



Secundum Artem

*Current & Practical Compounding
Information for the Pharmacist.*

COMPOUNDING FOR DIABETIC PATIENTS

GOALS AND OBJECTIVES

Goal: To provide supportive information to assist pharmacists to more effectively consult with physicians and to counsel diabetic patients concerning the treatment of complications that may accompany the disease.

Objectives: After reading and studying the article, the reader will be able to:

1. discuss the impact of diabetes on our society.
2. discuss the different types of diabetes and treatments indicated for diabetes.
3. describe the various complications that may accompany diabetes.
4. consult with physicians on some individualized compounded formulations that may be appropriate for complications experienced by specific diabetic patients.

INTRODUCTION

Did you know that in the United States:¹

1. Diabetes is one of the most costly health problems. The total costs, including health care and direct diabetes treatment costs as well as lost productivity, in 1997, ran 98 billion dollars. This includes 44 billion dollars in direct medical and treatment costs and 54 billion dollars in indirect costs attributed to disability and mortality. About 8.2% of all men and about 8.1% of all women in the U.S. have diabetes (undiagnosed in about 1/3 in both sexes).
2. There are 15.7 million diabetics in the U.S. (about 5.9% of the total population), including 10.3 million diagnosed diabetics and 5.4 million undiagnosed diabetics.
3. Daily, about 2,200 people are diagnosed with diabetes.
4. Diabetes is the 7th leading cause of death.
5. Diabetes is the leading cause of new cases of blindness in adults age 20-74, with 12,000 to 24,000 diabetics annually losing their sight because of diabetes.
6. Ten to 21% of diabetics develop kidney disease; diabetes is the leading cause of end-stage renal disease, responsible for about 40% of all new cases.
7. More than 56,000 amputations occur annually because of diabetes.
8. There are more than 77,000 diabetic deaths due to heart disease annually as a result of diabetes.
9. Diabetic nerve damage, which can lead to lower limb amputations occurs, in about 60-70% of diabetics. About 56,200 diabetics lose a foot or leg to diabetes annually.

10. Impotence affects about 13% of male Type I diabetics and 8% of male Type 2 diabetics. Over the age of 50, impotence rates as high as 50-60% have been reported.
11. About 10.8% of all African Americans have diabetes (undiagnosed in about 1/3 of them).
12. About 10.6% of all Mexican Americans have diabetes.
13. About 12.2% of Native Americans over 19 years of age have Type 2 diabetes.
14. About half of all diabetes cases occur in seniors 55 years and older.

DEFINITIONS

Diabetes is defined as a chronic syndrome characterized by abnormally high blood glucose levels and by defects in insulin production or utilization.² As can be seen from that definition, diabetes is not described as a single disease but as a "syndrome", composed of several specific diseases that are all characterized by hyperglycemia and a tendency to develop macro- and microvascular disease and neuropathy.

Under ordinary conditions, the cooperation and synergy of glucagon, somatostatin, growth hormone, cortisol, epinephrine and other hormones and endogenous insulin serve to maintain blood glucose levels between 50 and 150 mg/mL (mg%).² In the pancreas, the beta cells produce insulin and the alpha cells produce glucagon, the major hormones in control of glucose metabolism. When plasma glucose levels rise, as

after a meal, the pancreatic beta cells release insulin and the liver clears the hormone from the system. The insulin stimulates glucose storage in muscle and liver cells as glycogen, increases synthesis of fatty acids and triglycerides, decreases hepatic glucose output, stimulates lipolysis and production of ketone bodies and enhances incorporation of amino acids into proteins. Opposite to this, glucagon is released from the pancreatic alpha cells as a result of low blood glucose or high amino acid levels. This causes the breakdown of glycogen into glucose in the liver and a resultant rise in the blood glucose level.²

When all the systems are properly functioning, homeostasis and good health results. However, when the systems malfunction, diabetes can result. Some factors that are associated with the onset of diabetes include heredity, obesity, age, stress, hormonal imbalance, vasculitis of pancreatic blood supply vessels and viruses affecting the autoimmune responses of the body.²

TYPES OF DIABETES

There are four types of diabetes.

"Type I" (5-10% of diabetic patients) generally occurs during childhood or adolescence with an abrupt onset. Its primary cause is a pancreatic beta-cell deficiency resulting in impaired or absent insulin secretion. It is an auto-immune disorder and presenting symptoms include weight loss, tiredness, polydipsia, polyphagia, polyuria and possibly visual difficulties. Insulin is required in these patients. In addition, treatment includes a healthy diet (low in fat, moderate amounts of protein, high in complex carbohydrates) and exercise. A type I diabetic requires exogenous insulin to survive and maintain a healthy lifestyle; hence the name Insulin Dependent Diabetes Mellitus (IDDM).

"Type II" (85-90% of diabetic patients) generally occurs after about 35 years of age with a gradual onset. It commonly occurs in families with a history of diabetes. Its primary cause, a metabolic disorder, is either the insulin receptors become unresponsive to the action of insulin or there may be an insulin deficiency. Type II diabetes is nearly epidemic, probably due to an increased number of living older Americans and a greater prevalence of obesity and sedentary lifestyles. Type II diabetes is more common among African Americans, Latin Americans and Native Americans. In the Type II diabetic, the pancreas is usually producing insulin, but the body cannot utilize it properly, resulting in hyperinsulinemia and hyperglycemia. Interestingly enough, Type II diabetics may be symptom-free, at least in the initial stage of the disease. Insulin may be necessary in up to 20-30% of patients; others may be controlled by diet/exercise or by oral hypoglycemic agents. It has also been called Non-Insulin Dependent Diabetes Mellitus (NIDDM).

"Gestational onset diabetes" may occur in about 2-5% of pregnancies but is generally temporary, disappearing after delivery. It becomes evident after about 24 to 28 weeks of pregnancy. Of concern is that about 40% of these patients may progress to Type 2 diabetes.

"Other" (1-2% of diabetic patients) diabetics may result from a number of causes, including malnutrition, surgery, drugs, infections and other illnesses.

TREATMENT

Treatment of diabetes includes both pharmacologic and non-pharmacologic measures. Pharmacologic measures involve insulin and the oral hypoglycemic agents. Today's insulin is available in a form identical to human insulin and is available

in immediate acting and long acting forms. Mixtures can be prepared to tailor the insulin to the patient's needs. Pharmacologic measures also include the oral hypoglycemic agents, the sulfonylureas, biguanide, alpha glucosidase inhibitors, thiazolidinediones and meglitinide.

The sulfonylureas, glipizide (Glucotrol SL), tolbutamide (Orinase), tolazamide (Tolinase), glyburide (Diabeta) and glimepiride (Amaryl) act by stimulating the release of insulin from the pancreatic beta cells.

The biguanide, metformin (Glucophage) acts by decreasing liver glucose output and inducing a minor decrease in insulin resistance.

The alpha glucosidase inhibitors acarbose (Precose) and miglitol (Glyset) act by slowing the absorption of carbohydrates from the gastrointestinal tract.

The thiazolidinediones, or glitazones, pioglitazone-(Actos), and rosiglitazone (Avandia) act by decreasing insulin resistance and increasing insulin sensitivity.

Meglitinide, repaglinide (Prandin) acts by increasing insulin release from the pancreas.

Nonpharmacologic therapy has been divided into 5 categories: education, exercise, diet, blood glucose self-monitoring and others. Others include annual visits to an ophthalmologist and podiatrist, abstaining from smoking, monitoring blood pressure and blood lipids, patient assessment annually for the development of chronic diabetes complications and proper examination and care of the feet.³

Educational programs should include topics such as diet, exercise, self-monitoring of blood glucose, drug therapy, psychosocial issues, sick day activities, symptoms, hypoglycemia treatment and other patient-specific information.

Exercise is very important as it can aid in reducing blood glucose and improve circulation, generally resulting in a greater sense of well-being. Exercise activities at least three times weekly of the aerobic type are recommended. Exercise will also aid in achieving and maintaining normal body weight. The onset of Type 2 diabetes may be prevented or delayed by reducing lifestyle risk factors through weight loss and increased physical activity.

Diet therapy should include discussions of daily caloric intake, reduction of dietary fat (especially animal fats), increasing dietary fiber, moderating sodium and alcohol consumption as well as the daily intake of a vitamin/mineral/trace element supplement.

Self-monitoring of blood glucose is recommended by the American Diabetic Association. Consequently, patients need to be educated on drawing blood and how to correctly use, calibrate, clean and store their blood glucose meters.

COMPLICATIONS

Diabetes can result in three general types of problems: ketoacidosis, hypoglycemia and other complications. Pharmacists have been focusing on the prevention and treatment of ketoacidosis and hypoglycemia for years; today, there is increased emphasis on the prevention and treatment of complications from the disease. Complications in common with both Type 1 and Type 2 diabetics include retinopathy, neuropathy, renal failure and lower extremity disease.

Diabetic complications have been described as microvascular (involving retinopathy and nephropathy), macrovascular (including atherosclerosis and arteriosclerosis) and neuropathic. Neuropathic is further categorized as peripheral and autonomic. Peripheral neuropathy involves loss of function of nerves in the hands, feet and other peripheral tissues. Autonomic neuropathy involves loss of function of the nerves of the autonomic nervous system that can result in gastroparesis, constipation and other gastrointestinal and cardiovascular symptoms.

These complications provide the compounding pharmacist with numerous opportunities for compounding individualized medications, as detailed in the formulas presented later. According to Paul Lofholm, Pharm.D., the three primary-types of formulations being compounded include insulin mixtures, sugar-free preparations and foot-care preparations.⁴

PHARMACISTS WORKING WITH PATIENTS

Services that pharmacists can provide to diabetic patients include:

1. Educating them about diabetes, its causes, symptoms, prevention and treatment.
2. Diabetic ketoacidosis; its causes, symptoms, prevention and treatment.
3. Hypoglycemia; its causes, symptoms, prevention and treatment.
4. Hyperglycemia; its causes, symptoms, prevention and treatment.
5. Proper care of the feet.
6. Proper care of the eyes.
7. Proper care of the skin.
8. Use of blood glucose monitoring devices, their operation, care and cleaning.
9. Use of diabetic supplies, including lancets, alcohol swabs, syringes and insulin.
10. Use of glucose gels, glucose tablets and glucagon.
11. How to care for, mix and inject insulin.
12. Pre-filling insulin syringes; storage, handling and use.

Primary outcomes for which pharmacists can be actively involved in treating diabetes include preventing or relieving symptoms of diabetes, especially the complications. Self-care is vital to the proper treatment of diabetes. This can be enhanced and encouraged by pharmacists through educational programs and regular monitoring of the patients' medication needs and compliance.

TIGHT CONTROL

"Tight Control" is a program of intensive monitoring and maintenance of blood-glucose levels within narrow limits utilizing diet, oral medication or insulin. A special study, known as the Diabetes Control and Complications Trial (DCCT) showed that patients achieving tight control experienced a 50% reduction in the incidence of debilitating diabetes complications such as retinopathy, nephropathy and neuropathy.⁵ These study results were confirmed 5 years later in the United Kingdom Prospective Diabetes Study.⁶

The results of the studies have demonstrated that metabolic control is crucial and this should impact the diabetes health-care system to intensify treatment options to emphasize maintenance of normal blood sugar levels.

A program of tight control requires a significant investment of time and effort on the part of the patient and the caregivers, especially critical is patient education, self-monitoring of blood-glucose levels and regular checkups. Interestingly enough, managed care makes it more difficult for a dedicated program of "tight control".⁷

SUMMARY

It has been said that diabetes is a chronic disease without a cure. It can be a devastating disease to both the patient and the family. It requires a great deal of time, education and finances to properly care for a diabetic patient. Truly, comprehensive pharmaceutical care must incorporate pharmaceutical compounding to meet the individualized needs of patients with diabetes. As no two diabetics are alike, their therapeutic needs are different. Off-the-shelf products don't address individualized needs and nonavailability of needed preparations can only be met by individual preparations.

COMPOUNDING INSULIN MIXTURES

When it is necessary to compound insulin mixtures either by combining different types of insulin or diluting insulin to a lower concentration for use in insulin pumps, the following guidelines should be considered.

1. Regular insulin and NPH insulin can be mixed in any proportion (good for 30 days at room temperature).
2. Lispro insulin and NPH/lente insulin can be mixed (but should be injected immediately).
Note: Since lente insulin will bind with regular or lispro insulin (binding reaction starts immediately upon mixing and continues for up to 24 hours--resulting in decreased action of the regular insulin), it should either be injected immediately or allowed to stand for 24 hours before injection, routinely.
3. Lente and ultralente insulins may be combined in any ratio (good for 18 months if refrigerated).
4. Novo-Nordisk's Velosulin contains different buffers and should not be mixed with any lente preparation.
5. Using a dilution fluid to dilute regular insulin for pump use:
 - A. When using Lilly's Insulin Dilution Fluid, the regular insulin can be mixed in any ratio and will be stable indefinitely.
 - B. When using 0.9% sodium chloride injection to dilute insulin, it can be mixed in any proportion but should be used within 2-3 hours as there may be a change in pH and buffering that may adversely affect the stability of the insulin.
6. For pump use, Velosulin has an added phosphate buffer system that will minimize or prevent the crystallization of insulin in the tubing of insulin pumps.
7. The new basal insulin glargine, or Lantus, cannot be mixed with other insulins.

USEFUL FORMULATIONS FOR ORAL ADMINISTRATION

Rx Sugar-Free Suspension Structured Vehicle, USP

Xanthan gum	200 mg
Saccharin sodium	200 mg
Potassium sorbate	150 mg
Citric acid	100 mg
Sorbitol	2 g
Mannitol	2 g
Glycerin	2 mL
Purified water	qs 100 mL

1. Accurately weigh/measure each of the ingredients.
2. Using moderate heat, heat 30 mL of purified water in a beaker on a hotplate.
3. Stir to form a vortex and slowly sprinkle the xanthan gum into the vortex.
4. In a separate beaker, dissolve the saccharin sodium, potassium sorbate and citric acid in 50 mL of purified water.
5. Using moderate heat, incorporate the sorbitol, mannitol and glycerin into this mixture and then add to the previously prepared xanthan-gum dispersion.
6. Add sufficient purified water to volume and mix well.
7. Package and label.

(Text continued on fold over page)

Rx Oral Diabetic Vehicle

Sorbitol Solution 70%	50 mL
Methylparaben	200 mg
Propylparaben	50 mg
Flavor	qs
Methylcellulose 2% Soln	qs
	100 mL

1. Accurately weigh/measure each of the ingredients.
2. Mix the parabens and the desired flavor materials with a small quantity of glycerin.
3. Incorporate the sorbitol solution.
4. Add sufficient methylcellulose 2% solution to volume and mix well.
5. Package and label.

Rx Sorbitol Lollipop Vehicle

Active drug	qs
Sorbitol 70% Solution	99 mL
Saccharin sodium	150 mg
Flavor	qs

1. Accurately weigh/measure each of the ingredients.
2. Heat the sorbitol solution slowly until it reaches 150°C. Remove from heat.
3. When the temperature reaches about 100°C, incorporate the active drug, saccharin sodium and flavor.
4. Pour into lollipop molds that have been previously sprayed with a vegetable spray (Pam) providing a thin coating.
5. Allow to cool, package and label.

MODIFIED DEXTROSE SOLUTION FOR ORAL GLUCOSE TOLERANCE TEST

Rx Dextrose 50 g/100 mL

Dextrose, anhydrous	50 g
Citric acid	1.5 g
Lemon oil	0.01 mL
Ethanol 95%	2 mL
Methylparaben	10 mg
Propylparaben	3 mg
Purified water	qs
	100 mL

1. Accurately weigh/measure each of the ingredients.
2. Bring about 50 mL of purified water to boiling and add the methylparaben and propylparaben.
3. Add the dextrose with stirring until everything is dissolved; remove from heat.
4. Dissolve the lemon oil in the ethanol 95%.
5. Add the citric acid and lemon oil solution to step #3 and mix well.
6. Add sufficient purified water to volume.
7. Package and label.

USEFUL FORMULATIONS FOR MAINTAINING SKIN HYDRATION

Rx Glycolic Acid 10% Cream

Glycolic acid	10 g
Dermabase	90 g

1. Accurately weigh/measure each of the ingredients.
2. Mix the glycolic acid with a small quantity of glycerin or propylene glycol until smooth.
3. Incorporate the Dermabase and thoroughly mix.
4. Package and label.

Rx Lactic Acid 10%, Urea 10%, Glycolic Acid 10% Cream

Lactic Acid (88%)	11.4 mL
Urea	10 g
Glycolic acid	10 g
Dermabase	qs
	100 g

1. Accurately weigh/measure each of the ingredients.
2. Dissolve the lactic acid, urea and glycolic acid in about 15 mL of purified water.
3. Incorporate into the Dermabase and mix well.
4. Package and label.

USEFUL FORMULATIONS FOR FOOT CARE

Rx Foot Circulation Gel

Nifedipine	16 g
Diethylene glycol monoethyl ether	10 mL

NOTE: The nifedipine is very light sensitive so work quickly and in subdued light to minimize the exposure of the nifedipine to any light source.

1. Accurately weigh/measure each of the ingredients.
2. Mix the nifedipine with the diethylene glycol monoethyl ether.
3. Add the lecithin:isopropyl palmitate solution and mix well.
4. Add sufficient Pluronic F127 30% gel to volume and mix well using a shearing stress technique.
5. Package and label.

Rx Lanolin Foot Ointment

Lanolin	25 g
Aquabase	50 g
Wheat germ oil	10 g
Mineral oil	15 g
Aromatic oil	qs (optional)

1. Accurately weigh/measure each of the ingredients.
2. Using low heat (water bath), melt the lanolin.
3. Incorporate the Aquabase, wheat germ oil and mineral oil and mix well.
4. Remove from heat, add the aromatic oil and cool with intermittent stirring.
5. Package and label.

Rx Foot Cream

Glycerin	30 g
Purified water	30 g
Methylparaben	200 mg
Propylparaben	100 mg
Mineral oil	9 g
Petrolatum, White	20 g
Glycerol monostearate	3 g
Cetomacrogol 1000 BP	4 g
Lanolin	2 g
Stearyl alcohol	2 g

1. Accurately weigh/measure each of the ingredients.
2. Dissolve the parabens in a heated mixture of the glycerin and the purified water (about 60°C).
3. Heat all the remaining ingredients in a separate beaker to about 60°C.
4. Add the mixture from step #3 to the solution in step #2 with stirring while cooling.
5. Package and label.

USEFUL FORMULATION FOR TREATING DIABETIC NEUROPATHIC PAIN

Rx Ketamine HCl, Amitriptyline HCl and Gabapentin in PLO

Ketamine hydrochloride	5 g
Amitriptyline hydrochloride	2 g
Gabapentin	6 g
Diethylene glycol monoethyl ether	10 mL
Lecithin:isopropyl palmitate solution (1:1)	22 mL
Pluronic F127 30% gel	qs
	100 mL

1. Accurately weigh/measure each of the ingredients.
2. Mix the ketamine hydrochloride, amitriptyline hydrochloride and gabapentin with the diethylene glycol monoethyl ether.
3. Add the lecithin:isopropyl palmitate solution and mix well.
4. Add sufficient Pluronic F127 30% gel to volume and mix well using a shearing stress technique.
5. Package and label.

USEFUL FORMULATION FOR TREATING DECUBITUS ULCERS

Rx Topical Diabetic Skin Ulcer Cream

Misoprostol	2.5 mg
Phenytoin	2 g
Lidocaine	2 g
Glycerin	5 mL
Dermabase	qs 100 g

1. Accurately weigh/measure each of the ingredients.
2. Comminute the misoprostol, phenytoin and lidocaine to a fine powder.
3. Add the glycerin and mix to a smooth paste.
4. Add sufficient Dermabase, geometrically, to volume and mix well.
5. Package and label.

USEFUL FORMULATION FOR TREATING ORAL SORES

Rx Oral Sore Mouth Rinse

Misoprostol	1 mg
Lidocaine hydrochloride	500 mg
Methylparaben	200 mg
Glycerin	10 mL
Cherry flavor, anhydrous	1 drop
Syrup	40 mL
Sodium carboxymethylcellulose 0.25% solution	qs 100 mL

1. Accurately weigh/measure each of the ingredients.
2. Pulverize five of the 200- μ g misoprostol tablets.
3. Dissolve the methylparaben in the glycerin and add the lidocaine hydrochloride, pulverized misoprostol tablets and the cherry flavor.
4. Add the syrup and sufficient sodium carboxymethylcellulose 0.25% solution to volume and mix well.
5. Package and label.

USEFUL FORMULATION FOR GUM DISEASE

Rx Chlorhexidine 0.15% Solution

Chlorhexidine digluconate 20% solution	0.75 mL
Peppermint oil	2-3 drops
Propylene glycol	10 mL
Sorbitol 70% solution	10 mL
Aspartame	40 mg
Purified water	qs 100 mL

1. Accurately weigh/measure each of the ingredients.
2. Add the chlorhexidine digluconate, sorbitol 70% solution and aspartame to about 75 mL of the purified water and stir until dissolved.
3. Separately, mix the peppermint oil with the propylene glycol, then add to the solution in step #2.
4. Add sufficient purified water to make 100 mL and mix well.
5. Package and label.

USEFUL FORMULATION FOR TREATING OPHTHALMIC DRYNESS

Rx Sodium carboxymethylcellulose	1 g
0.9% Sodium chloride solution	99 g

1. Accurately weigh/measure each of the ingredients.
2. Slowly dissolve the sodium carboxymethylcellulose in the 0.9% sodium chloride solution.
3. Package, autoclave and label.

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