Vol 5 | Issue 3 | 2015 | 243-251.

International Journal
of
Pharmacy Review & Research
www.ijprr.com

e-ISSN: 2248 – 9207
Print ISSN: 2248 – 9193

Review on Diabetes Mellitus

B. Yamini, V. Leelaprabakar, P. Jayachandra Reddy

Krishna Teja Pharmacy College, Chadalawada Nagar, Tirupati-517605, Andhra Pradesh, India.

ABSTRACT

Diabetes mellitus has reached epidemic proportions and affects more than 170 million individuals worldwide. In more developed societies, the prevalence of diabetes mellitus has reached about 6% and even more alarmingly, among obese white adolescents 4% had diabetes and 25% had abnormal glucose tolerance. Some 90% of diabetic individuals have Type-2 (Non-Insulin-dependent) diabetes mellitus, and within this category no more than 10% can be accounted for monogenic forms such as maturity-onset diabetes of the young and mitochondrial diabetes or late-onset autoimmune diabetes of the adult, which is actually late-onset Type 1 diabetes. People with diabetes have high blood sugar. This is because: Their pancreas does not make enough insulin and their muscle, fat, and liver cells do not respond to insulin due to insulin resistance. Insulin resistance is a state in which normal amount of Insulin produces a subnormal amount of Insulin response. There is an impaired biological response to insulin by one or more of its target tissues leading to reduced glucose disposal. Defects in binding of insulin to it's receptors due to the reduction in their number or affinity would result in Insulin resistance. Clinically insulin resistance stage falls in two categories.

Key words: Diabetes mellitus, Insulin, Glucose level, Blood sugar.

INTRODUCTION

Diabetes mellitus is a chronic disorder characterized by impaired metabolism of glucose. Diabetes mellitus is a group of disorders involving distinct pathogenic mechanisms with hyperglycemia as the common denominator. Regardless of the cause, the disease is associated with insulin deficiency, which may be total, partial or relative when viewed in respect of co-existing insulin resistance.

Causes

Insulin is a hormone produced by the pancreas to control blood sugar. Diabetes can be caused by deficiency of insulin, resistance to insulin or both. People with diabetes have high blood sugar. This is because:

- Their pancreas does not make enough insulin
- Their muscle, fat, and liver cells do not respond to insulin due to insulin resistance.

Classification of Diabetes Mellitus

1. Type 1 diabetes (beta cell destruction, usually leading to absolute insulin deficiency)
a) Immune Mediated b) Idiopathic
2. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretary defect with relative insulin resistance).
3. Other Specific Types
a. Genetic defects of beta cell function and insulin action
b. Disease of the exocrine pancreas
c. Endocrinopathies
d. Drug induced
e. Infections
f. Gestational Diabetes

Symptoms of Diabetes Mellitus

The classical symptoms of diabetes mellitus are:

- ❖ Polydipsia (Increased intake of water due to increased thirst)
- ❖ Polyuria (Increased formation of urine)
- ❖ Polyphagia (Increased ingestion of food).

Diagnosis of Diabetes Mellitus [1-3]

Two kinds of blood estimations are done to estimate the normal plasma glucose levels. The first one is known as Random Plasma Glucose (RPG) in which a sample is drawn at any "random" time during the day without consideration to the "fed" state of the patient. The

*Corresponding Author **Yamini B** E mail: yamini.pharmafriend@gmail.com

other are samples known as Fasting Plasma Glucose (FPG) followed by Post–prandial Plasma Glucose (PPG). The patient is advised not to eat anything after dinner till the blood sample for FPG is withdrawn the next morning.

There are three ways to diagnose diabetes each must be confirmed on a subsequent day, by any one of the three methods.

1. FPG > 126 mg/dl (0.7 mmol/l), fasting is defined as no caloric intake for at least 8hours.
2. 2-h PPG > 200 mg/dl (11.1 mmol/1) during an Oral glucose Tolerance Test (OGTT).

The Expert Committee recognizes an intermediate group of subjects whose (FPG> 110 mg/dl (6.1 mmol/l) but < 126 mg/d; (7.0 mmol/l) or 2-h values in the OGTT of > 140 mg/dl (7.8 mmol/l) but <200 mg/dl (11.1 mmol/l). Thus, the categories of FPG values are as follows,

- FPG< 110 mg/dl (6.1 mmol/l) = normal fasting glucose
- FPG> 110 mg/dl (6.1 mmol/l) and < mg/dl (7.0 mmol/l) = FPG
- FPG> 126 mg/dl (7.0 mg/dl) = provisional diagnosis of diabetes (the diagnosis must be confirmed, as described above).

Abnormalities in Beta Cell Function in Type 2 Diabetes [4-6]

Glucose homeostasis that requires a balance between glucose production by the liver and glucose utilization by insulin – dependent tissues (such as fat and muscle) and insulin – independent tissues (such as the brain)., is regulated by insulin production in beta cells and glucagon production in alpha cells of the pancreatic islets. In Type 2 diabetes, there are defects in both peripheral tissue responses to insulin and beta cells response to glucose. In Type 2 diabetes there are two defects: reduction in the ability of peripheral tissues to respond to insulin (insulin resistance) and a relative insulin deficiency resulting from an inability of the beta cells to compensate for this resistance.

Biochemical Changes Associated With Insulin Deficiency

Insulin deficiency depresses glucose transport into the cell and glycogen synthesis in the muscle. At the same time there is an increase in protein breakdown. Insulin lack leads not only to underutilization of glucose at the cellular level but also promotes gluconeogenesis. All this lead to hyperglycaemia which is associated with polys. Low insulin levels leads to increased hormone sensitive lipase activity in adipose tissues cells. Long chain fatty acids released are broken down to large quantities of acetyl coenzyme – A, which instead of being burnt by the tricarboxylated acid cycle is diverted to the formation of acetoacetate. Acetoacetate is decarboxylated to give acetone or reduced to from betahydroxybutrate. Acetone, acetoacetate and betahydroxy butyric acid are collectively known as ketone bodies. Ketone bodies, being volatile are excreted in the breath and in the urine.

Insulin Resistance [7-11]

Insulin resistance is a state in which normal amount of Insulin produces a subnormal amount of Insulin response. There is an impaired biological response to insulin by one or more of its target tissues leading to reduced glucose disposal. Defects in binding of insulin to it's receptors due to the reduction in their number or affinity would result in Insulin resistance. Clinically insulin resistance stage falls in two categories.

Decreased sensitivity: where normal response can be obtained with supra maximal insulin levels.

Decreased responsiveness: Even massive doses of insulin cannot produce a normal level or response. There is an increase in Hepatic glucose output (which contributes primarily to fasting hyperglycemia) and reduction in peripheral glucose utilization. There is also elevation of plasma FFA (free fatty acids) resulting from activation of lipolysis.

Management of Type 1 Diabetes

Insulin therapy

Numerous preparations of Insulin are available to cater to the diverse requirements of different patients. The preparations differ in their:

1. Onset of action
2. Duration of action
3. Purity (Conventional, Purified)
4. Species of origin (Human, Pork, Bovine – in order of preference)

Based on their onset and duration of actions, the insulin may be divided into:

a) Rapid acting

Insulin Injection (Regular, Crystalline Zinc)

b) Intermediate Acting

Isophane (NPH) 70%, Regular Insulin 30%, Isophane (NPH) Insulin Suspension

c) Long Acting

Extended Insulin zinc suspension (Ultralente)

The intermediate acting Isophane (NPH) insulins are conjugated to Protamine, large-protein molecule which delays absorption thereby prolonging the duration of action. It is a mixture of 70% ultralente and 30% semi-lente. The long-acting Ultralente zinc-insulin suspension has a large particle size and crystalline form which retards the rate of absorption and thus prolongs the duration of action.

Management of Type 2 Diabetes [12-15]

The treatment of patients with Type 2 diabetes goes beyond normalizing blood glucose levels; therapy is also directed toward alleviating symptoms, minimizing acute complications (e.g., hypoglycemia), increasing the patient's sense of well-being and quality of life, minimizing chronic complications such as nephropathy, neuropathy, and macrovascular and microvascular disease. The initial therapy in Type 2 diabetes is nutrition and exercise, with a program designed to encourage weight loss. The decision to use oral glucose- lowering agents generally takes place after a trial period of diet and

exercise. To be maximally effective however, a nutritionally correct diet and regular exercise should support any pharmacologic intervention.

Oral Hypoglycemic Agents (OHA) [16]

Drugs that are used to lower blood glucose levels are typically called "oral hypoglycemic agents". Among oral hypoglycemic agents the older groups that means sulfonylureas and biguanies are still extensively used. Several new drugs have appeared in the recent years which act through different mechanisms of action. Their use as monotherapy or in combination with other drugs will help to get a better glycemic control.

Morbidity and Mortality of Type 2 Diabetes Mellitus [17]

Diabetes mellitus (DM) is the main cause of mortality and morbidity in the developed world. The low compliance with the prescribed and self – administered treatments is well know to be a great problem in treating chronic disease such as in the case of DM. Patients with Type 2 diabetes are prone to both acute and long – term complications. Long – term diabetic complications are related to the effects of chronic hyperglycemia on the microvasculature.

Diabetes – related complications may have grim outcomes: Diabetes is the leading cause of blindness in adults, of end – stage renal disease, and of non trauma necessitated amputations. Retinopathy is seen is 12% to 44% of patients with Type 2 diabetes 10 years after diagnosis and is present at the time of diagnosis in 10% to 20% of patients. Nephropathy leading to end – stage renal failure occurs in 4% to 20% of patients with Type 2 diabetes. It is well established that Type 2 diabetes is an independent risk – factor for cardiovascular disease – Type 2 diabetes patients have a 2- to 3- fold increase in morbidity and mortality related to coronary artery disease, as well as an increased incidence of peripheral vascular disease. In one study examining the prevalence of complications in patients with Type 2 diabetes, 48% had coronary artery disease, 56% were hypertensive, 15% exhibited signs of cerebrovascular disease and 35% has peripheral artery disease. The complexity of Type 2 diabetes and associated co-morbidities will continue to present a formidable challenge for successful pharmacological treatment.

Perspectives

Despite the magnitude of the disease, the choice of oral antihyperglycemic drugs for Type 2 diabetes was limited to sulfonylureas for over 40 years. The last 11 years have witnessed the introduction of four new classes of oral antihyperglycemic therapies. Each possesses a distinct mechanism of action, which enables their use independently and, in some cases, as combination therapy. Combination drug therapy is not new. Combinations were frowned upon in much of the 20th century because of the prevailing philosophy was to seek a single "silver bullet" to treat a disease rather than prescribe multicomponent formulations to be dispensed by Pharmacist (or) Physicians. Current guidelines for combination therapy advice the use of agents with differing and complementary mechanism of action which mainly arises in the treatment of diabetes in order to maximize therapeutic activity and reduce toxicity. This is important since most patients with Type 2 diabetes will require combination therapy to reach an acceptable level of glycemic control.

Oral solid dosage forms – A Convenient Drug Delivery System

The convenient oral drug delivery has been known for decades is the most widely utilized route of administration among all the routes. It remains the preferred route of administration in the discovery and development of new drug candidates. The popularity of oral route is attributed to patient acceptance, ease of administration, accurate dosing, cost effective manufacturing methods and generally improve the shelf life of the product. In fact the development of a pharmaceutical product for oral delivery, irrespective of its physical form (solid, semisolid or liquid dosage form) characteristics within the inherent constraints of gastrointestinal physiology.

Oral solid forms such as tablets and capsules has been formulated and developed nowadays since they are most effective routes of administration of a new drug. Pharmaceutical products designed for oral delivery and currently available on the prescription and over the counter markets are mostly the immediate release type, which are designed for immediate release of drug for rapid absorption. Many new generations of pharmaceutical products called controlled and sustained release drug delivery systems have also been developed. So the combination of both will be very much useful for immediate response and for maintaining the duration of action.

Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to the Indian Pharmacopoeia Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drugs or a mixture of drugs, with or without diluents. They vary in shape and differ greatly in size and weight, depending on amount of medicinal substances and the intended mode of administration. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of Tablet.

Advantages of the Tablet dosage form:

1. They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
2. Cost is lowest of all oral dosage form.
3. Lighter and compact.
4. Easiest and cheapest to package and strip.
5. Easy to swallowing with least tendency for hang-up.
6. Sustained release product is possible by enteric coating.
7. Objectionable odour and bitter taste can be masked by coating technique.

8. Suitable for large scale production.
9. Greatest chemical and microbial stability over all oral dosage form.

Disadvantages of Tablet dosage form

1. Difficult to swallow in case of children and unconscious patients.
2. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
3. Drugs with poor wetting, slow dissolution properties, may be difficult to formulate as a tablet that will still provide adequate or full drug bioavailability.
4. Bitter testing drugs, drugs with an objectionable odor or drugs that are sensitive to Oxygen may require encapsulation or coating.

Different Types of Tablets

(A) Tablets ingested orally:

1. Compressed tablet
2. Multiple compressed tablet
   - Compression coated tablet
   - Layered tablet
   - Inlay Tablet
3. Repeat action tablet
4. Delayed release tablet
5. Sugar coated tablet
6. Film coated tablet
7. Chewable tablet
8. Targeted Tablets

(B) Tablets used in oral cavity:

1. Buccal tablet
2. Sublingual tablet
3. Troches or lozenges
4. Dental cone

(**C) Tablets administered by other route:**

1. Implantation tablet
2. Vaginal tablet

(D) Tablets used to prepare solution:

1. Effervescent tablet
2. Dispensing tablet
3. Hypodermic tablet
4. Tablet triturates

Bilayered Tablets [18]

The term bilayered tablets refers to tablet containing subunits that may be either the same (homogeneous) or different (heterogeneous). Bilayer tablets allows for designing and modulating the dissolution and release characteristics. Bilayer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug, later, either as second dose or in an extended release manner. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances. Bilayer tablets are preferred when the release profiles of the drugs are different from one another.

Advantages of bilayer tablets over conventional tablets

- Better patient compliance, therapeutic efficacy and provide good treatment efficiency
- Reduced dosing intervals, number of dosing and number of dosage form
- Incompatible drugs are given by separating these drugs by inert materials

Applications of bilayer tablets

- ❖ Used in the combination therapy and to deliver the loading dose and sustained dose of the same (or) different drugs.
- ❖ Used for bi-layer sustained release tablet in which one layer is sustained layer and another one is immediate release layer of the drug and to deliver two different drugs having different release profiles.

Press designed for quality bilayer tablets

Several pharmaceutical companies are currently developing bi-layer tablets. For a variety of reasons: patent extension, therapeutic, marketing to name a few. To reduce capital investment quite often existing but modified tablet presses are used to develop and produce such tablets. The development and production of quality bi-layer tablets needs to be carried out on purpose-built tablet presses to overcome common bi-layer problems, such as layer-separation, insufficient hardness, inaccurate individual layer weight control, cross contamination between the layers, reduced yield, etc. Using a modified tablet press may therefore not be your best approach to producing a quality bi-layer tablet under GMP-conditions. Especially when in addition high production output is required.

Ideal properties for bilayer tablets press

To produce a quality bilayer tablet, in a validated and GMP – way it is important that the selected press is capable of:

- Preventing capping and separation of the two individual layers that constitute the bi-layer tablet.
- Preventing cross-contamination between the two layers.
- Producing a clear visual separation between the two layers and high yield
- Accurate and individual weight control of the two layers

Bi-Layer Compression Basics

a. Initial layer die filling and compaction.
b. Initial layer compaction showing the predominant stress transmission profile.
c. Density profile of initial layer before die filling of the final layer.
d. Final layer die filling and compaction.
e. Final layer compaction showing the predominant stress transmission profile.
f. Density profile of bilayer tablet before ejection.
g. Ejection of a bilayer tablet, dashed arrows show the postulated radial expansion

Due to energy dissipation, the measured axial topographic profile of the ejected tablet is also shown (Fig. 5).

Compression force of Bilayer Tablet

Since the material in the die cavity is compressed twice to pro- duce a bi-layer tablet, compressed first with layer one followed by both the layers, the compression force affects the interfacial interaction and adhesion between the two layers. A certain amount of surface roughness of the initial layer is required for particle interlocking and adhesion with the second layer. As the surface roughness of the first layer is reduced, the contact area for the second layer is significantly reduced at the interface and makes the adhesion weaker. Immediately after final compaction, the compressed second layer may release the stored elastic energy unevenly and may produce crack on the first layer which could act as a stress concentrator and eventually making the tablet interface weaker. This may result in capping or de-lamination of the tablet along the interface either during manufacturing or immediately after the level of compression force used in the first layer compaction determines the degree of surface roughness of the first layer. The higher the first layer compression force, the lesser the surface roughness resulting in reduced adhesion with the second layer. Therefore, for a given final compression force the strength of interfacial adhesion decreases with the increasing first layer compression force. It implies that the extent of plastic/elastic deformation of the first layer has profound effect on the strength of the interface. Thus, understanding the interaction and adhesion behavior between different layers composed of various ingredients with differing physico-chemical properties during compaction is critical to understand the failure mechanisms of bi-layer tablets. Understanding of material attributes of the excipients and API that undergoes compression and compaction is decisive in predicting the interaction.

Fig. 1. Metabolic Causes of Type 2 Diabetes

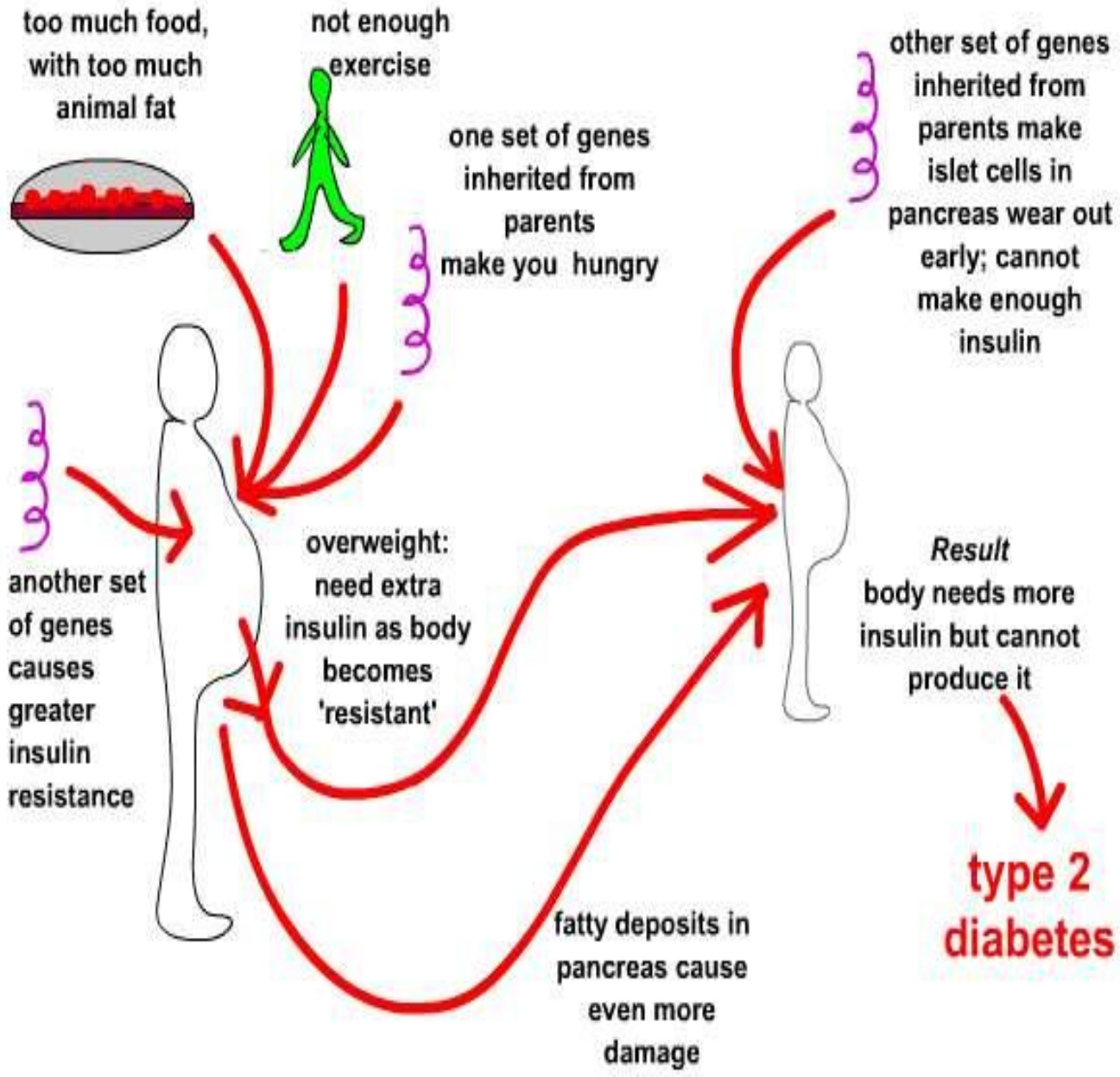


Fig. 2. Insulin Deficiency

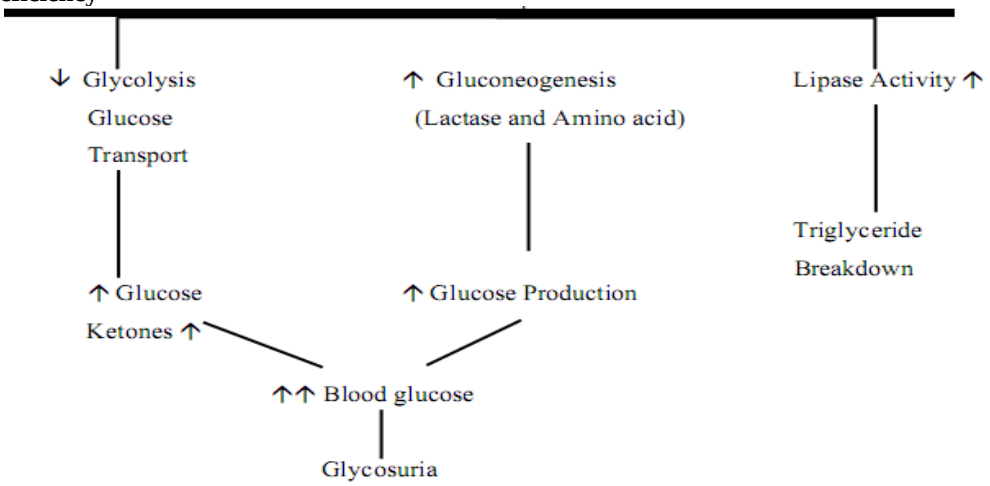


Fig. 3. Progression of Insulin Resistance towards Type 2 Diabetes

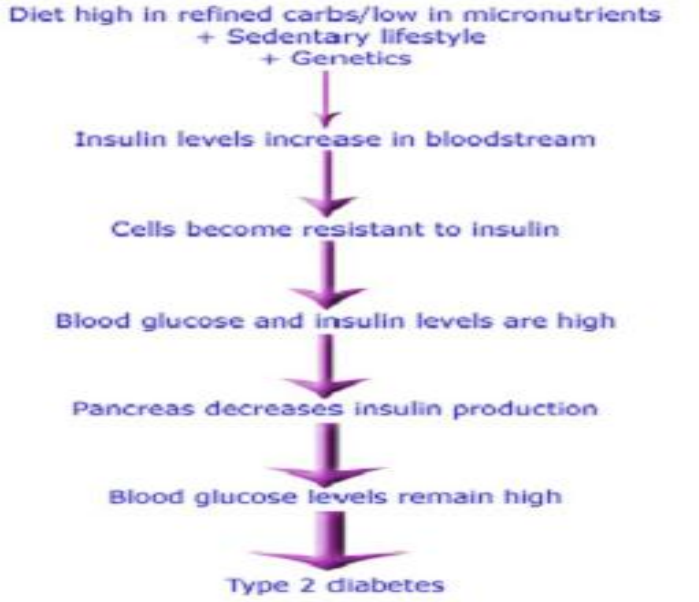


Fig. 4. Mechanism of Action Oral Hypoglycemic Agents

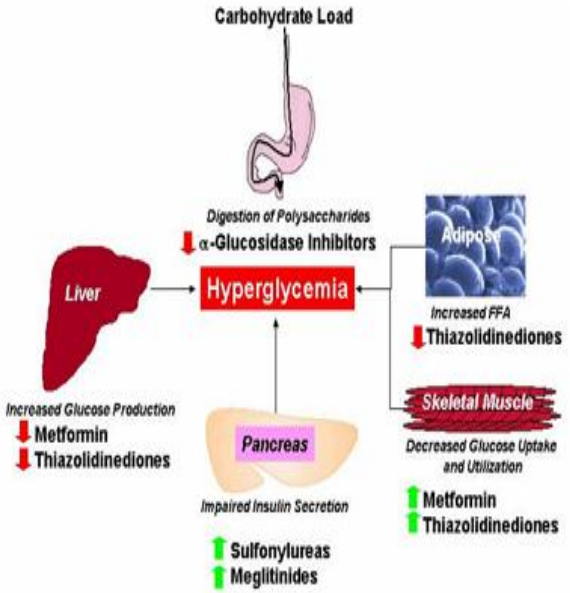


Fig. 5. A schematic diagram showing the different stages occurring during bilayer tablet uniaxial compaction

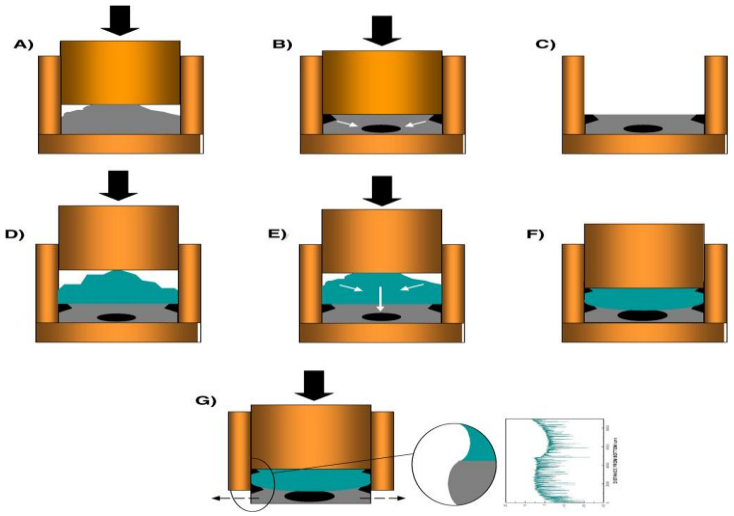
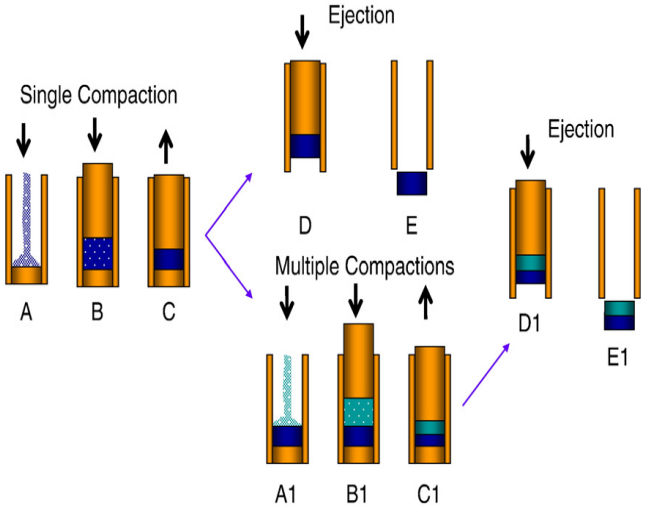


Fig. 6. Schematic diagram showing the manufacture of single and bilayered tablets utilising uniaxial compaction



A. Die filling; B. Compression; C. Decompression; D. Lower punch removal and reapplication of load to the upper punch; E. Tablet fully ejected

Table 1. Complications of Diabetes Mellitus

Acute Complications	Chronic Complications
1. Infections 2. Diabetic Ketoacidosis 3. Hyperosmolar Coma	**Micro-vascular** 1. Retinopathy 2. Neuropathy 3. Nephropathy **Macro- vascular** 1. Coronary Artery Disease 2. Stroke 3. Peripheral Vascular Disease 4. Non healing Ulcer(Amputions)

Table 2. Comparison of Type 1 & Type 2 DM

Parameters	Type 1	Type 2
Age at onset	< 40 years	>50 years
Classical symptoms	Usually present	Few or none
Duration of symptoms	Weeks	Months/Years
Body Weight	Normal/ Low	Obese usually
History of weight loss	Yes	No
Prone to ketoacidosis & ketonuria	Yes	No
Insulin levels	Very low	Low/Normal/High
Insulin resistance	Absent	Present
Rapid death without insulin	Yes	No
Presence of autoantibodies	Yes	No

Table 3. Goals of Therapy for Patients with Diabetes Mellitus

Biochemical index	Nondiabetic value	Goal value	When additional action is suggested
Preprandial glucose Measurement	<110 mg per dL (6.1 mmol per L)	80 mg per dL (4.4 mmol per L) to 120 mg per dl (6.7 mmol per L)	<80 mg per dL (4.4 mmol per L) or >140 mg per dL (7.8 mmol per L)
Bedtime glucose measurement†	<120 mg per dl (6.7 mmol per L)	100 mg per dl (5.6 mmol per L) to 140 mg per dl (7.8 mmol per L)	<100 mg per dl (5.6 mmol per L) or >160 mg per dl (8.9 mmol per L)
HbA1c (%)	<6	<7	>8

Table 4. Current Oral Pharmacological Therapies Used to Treat Type 2 Diabetes

Class	Brand	Manufacturer	Daily Dose (mg)
Sulfonylureas			
1st Generation			
Acetohexomide	Dymelor	Eli Lilly	250-1500mg qd-tid
Chlorpropamide Tolazamide	Diabenase	Pfizer	100-500 mg qd100-750 mg qd-tid
2nd Generation			
Glipizide	Glucotrol	Pfizer	10 qd or bid
Glipizide	Glucotrol XL	Pfizer	5-10 qd
Glimepiride	Amaryl	Aventis	1-4 qd
Meglitinides			
Repaglinide	Prandin	Novo Nordisk	1.5-2 tid
Nateglinide	Starlix	Novartis	60-120 tid
Biguanides			
Metformin	Glucophage	Bristol-Myers Squibb	500-2500 mg qd-tid dosing
Metformin	Glucophage XR	Bristol-Myers Squibb	500-2000 qd
Thiazolidinediones			
Rosiglitazone	Avandia	GlaxoSmithKline	4-8 qd, 2-4 bid
Pioglitazone	Actos	Takeda/Eli Lilly	15-45 qd

Table 5. Fixed Combination Therapies to Treat Type 2 Diabetes

Drug 1	Drug 2	Brand	Manufacturer	Available Doses (mg Drug 1/mg Drug 2
Glyburide	Metformin	Glucovance	Bristol-Myers Squibb	1.25/250;2.5/500; 5/500
Glipizide	Metformin	Metaglip	Bristol-Myers Squibb	2.5/250; 2.5/500; 5/500
Glimepiride	Pioglitazone	Duetact	Takeda	2/30; 4/30
Glimepiride	Rosiglitazone	Avandaryl	GlaxoSmithKline	1/4; 2/4; 4/4
Pioglitazone	Metformin	Actosplusmet	Takeda	15/500; 15/850
Rosiglitazone	Metformin	Avandamet	GlaxoSmithKline	1/500; 2/500; 4/500; 2/1000; 4/1000

Table 6. Dose-Response of Oral Agents for Type 2 Diabetes Mellitus

Agent	Average FBG Reduction (%)	Average PPG Reduction (%)	Average HbA1c Reduction (%)
Sulfonylureas*	25 to 40	20	2.0
Alpha-glucosidase inhibitors*	10 to 20	40 to 45	0.5 to 1.5
Metformin (Glucophage)*	20 to 40	25	1.5 to 2.0

FBG = Fasting Blood Glucose; PPG = Post Prandial Glucose; HbA1c = Glycosylated Hemoglobin A1c.
*--Combined with another oral agent or insulin.

Table 7. Activity, Advantages and Disadvantages of Oral Hypoglycemic Agents

Agent	Activity & advantages	Disadvantages
Thiazolidonediones	Decreases glucose production and plasma levels and increases glucose clearance; significantly increases insulin sensitivity; improves lipid profile (decreased small dense LDL-C, increased HDL-C); lowers DBP; beneficial effects on surrogate markers of cardiovascular parameters.	Not indicated in patients with hepatic impairment, heart failure, or receiving injected insulin associated with initial increase in total LDL-C, increased bodyweight and fluid retention (particularly with insulin); relatively expensive; lack of long term tolerability data.
Biguanides	Decreases hepatic production of glucose, peripheral insulin levels, total LDL-C, free fatty acid and triglyceride levels and slightly increases muscle insulin sensitivity; low risk of hypoglycaemia; beneficial effects on some cardiovascular parameters; doesn't cause bodyweight gain.	Contraindicated in patients with renal impairment (risk of lactic acidosis), liver disease, respiratory insufficiency, hypoxemia, severe infection, alcohol abuse or cardiac failure; associated with gastrointestinal adverse effects; does not decrease blood pressure nor increase HDLC; no direct effect on B-cell function.
Sulphonylureas	Increase endogenous insulin secretion; generally well tolerated; inexpensive.	No effects on insulin sensitivity, blood pressure, lipids or lipoproteins; adverse effects include hypoglycaemia (particularly in the elderly) and bodyweight gain; no positive effects on cardiovascular parameters; drug interaction
Meglitinides	Increases endogenous insulin secretion in the presence of glucose; well tolerated; can be used by patients with renal impairment.	Similar incidence of hypoglycaemia and similar efficacy to sulphonylureas; drug interactions with enzyme inhibitors or inducers.

CONCUSION

Diabetes mellitus has reached epidemic proportions and affects more than 170 million individuals worldwide. In more developed societies, the prevalence of diabetes mellitus has reached about 6% and even more alarmingly, among obese white adolescents 4% had diabetes and 25% had abnormal glucose tolerance. Some 90% of diabetic individuals have Type-2 (Non-Insulin-dependent) diabetes mellitus, and within this category no more than 10% can be accounted for monogenic forms such as maturity-onset diabetes of the young and mitochondrial diabetes or late-onset autoimmune diabetes of the adult, which is actually late-onset Type 1 diabetes. Thus, most diabetes in the world is accounted for by "common" Type 2 diabetes, which has a multifactorial pathogenesis caused by alterations in several gene products.

REFERENCES

1. Catherine CC. Diabetes-Vital Statistics. USA: American Diabetes Association. 1996: 65-8.
2. Harris MI. Diabetes in America, National Institute of Health, National Institute of Diabetes and Digestive and Kidney Disease. 2nd ed. NIH Publication, 95; 1995: 1468.
3. Consensus statement (ADA). *Diab Care*, 18, 1995, 1510-8.
4. Helping the pancreas produce insulin. [Online]. 2007 Sep 21 [cited 2011 Dec 10];Available from:URL: http://www.healthvalue.net/diabetespancreasbeta.html.
5. Simonson DC, Kourides IA, Feinglos M, Shamoon H, Fischette CT. Efficacy, safety, and dose-response characteristics of glipizide gastrointestinal therapeutic system on glycemic control and insulin secretion in NIDDM. Results of two multicenter, randomized, placebo-controlled clinical trials. The Glipizide Gastrointestinal Therapeutic System Study Group. *Diab Care*, 20, 1997, 597-606.
6. Lebov Citz HE, Leslie RD, Robbins DC. Diabetes: Clinical Science in Practice. New York: Cambridge University Press, 1995: 450-64.
7. Eurich DT, McAlister FA, Blackburn DF. Benefits and Harms of Antidiabetic Agents in Patients with Diabetes and Heart Failure: Systematic Review. *BMJ*, 335, 2007, 7618.
8. Haffner SM. Expert Column - A Diabetes Outcome Progression Trial (ADOPT). [Online]. 2007 Sep 21 [cited 2011 Dec 15]; Available from: URL:http://www.medscape.com/viewarticle/552484.
9. Kadhe G, Arasan RE. Advances in drug delivery of oral hypoglycemic Agent. *Current science*, 83(12), 2002, 1539-43.
10. Patel M, Sockan GN, Kavitha, Tamizh M. Challenges In The Formulation of Bilayered Tablets: A Review. *International Journal of Pharma Research and Development*, 2(10), 2010, 30-42.
11. Anisul Q, Karl KA. Comparative study of current Superdisintegrants. *Pharmaceutical Technology*, 2006, 1.
12. Rawlins EA. Bently's Text Book of Pharmaceutics, 8th edi. London, 1996: 269- 314.
13. Banker GS, Anderson IR. The Theory and Practice of Industrial Pharmacy. Mumbai: Varghese Publishing house; 1987: 293-345.
14. Chein YW. Novel Drug Delivery System. New York: Marcel Dekker Inc; 1982: 465- 574.
15. Gwen MJ, Joseph RR. Modern Pharmaceutics. 3rd edi. New York: Marcel Dekker; 72; 1996: 580-893.
16. Joseph RR. Sustained and Controlled Release Drug Delivery System. New York: Marcel Dekker; 1978.
17. Thomas wai YL, Joseph RR. The Science and Practices of Pharmacy. 20th ed. 1; 2001: 906-10.
18. Michihiro M, Matsuda M, Kohara K, Shimoda M, Yukiko K, Kazuhito T, Shigetoh M, Fumiko K, Kotani K, Kohei K. Pharmacokinetics and Pharmacodynamics of Glimepiride in type 2 diabetic patients: compared effects of once-versus twice-daily dosing. *Endocr J*, 54(4), 2007, 571-76.