Chapter

22 Insulin and Oral Hypoglycemic Agents

1. INTRODUCTION

A major portion of the **pancreas*** essentially comprises of glandular tissue which specially contains acinar cells that predominantly gives rise to the secretion of certain **digestive enzymes.** Besides, there also exist some '**isolated groups of pancreatic cells**' commonly known as the **islets of Langerhans** which usually made up of *four* cell types, each of which generates a **distinct polypeptide hormone**, namley :

(*a*) **Insulin** — in the beta (β) cells,

(*b*) **Glucagon** — in the alpha (α) cells,

(*c*) **Somatostatin** — in the delta (δ) cells, and

(*d*) **Pancreatic polypeptide** — in the PP or F cell.

Interestingly, the **β-cells** made up 60-80% of the **islets of Langerhans** most predominantly and distinctly.

Diabetes — a general term for diseases marked by excessive urination ; and is usually refers to *diabetes mellitus.*

However, the *clinical diabetes mellitus* invariably occurs in *two* forms, associated with different causes and methods of therapy.

Type 1 Diabetes : The **insulin-dependent diabetes mellitus (IDDM)**, normally takes place when the β-*cells* of the prevailing pancreatic *islets of Langerhans* are destroyed, perhaps by an **autoimmune, mechanism,** as a consequence of which the '**insulin production**' *in vivo* is overwhelmingly insufficient. Subjects undergoing such abnormalities in biological functions may show appreciable metabolic irregularity that may ultimately lead to develop **diabetic β-ketoacidosis** together with other manifestations of acute diabetes. Therapeutically Type-I diabetes is largely treated with **insulin.**

Type 2 Diabetes : The **noninsulin-dependent diabetes mellitus (NIDDM)**, *i.e.*, type 2 diabetes, is most abundantly linked with obesity in its adult patients largely. In such a situation, the **insulin** levels could be either elevated or normal ; and therefore, in short, it is nothing but a disease of abnormal **'insulin resistance'.** However, it has been duly observed that the impact of the disease is relatively

*Both an *exocrine* and *endocrine* orgin ; a compound acinotubular gland situated behind the stomach in front of the first and second lumbar vertebrae in a horizontal position, its head attached to the duodenum and its tail reaching to the spleen.

milder, occasionally leaving to **β-ketoacidosis** and may also be accompanied by certain other degenerative phenomena *in vivo.* The etiology of the condition bears a *strong genetic hereditary ;* and, hence, **insulin therapy** may not prove to be quite effective.

2. INSULIN-PRIMARY STRUCTURE

Sanger (in 1950s) put forward the primary structure of **insulin** as illustrated below in Fig. 22.1.

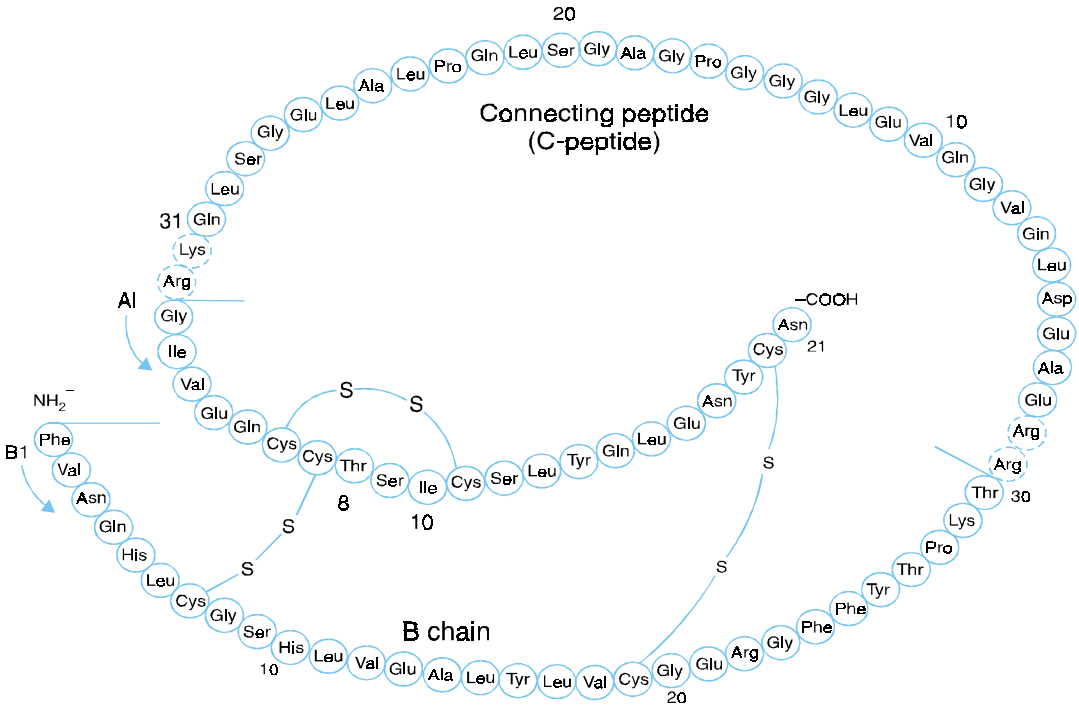

Fig. 22.1. Primary structure of proinsulin, depicting cleavage sites to produce insulin.

[Adapted from : **Foye's Principle of Medicinal Chemistry**, 5th International Student Edition, Lippincott Williams and Wlikin, New York, 2002]

The above Fig. 1 has the following **Salient Features,** namely :

(1) **Proinsulin** is the immediate precursor to **insulin** in the single-chain peptide.

(2) **Proinsulin** folds to adopt the 'correct orientation of the prevailing '**disulphide bonds**' plus other relevant conformational constraints whatsoever on account of its primary structure exclusively.

(3) **Proinsulin** in reality, has a precursor of its own, ***preproinsulin***–a **peptide**, that essentially comprises of hundreds of **'additional residues'.**

(4) At an emerging critical situation the **insulin** gets generated from ***proinsulin*** due to the ensuing cleavage of **proinsulin** at the *two points indicated.* This eventually produces **insulin,** that comprises of a **21-residue A chain** and strategically linked with **two disulphide bonds**

ultimately to a **30-residue B chain.** Interestingly, these bondages between the two aforesaid residual chains 'A' and 'B' are invariably oriented almost perfectly and correctly by virtue of the prempted nature of **proinsulin folding**.

2.1. Variants of Insulin Products

There are a number of variants of **insulin** products that are available as a **'drug'**, namely :

2.1.1. Insulin Injection

[***Synonyms*** **: Regular Insulin ; Crystalline Zinc Insulin**]

It is available as a sterile, acidified or neutral solution of **insulin**. The solution has a potency of 40, 80, 100 or 500 USP **Insulin Units** in each ml.

Mechanism of Action. It is a rapid-action insulin. The time interval from a hypodermic injection of this 'drug' until its action may be observed ranges between 1/2 to 1 hour. It has been observed that the duration of action is comparatively short but evidently a little longer than the plasma half-life that stands at nearly 9 minutes. Importantly, the duration of action is not linearly proportional to the size of the dose, but it is a simple function of the logarithm of the dose *i.e.*, if 1 unit exerts its action for 4 hours then 10 units will last 8 hours. In usual practice the duration is from 8 to 12 hour after the subcutaneous injection, which is particularly timed a few minutes before the ingestion of food so as to avoid any possible untoward fall in the prevailing blood-glucose level.

2.1.2. Isophane Insulin Suspension

[***Synonyms*** **: Isophane Insulin ; Isophane Insulin Injection ; NPH Insulin ; NPH Iletin** ;] :

The **'drug'** is a sterile suspension of **Zinc-insulin crystals** and **protamine sulphate** in buffered water for injection, usually combined in such a fashion that the *'solid phase of the suspension'* essentially comprises of crystals composed of **insulin**, **protamine***, and **zinc**.

Each mL is prepared from enough insulin to provide either 40, 80, or **100 USP Insulin units of insulin activity**.

Mechanism of Action. The **'drug'** exerts its action as an intermediate-acting insulin for being insoluble and obtained as repository form of insulin. In reality, the action commences in 1–1.5 hour, attains a peak-level in 4 to 12 hour, and usually lasts upto 24 hours, with an exception that '**human isophane insulin**' exerts a rather shorter duration of action. It is, however, never to be administered IV.

Note : Incidence of occasional hypersensitivity may occur due to the presence of 'protamine'.

2.1.3. Insulin Zinc Suspension

It is invariably obtained as a sterile suspension of insulin in buffered water for injection, carefully modified by the addition of zinc chloride ($ZnCl_2$) in such a manner that the *'solid-phase of the suspension'* comprises of a mixture of **crystalline** as well as **amorphous** insulin present approximately in a ratio of 7 portions of crystals and 3 portions of amorphous substance. Each mL is obtained from sufficient **insulin** to provide either 40, 80, or 100 USP Insulin Units of the **Insulin Activity.**

Mechanism of Action. It has been duly observed that the **'amorphous zinc-insulin component'** exerts a duration of action ranging between 6–8 hours, whereas the **'crystalline zinc-insulin component'**

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*The **protamine sulphate** is usually prepared from the sperm or from the mature testes of fish belonging to the genera **Oncorhynchus** Suckley, or **Salmo** Linne (*Family : Salmonidae*).

a duration of action more than 36 hour, certainly due to the sluggishness and slowness with which the larger crystals get dissolved. However, an appropriate dosage of the 3 : 7 mixture employed usually displays an onset of action of 1 to 2.5 hour and an intermediate duration of action which is very near to that of '**isophane insulin suspension**' (24 hour), with which preparation this **'drug'** could be employed interchangeably without any problem whatsoever. However, it must not be administered IV.

Note : The major advantage of 'zinc insulin' is its absolute freedom from '*foreign proteinous matter*', such as : *globin*, or *protamine*, to which certain subjects are sensitive.

2.1.4. Extended Insulin Zinc Suspension

[***Synonyms*** **: Ultra-Lente Iletin ; Ultralente Insulin/Ultratard**]

Mechanism of Action : The actual **'crystalline profile'** in this specific form are of sufficient size to afford a slow rate of dissolution. It is found to exert its *long-acting action* having an onset of action ranging between 4 to 8 hours, an optimal attainable peak varying between 10-30 hours, and its overall duration of action normally in excesss of 36 hours, which being a little longer than that of **Protamine Zinc Insulin.**

Note : Because the '*drug*' is free of both protamine and other foreign proteins, the eventual incidence of allergic reactions gets minimized to a significant extent.

2.1.5. Prompt Insulin Zinc Suspension

[**Synonyms : Semi-Lente Iletin ; Semitard**]

The '**drug**' is usually a sterile preparation of insulin in **'buffered water for injection'**, strategically modified by the addition of zinc chloride ($ZnCl_2$) in such a manner that the **'solid phase of the prevailing suspension'** is rendered amorphous absolutely.

Each mL of this preparation provides sufficient insulin either 40, 80, or 100 USP Insulin Units.

Mechanism of Action. The zinc-insulin in this particular form is a mixture of amorphous and extremely fine crystalline materials. As a result, the **'drug'** serves as a rapid-acting insulin with an onset of 1 to 1.5 hour, an attainable peak of 5-10 hours, and a duration of action ranging between 12-16 hours.

Note : Since this specific form of insulin is essentially free of any foreign proteins, the incidence of allergic reactions is found to be extremely low.

2.1.6. Lispro Insulin

[**Synonyms : Human Insulin Analog ; Humalog**] : It is a **human insulin** analogue of *r* DNA origin meticulously synthesized from a special nonpathogenic strain of *E. coli*, genetically altered by the addition of the gene for insulin lispro ; Lys (B28), Pro (B29). In fact, the prevailing amino acids at position 28 and 29 of **human insulin** have been reversed altogether.

Mechanism of Action. The *'drug'* is a very **rapid-acting insulin** which may be injected conveniently just prior to a meal. It exhibits an onset of action within a short span of 15 minutes besides having a relatively much shorter peak ranging between 0.5 to 1.5 hour, and having duration of action varying between 6 to 8 hours in comparison to the '**regular insulin injection**'.

2.1.7. Protamine Zinc Insulin Suspension

[***Synonyms :*** **Zinc Insulin ; Protamine Zinc Insulin Injection ; Protamine Zinc and Iletin** ;] :

The '**drug**' is a sterile suspension of insulin in buffered water for injection, that has been adequately modified by the addition of **zinc chloride ($ZnCl_2$)** and **protamine sulphate**. The **protamine sulphate**

is usually prepared from the sperm or from the mature testes of fish belonging to the genus *Oncorhynchus* Suckley or *Salmo* Linne (Family : *Salmonidae*). Each mL of the suspension prepared from sufficient insulin to provide wither 40, 80, or 100 USP Insulin Units.

Mechanism of Action. The '**drug**' exerts a long-acting action having an onset of action of 4 to 8 hour, a peak at 14 to 24 hour, and a duration of action nearly 36 hour. As a result this **'drug'** need not be administered with any definite time relation frame to the corresponding food intake. Besides, it should not be depended upon solely when a very prompt action is required, such as : in **diabetic acidosis** and **coma.** Since the *'drug'* possesses an inherent prolonged action, it must not be administered more frequently than once a day. It has been duly observed that **'low levels'** invariably persists for 3 o 4 days ; and, therefore, the dose must be adjusted at intervals of not less than 3 days. It is given by injection, normally into the **loose subcutaneous tissue.**

Note : The *'drug'* should never be administered IV.

3. ORAL HYPOGLYCEMIC AGENTS

The synthetic **oral hypoglycemic agents** have been added to the therapeutic armamentarium over the last five decades in lieu of the various **'insulin variants'** discussed earlier. In this particular section the focus shall be made on the different categories of **synthetic oral hypoglycemic agents** based on their chemical structures, namely :

(*i*) Sulfonylureas,

(*ii*) Non sulfonylureas,

(*iii*) Thiazolindiones,

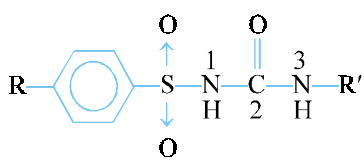
(*iv*) Bisguanides, and

(*v*) α-Glucosidase Inhibitors

The important **'drugs'** belonging to each of the above categories shall now be discussed individually in the sections that follows :

3.1. Sulfonylureas

The **sulfonylurea hypoglycemic agents** are basically sulphonamide structural analogues but they do not essentially possess any *'antibacterial activity'* whatsoever. In fact, out of 12,000 **sulfonylureas** have been synthesized and clinically screened, and approximately 10 compounds are being used currently across the globe for lowering blood-sugar levels significantly and safely. The **sulfonylureas** may be represented by the following general chemical structure :



Salient Features : The salient features of the **'sulfonylureas'** are as given below :

(1) These are urea derivatives having an arylsulfonyl moiety in the 1 position and an aliphatic function at the 3-position.

(2) The aliphatic moiety, R′, essentially confers lipophilic characteristic properties to the newer drug molecule.

(3) Optimal therapeutic activity often results when R′ comprises of 3 to 6 carbon atoms, as in **acetohexamide**, **chlorpropamide** and **tolbutamide**.

(4) Aryl functional moieties at R′ invariably give rise to toxic compounds.

(5) The R moiety strategically positioned on the **'aromatic ring'** is primarily responsible for the duration of action of the compound.

However, these agents are now divided into *two* sub-groups, namely :

(*a*) First-generation sulfonylureas, and

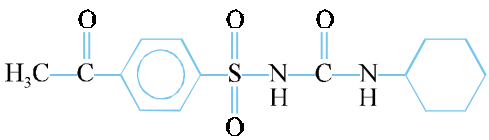
(*b*) Second-generation sulfonylureas.

These two aforesaid classes of **sulfonylureas** will be dealt with separately as under :

3.1.1. First-Generation Sulfonylureas

The various important drugs that belong to this category are, namely : **Acetohexamide** ; **Chlorpropamide** ; **Tolazamide** ; and **Tolbutamide**. These drugs shall be treated individually as under :

3.1.1.1. Acetohexamide BAN, USAN, INN



1-[(*p*-Acetylphenyl) Sulfonyl]-3-cyclohexyl urea ; USP ;

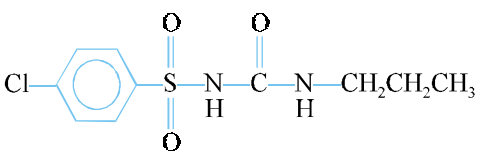
Dymelor(R) ;

It lowers the blood-sugar level particularly by causing stimulation for the release of endogenous insulin.

Mechanism of Action. The '**drug**' gets metabolized in the liver solely to a reduced entity, the corresponding **α-hydroxymethyl structural analogue**, which is present predominantly in humans, shares the prime responsibility for the ensuing hypoglycemic activity.

SAR of Acetohexamide. It is found to be an intermediate between **'tolbutamide'** and **'chlorpropamide'** *i.e.*, in the former the cyclohexyl ring is replaced by butyl moiety and *p*-acetyl group with methyl group ; while in the latter the cyclohexyl group is replaced by propyl moiety and the *p*-acetyl function with chloro moiety.

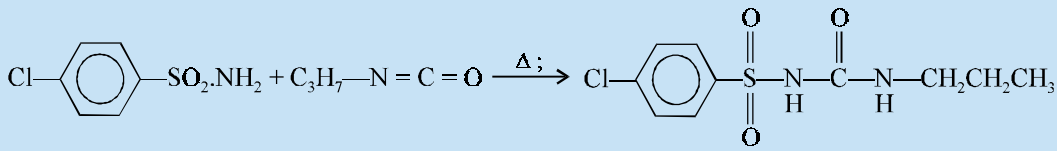
3.1.1.2. Chlorpropamide USAN, BAN, INN,



1-[(*p*-Chlorophenyl)-Sulphonyl]-3-propyl urea ;

Diabinese(R) ;

Synthesis



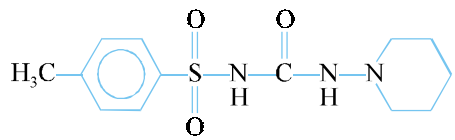
p-Chlorobenzene Sulphonamide — Propylisocyanate — Chlorpropamide

The interaction between *p*-chlorobenzenesulphonamide and phenyl isocyanate in equimolar concentrations under the influence of heat undergoes **addition reaction** to yield the desired official compound.

The therapeutic application of this **'drug'** is limited to such subjects having a history of stable, mild to mderately severe diabetes melitus who still retain residual pancreatic β-cell function to a certain extent.

Mechanism of Action. The **'drug'** is found to be more resistant to conversion to its corresponding **inactive metabolites** than is **'tolbutamide' ;** and, therefore, it exhibits a much longer duration of action. It has also been reported that almost 50% of the **'drug'** gets usually excreted as metabolites, with the principal one being hydroxylated at the C-2 position of the **propyl-side chain**.*

3.1.1.3. Tolazamide USAN, BAN, INN



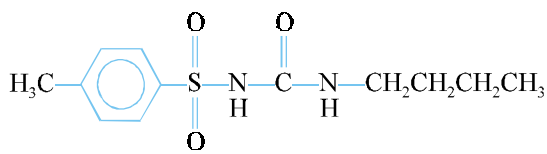
1-(Hexahydro-1H-azepin-1-yl)-3-(*p*-tolylsulphonyl) urea ;

Tolinase(R) ;

It is found to be more potent in comparison to **'tolbutamide'**, and is almost equal in potency to **chlorpropamide**.

Mechanism of Action. Based on the radiactive studies it has been observed that nearly 85% of an oral dose usually appears in the urine as its corresponding metabolites which were certainly more water-soluble than the parent **tolazamide** itself.

3.1.1.4. Tolbutamide

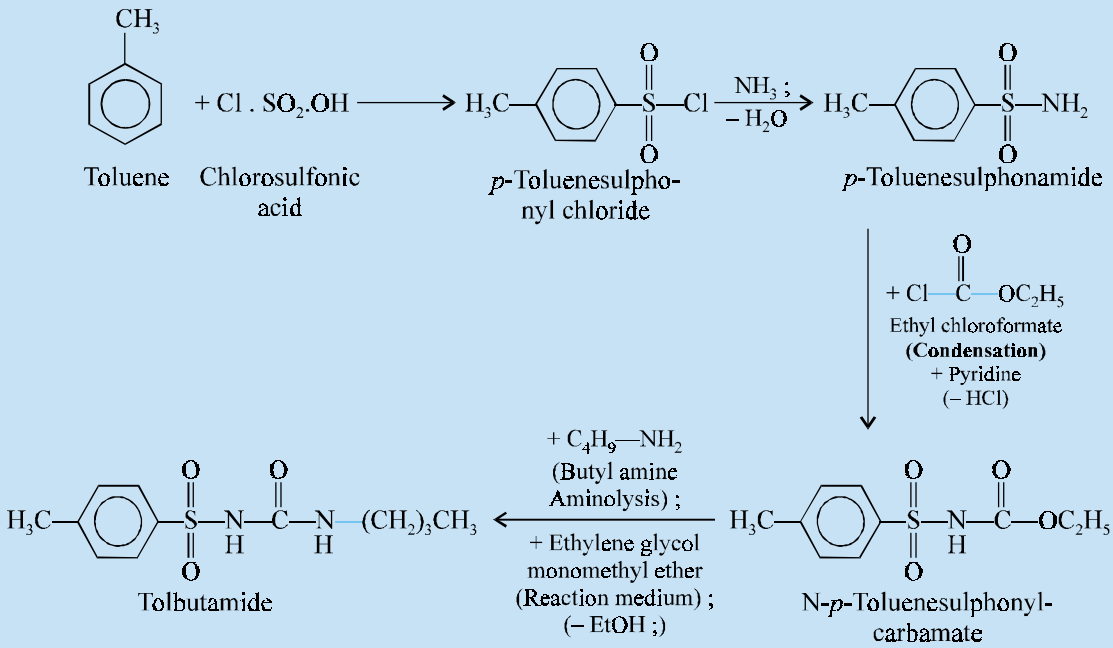


Benzenesulphonamide, N-[(butylamino) carbonyl]-4-methyl- ;

Orinase(R) ;

*Thomas RC *et al. J Med Chem*, **15,** 964, 1972**.**

Synthesis



First of all toluene is treated with chlorosulfonic acid to yield *p*-toluenesulphonyl chloride, which on treatment with ammonia gives rise to the formation of *p*-toluenesulphonamide. The resulting product on condensation with ethyl chloroformate in the presence of pyridine produces N-*p*-toluenesulphonyl carbamate with the loss of a mole of HCl. Further aminolysis of this product with butyl amine using ethylene glycol monomethyl ether as a reaction medium loses a mole of ethanol and yields **tolbutamide**.

It is mostly beneficial in the treatment of selected cases of **non-insulin-dependent diabetes melitus (NIDDM)**. Interestingly, only such patients having **some residual functional islet β-cells** which may be stimulated by this drug shall afford a positive response. Therefore, it is quite obvious that such subjects who essentially need more than 40 Units of insulin per day normally will not respond to this drug.

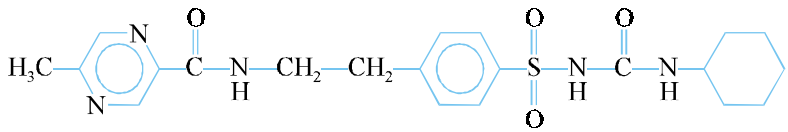
Mechanism of Action. The **'drug'** usually follows the major route of breakdown ultimately leading to the formation of butylamine and *p*-toluene sulphonamide respectively.

Importantly, the observed hypoglycemia induced by rather higher doses of the **'drug'** is mostly not as severe and acute as can be induced by **insulin ;** and, therefore, the chances of severe hypoglycemic reactions is quite lower with tolbutamide ; however, one may observe acute refractory hypoglycemia occasionally does take place. In other words, refractoriness to it often develops.

3.1.2. Second-Generation Sulfonylureas

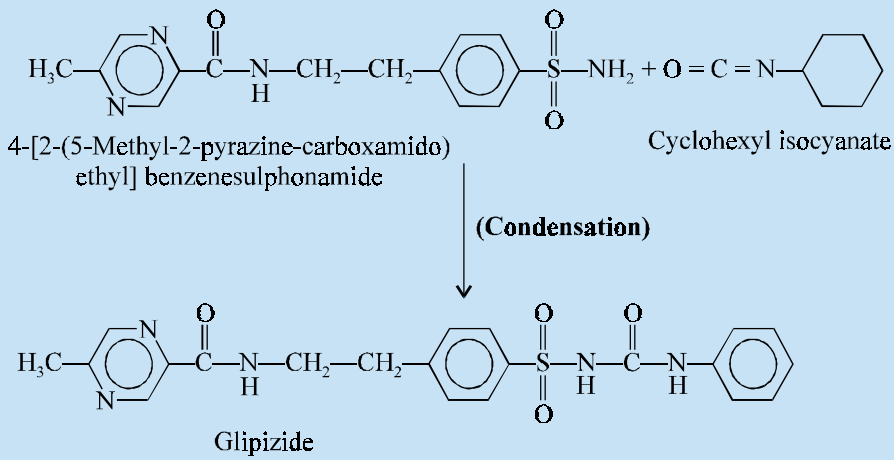
The vital and important members of this class of compounds are, namely : **Glipizide** ; **Glyburide** ; and **Glumepiride**. These drug substances will be dealt with separately in the sections that follows :

3.1.2.1. Glipizide USAN, INN



Pyrazinecarboxamide, N-[2-[4-[[[(cyclohexylamino) carbonyl] amino] sulfonyl] ethyl]-5-methyl-; Glucotrol$^{(R)'}$;

Synthesis



Glipizide may be prepared by the condensation of 4-[2-(5-methyl-2-pyrazine-carboxamido)-ethyl] benzenesulphonamide with cyclohexylisocyanate in equimolar proportions.

It is employed for the treatment of **Type 2 diabetes mellitus** which is found to be 100 folds more potent than **tolbutamide** in evoking the pancreatic secretion of insulin. It essentially differs from other oral hypoglycemic drugs wherein the ensuing tolerance to this specific action evidently does not take place.

Mechanism of Action. The primary hypoglycemic action of this **'drug'** is caused due to the fact that it upregulates the insulin receptors in the periphery. It is also believed that it does not exert a direct effect on **glucagon secretion.**

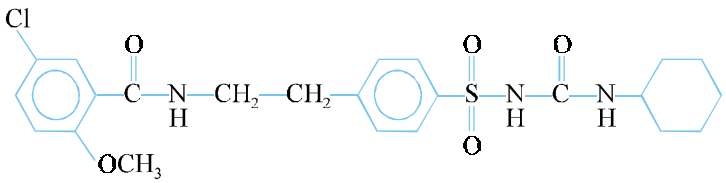
The '**drug**' gets metabolized *via* oxidation of the cyclohexane ring to the corresponding *p*-hydroxy and *m*-hydroxy metabolites. Besides, a *'minor metabolite'* which occurs invariably essentially involves the N-acetyl structural analogue that eventually results, from the acetylation of the primary amine caused due to the hydrolysis of the amide system exclusively by **amidase enzymes.**

Note : The '*drug*' enjoys *two* special status, namely :

(*a*) Treatment of non-insulin dependent diabetes mellitus (NIDDM) since it is effective in most patients who particularly show resistance to all other hypoglycemic drugs ; and

(*b*) Differs from other oral hypoglycemic drug because it is found to be more effective during eating than during fasting.

3.1.2.2. Glyburide USAN, INN



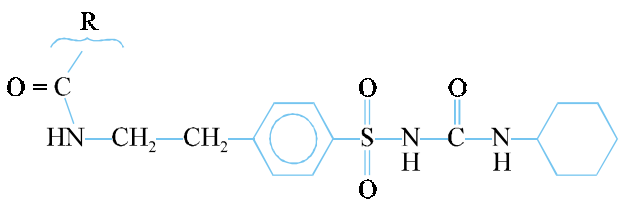
Benzamide, 5-chloro-N-[2-[4-[[[(Cyclohexylamino) carbonyl] amino] sulphonyl] phenyl] ethyl]-2-methoxy- ;

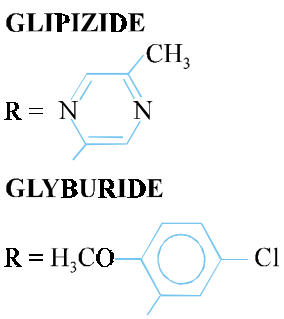
Dia Beta(R) ; Glynase Press Tab(R) ; Micronase(R) ;

It is mostly used for Type 2 diabetes melitus. It is found to be almost 200 times as potent as *tolbutamide* in evoking the release of **insulin** from the pancreatic islets. However, it exerts a rather more effective agent in causing suppression of *fasting* than *postprandial* hyperglycemia.

Mechanism of Action. The **'drug'** gets absorbed upto 90% when administered orally from an empty stomach. About 97% gets bound to plasma albumin in the form of a weak-acid anion ; and, therefore, is found to be more susceptible to displacement by a host of weakly acidic drug substances. Elimination is mostly afforded by *'hepatic metabolism'*. The half-life ranges between 1.5 to 5 hours, and the duration of action lasts upto 24 hours.

SAR of Glyburide. The SAR of **Glyburide** and **Glypizzide** are discussed below :

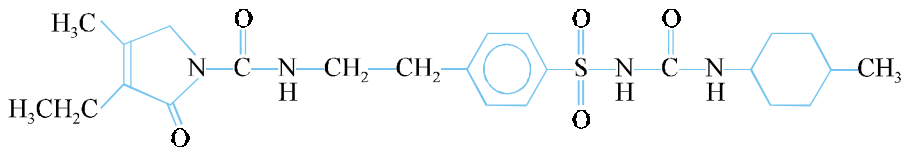




DRUG	pKa	Potency Compared to Tolbutamide
Glipizide	5.9	100 times more potent
Glyburide	5.3	200 times more potent

Obviously the presence of 'R' in **glyburide** potentiates the hypoglycemic activity 200 times, whereas the heterocylic nucleus in **glipizide** potentiates 100 times in comparison to tolbutamide.

3.1.2.3. Glimepiride USAN, INN



1-[[*p*-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido) ethyl] phenyl] sulphonyl]-3 (*trans*-4-methylcyclohexyl) urea ;

Amaryl$^{(R)}$;

Its hypoglycemic activity is very much akin to **glipizide**.

Mechanism of Action. The '**drug**' is found to be metabolized primarily through oxidation of the alkyl side chain attached to the pyrrolidine nucleus *via* a minor metabolic path that essentially involves acetylation of the amine function.

SAR of Glimepiride. The only major distinct difference between this '*drug*' and **glipizide** is that the former contains a five-membered **'pyrrolidine ring'** whereas the latter contains a six-membered **'pyrazine ring'.**

3.2. Non-Sulfonylureas-Metaglinides

Metaglinides are nothing but **non sulphonylurea oral hypoglucemic agents** normally employed in the control and management of **type 2 diabetes** (*i.e.*, **non-insulin-dependent diabetes mellitus, NIDDM**). Interestingly, these agents have a tendency to show up a quick and rapid onset and a short duration of action. Just like the **'sulphonylureas'**, they also exert their action by inducing insulin-release from the prevailing functional pancreatic β-cells.

Importantly, the mechanism of action of the **'metaglinides'** is observed to differ from that of the '**sulphonylureas**'. In fact, the mechanism of action could be explained as under :

(*a*) through binding to the particular receptors in the β-cells membrane that ultimately lead to the closure of ATP-dependent K^+ channels, and

(*b*) K^+ channel blockade affords depolarizes the β-cell membrane, which iN turn gives rise to *Ca^{2+} influx, enhanced intracellular Ca^{2+}*, and finally stimulation of **insulin** secretion.

Based on the altogether different mechanism of action from the two aforesaid '**sulphonylureas**' there exist *two* distinct, major and spectacular existing differences between these two apparently similar categories of *'drug substances'*, namely :

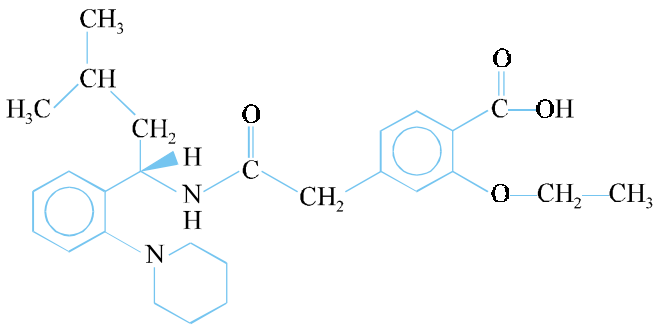
(*i*) **Metaglinides** usually produe substantially faster insulin production in comparison to the '**sulphonyl ureas**', and, therefore, these could be administered in-between meals by virtue of the fact that under these conditions pancreas would produce **insulin** in a relatively much shorter duration, and

(*ii*) **Metaglinides** do not exert a prolonged duration of action as those exhibited by the '**sulphonylureas**'. Its effect lasts for less than 1 hour whereas **sulphonylureas** continue to cause **insulin** generation for several hours.

Note : The glaring advantage of short duration of action by the metaglinides being that they possess comparatively much lesser risk of hypoglycemia in patients.

A few typical examples from this category are : **repaglinide**, **nateglinide** which would be treated as under :

3.2.1. Repaglinide USAN, INN



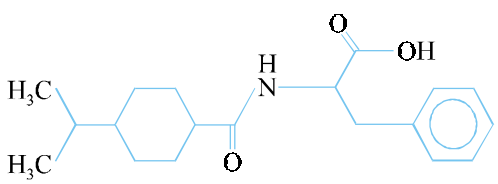
p-Toluic acid, (+)-2-ethoxy-α-[[(S)-α-isobutyl-*o*-piperidino-benzyl] carbamoyl]- ;

Prandin$^{(R)}$;

It is used in the control and management of **Type-2 diabetes mellitus**. It must be taken along with meals.

Mechanism of Action. The **'drug'** is found to exert its action by stimulating **insulin** secretion by binding to and inhibiting the ATP-dependent K^+ channels in the β-cell membrane, resulting ultimately in an opening of Ca^{2+} channels. It gets absorbed more or less rapidly and completely from the GI tract ; and also is exhaustively metabolized in the liver by *two* biochemical phenomena, such as : (*a*) glucuronidation ; and (*b*) oxidative biotransformation. Besides, it has been established that the **hepatic cytochrome P-450 system 3A4** is predominantly involved in the ultimate metabolism of **repaglinide**. However, this specific metabolism may be reasonably inhibited by certain drug substances', for instance : **miconazole**, **ketoconazole**, *and* **erythromycin**.

3.2.2. Nateglinide



N-(4-Isopropylcyclohexanecarbonyl)-D-phenylalanine ;

Starlix$^{(R)}$;

It is a phenylalanine structural analogue and belongs to the class of **'metaglinides'**. It is mostly employed in the control and management of **type 2 diabetes.**

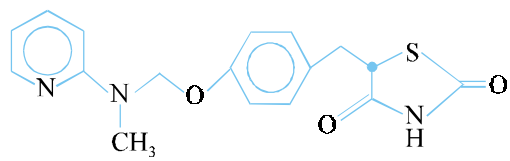
3.3. Thiazolindiones

The **thiazolindiones** exclusively designate a distinct and novel nonsulphonylurea group of potent hypoglycemic agents that are used invariably for the treatment of **NIDDM**. However, these **'drugs'** essentially needs a **'functioning pancreas'** which may give rise to the reasonably adequate secretion of insulin from β-cells, very much akin to the sulphonylureas. It has been observed duly that insulin may be released in *'normal levels'* from the β-cells ; however, the peripheral sensitivity to this particular hormone may be lowered appreciably. It has been amply established that **'thiazolindiones'** are highly selective agonists for the **peroxisome proliferator-activated receptor-r (PPARr)**, that is primarily responsible for improving **'glycemic control'** exclusively *via* the marked and pronounced efficacy of **insulin sensitivity** in the *adipose tissue* and *muscles.* Besides, they also prevent and inhibit the prevailing **hepatic gluconeogenesis.** In short, one may add that **thiazolindiones** invariably help to normalize blood-sugar level in two ways : (*a*) through glucose metabolism ; and (*b*) through reduction of the amount of **insulin** required to accomplish glycemic control.

Note : These agents are effective exclusively in the presence of 'insulin'

A few typical examples belonging to this class of compounds shall be discussed in the sections that follows :

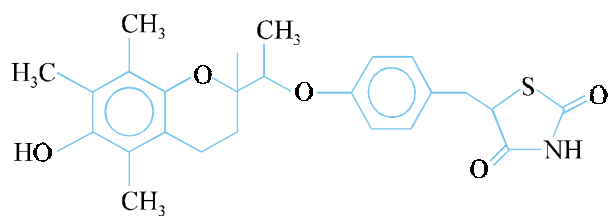
3.3.1. Rosiglitazone USAN



(±)-5-[[4-[2-(Methyl-2-pyridinylamino) ethoxy] phenyl] methyl]-2, 4-thiazolidinedione ; Avandia(R) ;

The **'drug'** has a single chiral centre (marked ●) ; and, therefore, exists as a racemate. Importantly, the enantiomers are found to be **'absolutely indistinguishable'** by virtue of their rapid *interconversion.*

3.3.2. Troglitazone



2, 4-Thiazolidinedione, (±)-5-[[4-[3, 4-dihydro-6-hydroxy-2, 5, 7, 8-tetramethyl-2H-1-benzopyran-2-yl) methoxy] phenyl] methyl]- ;

Rezulin(R) ;

The **'drug'** improves the responsiveness to insulin in such patients that experience **Type 2 diabetes mellitus** problems of **insulin** *resistance* initiated and sustained by a **'unique mechanism of action'** which is fairly comparable with those of other similar drugs. Importantly, it is at present **only approved for use with insulin.**

Mechanism of Action. The **'drug'** exerts its action by decreasing blood glucose in diabetic patients having *hyperglycemia* by improving target organ response to insulin. Besides, in the presence of both exogenous and endogenous insulin the **'drug'** minimizes the hepatic glucose output, enhances insulin-dependent glucose uptake, and finally lowers fatty acid output in adipose tissue.

It also gets bound to the nuclear receptors usually termed as **peroxisome proliferator-activated receptors** (**PPARs**) which predominantly regulate solely the transcription of a host of **insulin-responsive genes** that are found to be critical to **'glucose' and 'lipid' metabolism**.

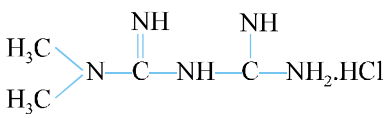
Note : The *'drug'* is not an insulin secretagogue.

Troglitazone is highly bound (> 99%) to serum albumin. It gets metabolized solely in the liver to several **inactive compounds,** including a *sulphate-conjugate*—a major metabolite, and mostly excreted in the faeces.

3.4. Bisguanides

The medicinal compounds included in this classification essentially comprise of two **'guanidine residues'** (*i.e.*, $H_2N—C(=NH)—NH_2$) joined together. A few typical examples belonging to this category, namely ; **metoformin**, **phenoformin**, are described as under :

3.4.1. Metoformin Hydrochloride USAN



Imidodicarbenimidic diamide, N, N-dimethyl-, monohydrochloride ;

Glucophage$^{(R)}$; Metiguanide$^{(R)}$;

It is used as an oral antihyperglycemic drug for the management of **Type 2 diabetes mellitus**. It is invariably recommended either as monotherapy or as an adjunct to diet or with a **sulphonylurea** (combination) to reduce blood-glucose levels.

Mechanism of Action. The **'drug'** is found to lower both basal and postprandial glucose. Interestingly, its mechanism of action is distinct from that of **sulphonylureas** and does not cause hypoglycemia. However, it distinctly lowers hepatic glucose production, reduces intestinal absorption of glucose, and ultimately improves **insulin sensitivity** by enhancing appreciably peripheral glucose uptake and its subsequent utilization. The **'drug'** is mostly eliminated unchanged in the urine, and fails to undergo hepatic metabolism.

3.4.2. Phenoformin

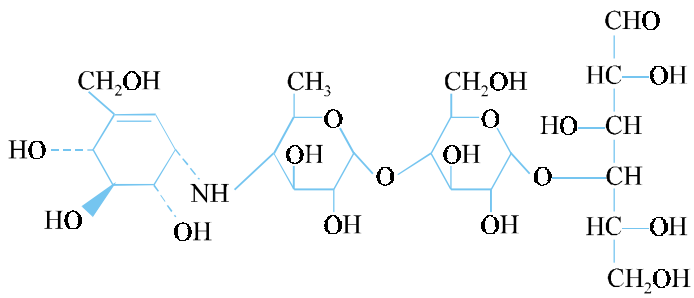
The **'drug'** is obsolete nowadays.

3.5. α-Glucosidase Inhibitors

It is quite well-known that the specific **enzyme α-glucosidase** is strategically located in the *brush-border* of the small intestine ; and, is exclusively responsible for affording cleavage of the dietary carbohydrates and thereby augmenting their rapid absorption into the body. Therefore, any means by which the inhibition of this enzyme is affected would certainly permit less-dietary carbohydrate to be available for absorption ; and, hence, less available in the blood-stream soon after ingestion of an usual meal. It has been observed that the prevailing inhibitory characteristic features of such agents are maximum for **glycoamylase,** followed by **sucrose**, **maltase** and **dextranase** respectively.

A few classical examples are discussed below :

3.5.1. Acarbose USAN, INN



Glucose, *o*-4, 6-dideoxy-4-[[[15-(1α, 4α, 5(3, 6α)]-4, 5, 6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl] amino]-α-*o*-glucopyranosyl-(1-4)-*o*-α-D-glucopyranosyl-(1-4)- ;

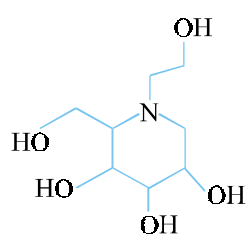
Precose(R) ;

It is used in the control and management of **Type 2 diabetes mellitus.**

Mechanism of Action. The '**drug**', which is obtained from the microorganism *Actinoplanes utahensis*, is found to a **complex oligosaccharide** that specifically delays digestion of indigested carbohydrates, thereby causing in a smaller rise in blood glucose levels soonafter meals. It fails to increase insulin secretion ; and its antihyperglycemic action is usually mediated by a sort of competitive, reversible **inhibition of pancreatic α-amylase membrane-bound intestinal α-glucosidase hydrolase enzymes.**

The **'drug'** is metabolized solely within the GI tract, chiefly by intestinal bacteria but also by diagestive enzymes.

3.5.2. Miglitol USAN, INN



1-(2-Hydroxyethyl)-2-(hydroxy-methyl)-[2R-(2α, 3β, 4α, 3β)]-piperidine ;

Glyset$^{(R)}$;

It also lowers blood-glucose level.

Mechanism of Action. It resembles closely to a sugar, having the heterocyclic nitrogen serving as an isosteric replacement of the *'sugar oxygen'*. The critical alteration in its structure enables its recognition by the **α-glycosidase as a substrate**. The ultimate outcome is the overall competitive inhibition of the enzyme which eventually delays complex carbohydrate absorption from the ensuing GI tract.

Probable Questions for B. Pharm. Examinations

1. (*a*) What are type-I and type-II 'Diabetes' ? Explain with some typical examples.

(*b*) Enumerate the various **'Salient Features'** of the *Insulin-Primary Structure.*

2. What are the various **'Insulin Products'** you have come across ? Discuss briefly any FIVE such products that are used abundantly.

3. How would you classify the 'Oral Hypoglycemic Agents' ? Give the structure, chemical name and uses of at least ONE potent compound that you have studied.

4. Give a brief account of the following with a few typical and important examples :

(*a*) First-Generation Sulfonylureas

(*b*) Second-Generation Sulfonylureas

5. How would synthesize the following 'Drugs' ? Explain the course of reaction(s) involved in the synthesis.

(*i*) Chlorpropamide

(*ii*) Tolbutamide

(*iii*) Glipizide

6. Explain the following :

(*i*) **Glyburide** is 200 times more potent than Tolbutamide.

(*ii*) **Glipizide** is 100 times more potent than Tolbutamide.

(*iii*) SAR of Glymepiride

(*iv*) Mechanism of action of Tolbutamide.

7. (*a*) Discuss the **'Metaglinides'** with regard to their specific 'mechanism of actions'.

(*b*) Give the structure and uses of any ONE of the following drugs :

(*i*) Repaglinide

(*ii*) Nateglinide.

8. Give a comprehensive account on **'Thiazolindiones'** with specific reference to the following potent **drugs** :

(*a*) Rosiglitazone

(*b*) Troglitazone.

9. Write a short note on the following **'oral hypoglycemic agents'** :

(*a*) Bisguanides ; and

(*b*) α-Glucosidase Inhibitors.