Al Chemistry Group Project
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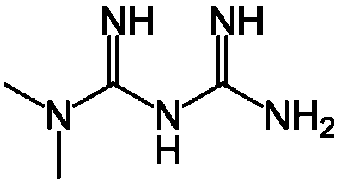
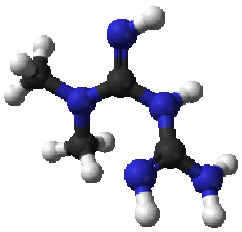
Drug: Metformin

-Introduction

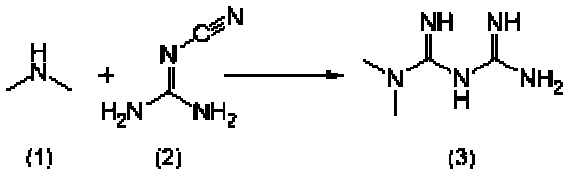
Metformin (*N*,*N*-dimethylimidodicarbonimidic diamide) is believed to be the most widely prescribed anti-diabetic drug in the world now. It reduces insulin resistance of peripheral tissue and allows muscle and adipose cells to utilize glucose at normal insulin levels, which is the first-line drug of choice for the treatment of type 2 diabetes. It suppresses hepatic glucose production, increases insulin sensitivity, enhances peripheral glucose uptake, increases fatty acid oxidation, and decreases absorption of glucose from the gastrointestinal tract. In the United States alone, more than 40 million prescriptions were filled in 2008 for its generic formulations.





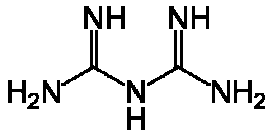
-Lead Compound discovery

Metformin was first discovered as a product in the synthesis of *N*,*N*-dimethylguanidine by Emil Werner and James Bellandin 1922. Later in 1929, it was found to reduce blood sugar. However,in the next two decades, as research shifted to insulin and other anti-diabetic drugs, the development of metformin stopped until the late 1940s.In 1950, metformin, unlike some other similar compounds, was found not to decrease blood pressure and heart rate in animals. That same year, a physician, Garcia, used it to treat influenza and discovered it can lower the blood sugar to minimum physiological limit and it is non-toxic. He also believed metformin to have bacteriostatic, antiviral, antimalarial, antipyretic and analgesic actions. Prompted by Garcia's report, a French diabetologist Jean Sterne tried to re-investigate the blood sugar lowering activity of metformin and several biguanide analogs. Sterne was the first to try metformin on humans for the treatment of diabetes and published his results in 1957.

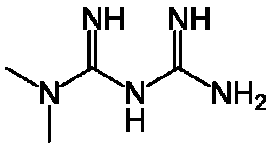


-Molecular modification

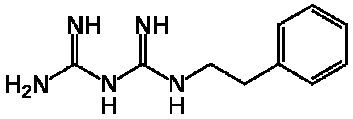
Galega officinalis (French lilac) was used for diabetes treatment in traditional medicine for centuries. In the 1920s, guanidine compounds were discovered in Galega extracts. Animal studies showed that these compounds lowered blood glucose levels, but were too toxic for human use. Initially phenformin derived from Galega officinalis was widely used, but its potential for sometimes fatal lactic acidosis. Maybe it is because the phenyl group present in it. Metformin, which has structure similar to phenformin (both belong to biguanide), is then used and found to be less toxic. The structures of biguanide, phenformin and metformin are shown below:



Biguanide



Metformin



Phenformin

-Formulation development

In diabetes treatment, metformin alone can work by decreasing glucose (sugar) production in the liver and decreasing absorption of glucose by the intestines. However, to make the treatment more comprehensive, patients are always treated by combination of metformin and other drugs. The followings are some examples that are oral type 2 diabetes medications that help control blood sugar levels in people who do not use daily insulin injections:

Metformin and repaglinide

Repaglinide lowers blood glucose by stimulating the release of insulin from the pancreas. It achieves this by closing ATP-dependent potassium channels in the membrane of the beta cells. This depolarizes the beta cells, opening the cells' calcium channels, and the resulting calcium influx induces insulin secretion. This combination is used together with diet and exercise to treat type 2 (non-insulin dependent) diabetes.

Metformin and pioglitazone

Pioglitazone can reduce insulin resistance in the liver and peripheral tissues; increase the expense of insulin-dependent glucose; decrease withdrawal of glucose from the liver; reduce quantity of glucose, insulin and glycated haemoglobin in the bloodstream. In this treatment, the amount of metformin and pioglitazone combination must be balanced .

Metformin and rosiglitazone

Rosiglitazone is a member of the thiazolidinedione class of drugs. Thiazolidinediones act as insulin sensitizers. They reduce glucose, fatty acid, and insulin blood concentrations. Rosiglitazone also appears to have an anti-inflammatory effect in addition to its effect on lowering insulin resistance. Thus, rosiglitazone helps your body use insulin better and it reduces the amount of insulin in your body.

Metformin and sitagliptin

Sitagliptin works to competitively inhibit the enzyme dipeptidyl peptidase 4 (DPP-4). This enzyme breaks down the incretins GLP-1 and GIP, which are the gastrointestinal hormones that released in response to a meal. Preventing the break down of these hormones, the hormones are able to potentiate the secretion of insulin and suppress the release of glucagon by the pancreas. This drives blood glucose levels towards normal.

-Safety test and human trials

Response to all diabetic therapies should be monitored by **periodic measurements of fasting blood glucose and glycosylated hemoglobin levels**, with a goal of decreasing these levels toward the normal range. During initial dose titration, fasting glucose can be used to determine the therapeutic response. Then, both glucose and glycosylated hemoglobin are monitored. Measurements of glycosylated hemoglobin may be especially useful for evaluating long-term control.

Initial and periodic **monitoring of hematologic parameters**, such as hemoglobin, hematocrit and red blood cell indices, and renal function should be performed, at least on an annual basis.

Human trials:

In a U.S. double-blind clinical study of Metformin hydrochloride tablets in patients with type 2 diabetes, a total of 141 patients received Metformin hydrochloride tablet therapy (up to 2550 mg per day) and 145 patients received placebo. Adverse reactions reported in greater than 5% of the Metformin hydrochloride tablet patients, and that were more common in Metformin hydrochloride tablet- than placebo-treated patients, are listed below.

Most Common Adverse Reactions (> 5.0 %) in a Placebo-Controlled Clinical Study of Metformin Hydrochloride Tablets Monotherapy		
Adverse Reaction	Metformin Hydrochloride Tablets Monotherapy (n = 141)	Placebo (n = 145)
	% of Patients	
Diarrhea	53.2	11.7
Nausea/Vomiting	25.5	8.3
Flatulence	12.1	5.5
Asthenia	9.2	5.5
Indigestion	7.1	4.1
Abdominal Discomfort	6.4	4.8
Headache	5.7	4.8

In addition, , the following adverse reactions were reported in ≥ 1.0 to ≤ 5.0% of Metformin hydrochloride tablet patients : abnormal stools, hypoglycemia, myalgia, lightheaded, dyspnea, nail disorder, rash, sweating increased, taste disorder, chest discomfort, chills, flu syndrome, flushing, palpitation.

Pediatric Patients:

In clinical trials with pediatric patients , the profile of adverse reactions was similar to that observed in adults.

Metformin hydrochloride tablets USP have been shown to effectively lower glucose levels in children (ages 10 to 16 years) with type 2 diabetes. However, Metformin hydrochloride tablets USP have not been studied in children younger than 10 years old.

Special conditions:

Patients should not take Metformin if they have the following problems, which may increase the chance of getting lactic acidosis.

- have kidney problems
- have liver problems
- have heart failure that is treated with medicines, such as digoxin or furosemide
- drink a lot of alcohol. This means you binge drink for short periods or drink all the time
- are seriously dehydrated (have lost a lot of water from your body)
- are going to have an x-ray procedure with injection of dyes (contrast agents)
- develop a serious condition, such as heart attack, severe infection, or a stroke

-Approval for marketing

Metformin was described in 1957 and became available in the British National Formulary in 1958. It was first marketed in France in 1979, but did not receive approval by the U.S. Food and Drug Administration (FDA) for Type 2 diabetes until 1994.

FDA Approval History (simplified) :

1995 - March 3 - **New molecular entity (NME)**
GLUCOPHAGE TABLET; ORAL (500MG, 850MG, 625MG, 750MG, 1GM)
Applicant: BRISTOL MYERS SQUIBB

2000 - October 13 - **New formulation**
GLUCOPHAGE XR TABLET, EXTENDED RELEASE; ORAL (500MG, 750MG)
Applicant: BRISTOL MYERS SQUIBB

2003 - September 11 - **New formulation**
RIOMET SOLUTION; ORAL (500MG/5ML)
Applicant: RANBAXY

2004 - April 28 - **New formulation**
FORTAMET TABLET, EXTENDED RELEASE; ORAL (500MG, 1GM)
Applicant: ANDRX LABS LLC

2005 - June 3 - **New manufacturer**
GLUMETZA TABLET, EXTENDED RELEASE; ORAL (500MG, 1GM)
Applicant: DEPOMED INC

2008 - October 20 - **New formulation**
RIOMET SOLUTION; ORAL (500MG/5ML)
Applicant: RANBAXY