasner, 1999). Fewer hypoglycemic episodes compared with a second-generation SU make these agents good option for aged patients and when other agents are contraindicated (Kristensen et al., 1999; ICMR, section 7, 2013).

c. Thiazolidinediones:

These agents act by improving insulin sensitivity in adipose tissue and skeletal muscles. This effect is brought about by binding to nuclear peroximal proliferator activated receptor-gama (PPAR-γ) leading to increase glucose transporter expression. This is major mechanism for restoring insulin sensitivity. It also inhibits hepatic glucose output. Thiazolidinediones are also good at β-cell function and decrease insulin resistance but, weight gain, increase in bone loss and peripheral edema are major disadvantage associated with it (Fowler, 2007). They are also associated with increased risk of heart attack and stroke and because of this rosiglitazone has been suspended by medical authorities in Europe (NHS, 2010).

d. Biguanides

Metformin is the preferred biguanide acts by decreasing hepatic glucose output, as well as enhancing sensitivity of the hepatic and peripheral tissues to circulating insulin and thus also referred as insulin sensitizing drug. It also inhibits the intestinal absorption of glucose and exerts anorexic effect. In monotherapy it rarely produces hypoglycemia and it is having side effects abdominal discomfort, diarrhea and some time lactic acidosis. Metformin has favorable effect on lipids, decreasing triglycerides and LDL cholesterol. Due to its safety and efficacy it is being considered first line monotherapy for diabetes. Metformin effect reduces if there is not enough
endogenous/ exogenous insulin and patients cannot maintain perfect glycemic control (Hundal et al., 2000). It is believed that Metformin is the most extensively prescribed antidiabetic agent and the record says that in year 2011 only more than 59.1 million prescriptions were filled in USA for its generic formulations according to -The Use of Medicines in the US: Review, 2011. Metformin is also popular in combination with sulphonylurea and other oral hypoglycemic agents.

Available combinations with Metformin are: metformin with rosiglitazone, sold as ‘Avandamet’; with pioglitazone ‘Actoplus Met’; with glipizide ‘Metaglip’; with glibenclamide ‘Glucovance’; with sitagliptin ‘Janumet’; with repaglinide ‘PrandiMet’

1.2 CURRENT INVESTIGATION

Repaglinide (RG) and Metformin HCL (MH) in conventional form was approved by FDA June, 2008 with its first and only fixed-dose combination and brand name PrandiMet® for the treatment of T2DM (PrandiMet®, Novo Nordisk. Inc). PrandiMet® is prescribed by doctors with a diet and regular work-out; to control high sugar in blood in T2DM patients. Since then it has been prescribed in conventional dosage form to large amount of population for the treatment of T2DM without any adverse event or death (FDA Adverse Events Reporting System (FAERS), August- 2012; Medpagetoday, 2014). It has been proved that combining MH with RG provided effective and a safe strategy for diabetes therapy when Metformin-monotherapy is no longer sufficient in adult-patients with T2DM (Hermans and Hooge, 2009).

RG is a megitinide class or also called as glinides, increase insulin secretion similar to sulfonylureas bind with weak affinity and faster dissociate from binding site hence act for shorter time. Although the researches show that Glinides act rapidly than sulfonylurea (Shigeto et al.,2007) and has no effect on insulin release in the absence of glucose like sulfonylurea (Repaglinide Apollo, 2012). RG is BCS class II drug with with poor solubility (Raskin et al., 2003). MH a highly water-soluble anti-hyperglycaemic class API, is first-line treatment of T2DM. It is the favorite biguanide class drug acts by decreasing hepatic glucose output, as well as enhancing sensitivity of the hepatic and peripheral tissues to circulating insulin and thus also referred as
insulin sensitizing drug (Veltkamp et al., 2012). It also inhibits the intestinal absorption of glucose and exerts anorexic effect. MH effect reduces if there is not enough endogenous/exogenous insulin and patients cannot maintain perfect glycemic control (Hundal et al., 2000). Pathophysiologically, Metformin and Repaglinide target different components of T2DM (insulin resistance and insulin secretion, respectively) and different aspects of hyperglycemia (fasting and postprandial, respectively). In a recent study, Lund et al., 2008 have demonstrated that T2DM in nonobese patients, metformin reduced triglycerides, postprandial glycemia and free fatty acids similarly to repaglinide (Lund et al., 2008). These data support a likely synergistic effect on hyperglycemia (postprandial) by combining metformin and repaglinide.

However, both drug have short half-life of the drugs (MH/ 0.9–2.6 h, RG/1.3 h) (Soegondo et al., 2004; Corti et al., 2008), patients usually have to take the tablets 2 to 3 times/day; thus, causing inconvenience to patient and fluctuations. MH is poorly permeable in the GI tract. Its oral bioavailability 40-60% and decrease with increase in dosage, which suggests some kind of saturation dependent absorption process. It also has very high water solubility leading problems in controlling the initial burst of drug (Kumar and McGuffy, 2003). RG is having bioavailability 56% and metabolize completely by oxidative bio-transformation; its metabolites do not contribute to antidiabetic action. RG is rapidly eliminated from the blood stream with a t1/2 ≤ 1 thus, frequent administration required that make patients compromised for the treatment (Thanda et al., 2012). Providing both drug in a separate layer in sustain release formulation for 12 h, can reduce dosing frequency, improve bioavailability and combination of different glucose lowering mechanism will assure patient therapy and compliance especially for 2nd line treatment of T2DM.
1.3 INTRODUCTION TO CONTROLLED DRUG DELIVERY SYSTEM

An ideal oral medication is that which after ingestion quickly achieve therapeutic concentration and maintain steady state plasma concentration for longer period of time so less dosage amount required, less frequency of administration and increase patient compliance with higher bioavailability of active constituent can be achieved (Robinson and Lee, 2003; Wai et al., 2000).

In recent decades, attention has been given on the development of new drug delivery system, as pharmaceutical scientists are now well aware with the fact that the in general, action of a drug molecule is not only reliant on its inherent therapeutic activity but rather on efficiency of delivery system and preferably at site of action. In oral dosage form an ideal medication can be developed by formulation of controlled formulations (CDDS) which release drug at a predetermined rate, systemically or locally, with reproducible release kinetics for a required time period (Robinson and Lee, 2003).

The conventional dosage forms are IR type; other than that, delivery systems may be divided conveniently as per given categories (Wells, 2002):

- Delayed Release
- Sustained Release
- Prolonged Release
- Site-specific and Receptor release

- **Delayed release** formulations are formulated to give predetermined time release rather than release immediately after ingestion. These systems use intermittent, repetitive dosing of a drug in one or more IR units united into a single dosage form. Examples of these systems include, repeat action capsules and tablets. A delayed release systems does not create or maintain uniform drug-blood levels within the therapeutic range.
- A **sustained release formulation includes**, any delivery system that attains its API release, slowly for long period of time & maintain steady state concentration.

- **Prolonged release** formulation provides drug release without keeping constant level, the duration of action is stretched over that achieved by normal delivery; it is considered as a prolonged release system.

- **Site-Specific and Receptor Release:**
  It refers to targeting of a drug directly to a certain location in body. In the case of specific release at particular site, the target is a certain tissue-organ, while for receptor release; the target is the particular receptor in that tissue or organ. Both of these systems satisfy the spatial aspects of drug delivery.

![Figure 1.5 Plasma level profiles following conventional and controlled release dosing](image)
Advantages and Disadvantages of controlled drug delivery system (Chiao & Robinson, 1995; Lachman, 2008; Robinson and Lee, 2003)

Advantages

1. Better control of plasma drug concentration for drugs permit,
   a. Improved treatment: For some chronic disorders if the plasma-concentration of drug falls, breakthrough in symptom occurs particularly when falls below the least effective concentration, e.g. depressive illnesses, asthma.
   b. Maintains overnight plasma concentration, for conventional dosage, it is no-dose periods, e.g. pain management of in terminally ill patients can be possible overnight with these formulations permits improved sleeps;
   c. A reduction in the incidence and severity of untoward systemic side-effects related to high peak plasma drug concentrations due to rapid absorption of API.

2. A reduction in the total amount of drug administered over the period of treatment. Because of this reduction in occurrence of systemic and local unwanted events observed in the cases of many drugs administered in MR formulations.

3. Patient compliance: The Improved patient compliance resulting from the reduction in the number and frequency of doses requires maintaining the desired therapeutic response, e.g. one peroral MR product every 12 hours contributes to the improved control of therapeutic drug concentration achieved with such products.

4. Reduced side effect: There is a reduction in the incidence and severity of localized GI side-effects occurred by 'dumping of dose' of irritant drugs from IR dosage forms, e.g. potassium chloride. The more controlled, slower release of potassium chloride from its peroral MR formulations less the build-up of localized irritant concentrations in the gastrointestinal tract. Consequently,
now potassium chloride is administered perorally almost exclusively in MR form.

5. Economy: It is claimed that cost savings are made from the better disease management that can be achieved with MR products.

6. Improve bioavailability of some drugs

7. Cure or control condition more promptly

8. High safety margin in case of highly potent API and the occurrence of both systemic and local adverse side effects can be decreased for sensitive patients

**Disadvantages**

1. Decreased systemic availability in contrast to immediate release conventional dosage forms.
2. Chances of dose throwing away due to physiologic, food, or formulation variables or also can by grinding or chewing of formulations by the patient.
3. Poor IVIVC.
4. Increased risk of toxicity.
5. Dependence on GI residence time of dosage form
6. Difficulty of retrieval of API in case of poisoning, toxicity or hypersensitivity reactions.

**Design and fabrication of control release system** (Robinson & Lee, 2003):

The basic concept for fabrication of control release system is alteration of alter the pharmacokinetics and pharmacodynamics of active material being used to treat diseases. There are different novel techniques being used for such formulations but in any design, physicochemical and biological properties of active ingredient influence the control release formulation. Such physicochemical factors are aqueous solubility, partition coefficient, molecular size, drug stability, drug protein binding, drug pka and ionization and biological factors are liberation of drug from dosage form, absorption, distribution, metabolism and excretion, side-effects, margin of safety of the drug. The majority of oral controlled release systems are based on dissolution, diffusion or both
mechanisms, to make slow release of drugs into the gastrointestinal milieu (Wen & Par, 2010).

The following techniques are employed in the design and fabrication of oral control release dosage forms.

1. Dissolution controlled release  
   a) Encapsulation  
   b) Matrix
2. Diffusion controlled devices  
   a) Reservoir  
   b) Matrix
3. Release systems controlled by both Dissolution and Diffusion
4. Ion Exchange resins
5. Osmotically controlled release
6. pH-Independent formulations
7. Altered Density Formulations

Monolithic Matrix System:

In formulation design of release controlling systems, matrix based tablet formulation systems are the most preferred approach due to modest manufacturing process. The formulation of a tablet with the matrix approach simply involves compression of mixture prepared with of release-retardant, API, and other additives. Alternatively, if drug-excipients properties not suitable for direct compression then blends may be granulated either by (a) dry granulation (b) wet granulation or (c) melt granulation to make the blend suitable for the compression and other physical properties.

Based on the chemical nature of the release retardant(s), the matrix systems are classified as given in Table 1.2 (Patel et al., 2011).
### Table 1.3 Type of Matrix Tablets based on release retardant material used

<table>
<thead>
<tr>
<th>Type of the Mechanism</th>
<th>Mechanism</th>
</tr>
</thead>
</table>
| Hydrophilic           | Limited swelling controlled delivery, swallable soluble polymer  
                        | eg: Hydroxy ethylcellulose, Hydroxy propyl methyl cellulose |
| Inert                 | Inert in nature, Controlled delivery by diffusion, inert- insoluble polymer  
                        | eg: Ethylcellulose |
| Lipophilic            | Delivery by diffusion & erosion, Lipid waxes  
                        | eg: Carnauba wax. |
| Biodegradable         | Non lipidic nature  
                        | Controlled delivery by surface erosion |
| Resin Matrices        | Drug release from drug-resin complex  
                        | eg: Ion exchange resins |

**Drug Release Mechanism**

In matrix tablets prepared by erodible matrices, erosion of polymer occurs from the surface and that regulates the release; when tablets are prepared by hydrophilic matrices, the swelling of polymer and gelation occurs. The formation of gel with time controls the drug release. With time gel layer increases its thickness, drug diffusion path length increases, thus slowing the drug release. When polymer reached its hydration limit, it stops swelling and dispatched from matrix surface, subsequent reducing size and an increased dissolution rate (Liu et al., 2001)
1.4 EFFECT OF DIFFERENT FACTORS THAT AFFECT DRUG RELEASE

I. Hydration of polymer

There are various kinds of polymers that are used for controlling drug release. The numbers of such polymers as examples are given in table 1.3. When the type of polymers used in formulation is hydrophilic, drug release essentially depends on hydration process. For them the important step in dissolution include absorption/adsorption of water, rupture polymer-polymer linking with the simultaneous formation of polymer-water link, swelling of polymeric chains, and finally separation & distribution in dissolution medium (Patel H et al., 2011).

II. Polymer Diffusivity

Permeation of drug molecule through polymers depends mainly on solubility and diffusivity. The diffusivity is an ability to pass through polymer membrane, which depends on molecular size of material being passed. The drug molecules larger than 600 Daltons are poor candidate for passive diffusion (Brahmankar & Jaiswal, 2000). The process required little energy for the activation. Once it is activated drug molecules start replacing other molecules and move forward without changing physical structure. Thus it makes a way through polymer. The diffusivity depends on molecular size of polymer, its
Figure 1.7 Diffusion of molecules through polymers

concentration and viscosity. Increase in value of any/all of these three factor will decrease diffusion and dissolution of drug from that polymer matrix.

III. Solubility of Drug

Good aqueous solubility with pH independent drug candidates can provide good controlled release formulation c For swelling and erosion controlled polymeric matrices, good aqueous solubility provides predictable results (Patel H et al., 2011 ). For diffusion, drug must available in molecular level, so diffusion will be solubility dependent step in dissolution studies.

IV. Partition Coefficient:

Poor bioavailability results may be due to drugs with high partition coefficient as they are lipid soluble and thus presents less aqueous solubility. Active constituents having law partition coefficients present trouble in penetrating membranes and give poor bioavailability (Brahmankar & Jaiswal, 2000).

V. pKa

Since the unchanged drug favorably passes through lipid membranes, it is significant to note the relationship between the pka of the compound and the absorptive environment (Jantzen & Robinson, 2002). Presenting the drug in an unchanged form is advantageous for drug permeation. For optimal absorption, the
drugs should be unchanged at that site. Jantzen & Robinson, 2002 also stated that the situation is made more complex by the fact that the drug’s aqueous solubility will generally be reduced by change to ionized form drugs with solubility <0.01mg/ml are integrally sustained, as their release with time in the GI tract will be limited by dissolution of the drug. So it is obvious that the solubility of the compound will not be good choices for poorly soluble API, since the driving force for diffusion, which is the API’s concentration in solution, will be low.

VI. Half life

To maintain therapeutic blood concentration for prolonged period, drug must circulate at about same rate of which it is eliminated. The elimination rate is quantitatively defined by half-life ($t_{1/2}$). Drugs with shorter $t_{1/2}$ are candidates of choice for SR formulations since it reduces dosing frequency. In general drugs with $t_{1/2} < 3h$ are poor candidates of SR dosage forms; compounds with long $t_{1/2} > 8h$ are also not used in SR forms.
1.5 LAYER TABLETS

Compressed tablets are the most widely used dosage form and dominating therapeutic formulations due to their ease in ingestion, compactness and ease of manufacturing. In recent years, expansion in technology and novelty have convinced the pharmaceutical industry in developing single tablets with two or more therapeutic agents and that has attract, convenience and fulfill market and customer need (Banker, 1987).

The manufacturing of such tablets involves pre-defined but different drug release profiles of two active components in single dosage form. Layered tablet can be defined as unit dosage form having two or more therapeutic compound in a system containing different drug release mechanism.

Figure 1.8 Bi-layer Tablet press mechanism

The layers of tablets can be combination of immediate release, conventional release, controlled release mechanism with same or two different therapeutic agents or combination of therapeutic agents with release modifying agents example, floating enhancer, osmogens, bio-adhesive agents etc. These tablets are manufactured by the use of different types and grades of granules from individually located different
hopper on tablet press onto die and here granules are guided by feed frame individually where individual layer if blend weight is controlled. Tablet press with two or three compaction rollers can be used for layer tablet manufacturing like Rotary tablet presses (Lieberman et al., 1992). Numbers of marketed bilayer tablet press are available. Example Bilayer Nova tablet press by SMI®, NJ, USA and Mini Bi-Layer Press by Ayush Techno Pvt. Ltd., Ahmadabad, India. In technologies like osmotic bilayer tablet after compression a coating of semi-permeable membrane is required before packaging.

Bi-layer tablet designs applicable to:

1) Development of FDC: WHO states that ‘A combination of two or more actives in a fixed ratio of doses to cure disease’ (WHO, 2005) for example, in anti-infective treatment combination of Sulfamethoxazole and Trimethoprim, In treatment of Tuberculosis combination of Rifampicin and Isoniazid, In treatment of Maleria combination of Amodiaquine and Artesunate are required, Antiviral combination of Lamivudine, Stavidine, and Neviparine. For such instances bi-layered or multilayer tablets are ideal.

2. Reduced Pill Burden for example ‘two tablet for three times a day for 5 day’. Bi-layer controlled release tablet can reduce it to ‘once a day single tablet for 5 day’ and in thus cases patient adherence and convenience. It also prevents, drug resistance developed by monotherapy.

3. Combination drugs that target the same indication

4. At the same time, treat different ailments in the same patient (co-morbidity) with one pill and allows possibility for synergistic combination

5. Reduction in side-effects by using one drug of the combination for this purpose. For example Amiloride may prevent hypokalemia caused by hydrochlorthiazide
Merits and Demerits of Bi-layer tablet (Harika & Kumar, 2012)

Merits

1. Incompatible components can be separated
2. Enhanced patient compliance
3. Physical and chemical stability and microbial stability can be maintained
4. Low cost compared to individual dosage form
5. Lighter and compact
6. Easiest to package and strip
7. Reduction in the dosage regimen
8. Potency is retained and dose accuracy is ensured
9. Large scale production possible

Demerits

1. Difficult to swallow in case of children and particularly adults if multi layered tablet more than 1 g weight.
2. Inaccuracy in individual layer may impart
3. Cross contamination between layers. Although it can be eliminated by coating on of the granules.
4. Insufficient hardness and layer separation.
5. Such tablet presses are expensive and adds complexity during manufacture.

Manufacturing challenges

1. Hygroscopicity:

It may lead to poor compression and stability problems. For instance, combination therapy of Glipizide and Metformin; Metformin is poorly compressible and it requires residual moisture for good compression on contrast Glipizide, degrades in moisture (Li et al., 2009). In such case separate granulation and then compression or Glipizide particles can be coated with suitable polymer.

2. Different release kinetics (De & Kaur Gill, 2013):
For example Rabeprazole and Domperidone bilayer tablet can be formulated with different release kinetics Domperidone (IR) and Rabeprazole (SR)

3. Disproportionate doses (Khedkar, 2008):

For example Metformin and Glibenclamide bilayered tablet dose 400 mg and 2.5 mg respectively and in such case content uniformity and assay are difficult to be accurate. Such phenomenon can be altered by formulating bilayered tablet with dilution for low dose drug with other excipients or adsorption on excipients can be done

4. Altered solubility/ stability (Khedkar, 2008):

For example combination of Atorvastatin, Ramipril and Aspirin having good Synergistic action but stability issue arises as Atorvastatin is acid labile and Aspirin undergoes alkaline hydrolysis. In such condition suitable excipients are required in formulation of layer tablets.