Advances in drug delivery of oral hypoglycemic agents

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Despite many advances in the development of oral hypoglycaemic agents, an ideal drug for treating Type 2 diabetes is still a distant reality. Today, physicians can choose from among a variety of medications targeting numerous facets of disease, but each drug class poses some problems. The age-old molecules such as sulfonylureas and biguanides are still considered drugs of choice because of their well-studied mode of action, safety, better tolerability and ideal pharmacodynamic effects. Until we find an ideal drug for Type 2 diabetes, there is much scope and interest for pharmaceutical companies to modify the phamacokinetics of older molecules in order to better suit larger sections of patients. This compilation is an attempt to describe the advances in drug delivery of oral hypoglycaemic agents, particularly the extended and sustained release formulations of glipizide and metformin, both of which have great promise in treatment of Type 2 diabetes mellitus.

PATIENTS with type 2 diabetes, formerly known as non-insulin-dependent diabetes mellitus (NIDDM), have increased morbidity and mortality mainly because of its chronic complications. Type 2 diabetes is associated with a loss of life of five to ten years[1]. Diabetes is currently the fourth leading cause of death by disease in the United States. Type 2 diabetes represents about 98% of all diabetes cases among persons older than 45 years of age[2], approximately 18% of persons 65 to 75 years of age and 40% of those older than 80 years of age[3].

There are two widely advocated hypotheses about the primary etiologic factor in type 2 diabetes. The first holds that a primary beta-cell defect causes insufficient insulin secretion, resulting in hyperglycemia. The peripheral tissues (primarily muscle and liver) are normally insulin-responsive at first, but may become insulin-resistant in response to ongoing hyperglycemia. The alternate hypothesis proposes that the basic underlying abnormality is insulin resistance in the peripheral tissues, occurring first in muscle tissue and later in the liver. The beta cells initially compensate to maintain normal glucose metabolism by increasing the amount of insulin that is secreted. However, in time, the demand exceeds the ability to compensate. This ultimately leads to pancreatic exhaustion. Considerable evidence exists for both theories. The first theory is supported by several studies showing abnormalities in insulin secretion and normal insulin action in patients with type 2 diabetes[4]. The second is supported by other studies that find insulin resistance (but normal glucose metabolism) in first-degree relatives of patients with type 2 diabetes[5].

Patients who are able to achieve good glycemic control with diet and exercise usually show significant improvement within six weeks and often have near-target blood glucose values within three months. However, this approach ultimately fails to control hyperglycemia in up to 90% of patients[6]. When a patient does not show reasonable improvement within six weeks to three months of intervention with diet and exercise, pharmacotherapy should be added to the treatment plan.

While each agent is effective in monotherapy, there are several factors that have to be considered before writing the prescription. The physician should review each of the drug options and weigh the clear benefits of each drug against cost, contraindications, degree of glycemic-lowering needed to achieve patient's goal, ease of compliance, duration of action, patient's weight and ideal weight, and patient's lipid profiles. The choice is not often clear cut[7].

Newer agents for type 2 diabetes

Until as recently as a decade ago, the only pharmacological treatments were oral sulfonylureas or insulin by injection, both of which act to heighten the patient's already elevated but insufficient insulin levels. Today, physicians can choose from among a variety of medications targeting numerous facets of the disease; the drugs that augment pancreatic insulin secretion, improve peripheral glucose disposal (as occurs in muscle and adipose tissue), decrease glucose release from the liver, or limit absorption of carbohydrate and fat from the gut.

New additions in antidiabetic agents

Benzoic acid derivatives (repaglinide)

Repaglinide stimulates insulin secretion in a different way from the sulfonylureas. It is rapidly absorbed and

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quickly metabolized in the body; this means that patients will need three doses each day. For many patients, this presents an inconvenience. Repaglinide seems to have little effect on lipids and can, like the sulfonylureas, cause weight gain and hypoglycemia[8].

Thiazolidinediones

The thiazolidinediones (TZDs) enhance insulin action in muscle, fat and other tissues and are known as insulin sensitizers. The major side effect, seen with troglitazone, the first TZD to be approved by the FDA, is liver damage. Other side effects of TZD are mild elevations of LDL (the 'bad') cholesterol and fluid retention – If you have heart trouble, TZDs may not be a good choice. TZDs do not cause hypoglycemia when used alone[9].

Glucosidase inhibitors

After you eat, the food is digested, and then passes into the bloodstream and, thus, the level of sugar in the blood rises. Glucosidase inhibitors act in the intestine to block the action of enzymes that are responsible for breaking down complex carbohydrates into simple sugars. Gastrointestinal side effects are common, affecting up to 30% of patients. Bloating, flatulence, diarrhea and abdominal discomfort and pain are the major complaints[10].

Thus, many new molecules are in the offing; their utility is limited either by their side effects and contraindications or by their fewer efficacies. Each drug class has a proportion of non-responders, requiring the selection of an alternative drug. Each drug class also has patients for whom the agents are contraindicated. In this scenario, sulphonylureas and biguanides, are age-old molecules in the therapeutic armamentarium for the management of diabetes mellitus.

New drug formulations for type 2 diabetes mellitus

The sulphonylureas and biguanides have well-established experimental, clinical documentation proving their safety, better tolerability and superior pharmacodynamic effects. Therefore, it is very interesting for pharmaceutical companies to modify the pharmacokinetics of these molecules in order to make them more patient convenient.

Fast but short-acting agents

The advantages of controlled release products are well known and documented in the pharmaceutical art. Advantages include the ability to maintain a desirable blood level of a medicament over an extended period, such as twenty-four hours, by minimizing the peak-to-trough variations in plasma concentrations. Reducing the number of administrations necessary to achieve a desired therapeutic effect increases patient compliance.

Agents which are fast acting but have very short half life resulting either in shorter duration of action or fluctuations in the plasma levels are the best candidates for controlled release formulation as this pharmacokinetic modification will not only preserve the fast action but also increase the T_{max} and thus, extending elimination half life.

Drug characteristics

Physical and chemical characteristics of the drug also, to a great extent decide its suitability for controlled release preparation. While many controlled and sustained release formulations are already known, certain moderately to poorly soluble drugs present formulation difficulties, which render them unsuitable for sustained release carriers, which might be acceptable for other drugs, such as those that are relatively soluble. It is often impossible to predict whether a particular sustained release formulation will provide the desired release profile for a relatively insoluble drug, and it has generally been found that it is necessary to carry out considerable experimentation to obtain sustained release formulations having the desired bioavailability when ingested, particularly for drugs that are poorly soluble in water.

An example of relatively insoluble drugs, which are difficult to formulate into controlled release formulations, is the sulphonylurea class of antidiabetic drugs. Sulfonylureas are effective to control blood sugar levels in diabetics, in particular, type II diabetic patients who are unable to achieve control through dietary restriction alone. Sulfonylureas are believed to stimulate the release of insulin from the pancreatic islet cells via receptors that are reported to be ATP sensitive potassium channels.

Pathophysiological needs

Further, oral controlled release delivery systems should ideally be adaptable so that release rates and profiles can be matched to physiological and chronotherapeutic requirements. Controlled release formulations should be developed taking into consideration the patient's habits and their physiological responses.

Extended release sulphonylurea formulations with improved dissolution properties, and particularly, extended release formulations of second generation sulfonylureas along with biguanides, are therefore desirable additions to the medical treatment of diabetes, including type II diabetes. Of these second generation drugs, efforts to provide controlled release have focused on glipizide and metformin.

Extended release glipizide. Glipizide is representative of the second generation sulfonylureas having being syn-

thesized in 1971. This compound appears to be the most effective insulin secretogogue both in first phase insulin secretion and in sustained stimulatory response during long term administration. A rise in immunoreactive insulin and decrease in blood glucose concentration level occur within 30 min of ingestion of glipizide on a weight basis. Glipizide is approximately 100 times more potent than tolbutamide[11]. Gastrointestinal absorption of glipizide is uniform, rapid and essentially complete, providing peak plasma level concentrations about 1–3 h after a single oral dose. Normal subjects demonstrate an elimination half-life ranging from about 2 to 4 h after both intravenous and oral administration. In addition, glipizide does not accumulate in the plasma following repeated oral dosing.

Differences in the pharmacokinetic and pharmacodynamic characteristic of the various sulphonylurea compounds produce different therapeutic and side effect profiles. Longer acting agents like glyburide (taken once or twice per day) or chlorpropamide (taken once a day) are efficacious but tend to produce more sustained hyperinsulinaemia and higher rates of hyperglycemia during routine clinical use. Conversely shorter acting sulphonylureas such as immediate release glipizide or tolbutamide are thought to be more efficacious in enhancing meal-stimulated insulin secretion and generally have a lower risk of hyperglycemia but often need to be taken more than once per day which may decrease compliance and produce greater chances in plasma drug levels both above and below the therapeutic range[12].

Dissolution profile. The extended release according to the present invention, releases glipizide in a controlled manner which provides an effect over a time period up to 24 h, and preferably for more than 18 h. Glipizide-sustained release formulations show the *in vitro* drug release characteristics as shown in Table 1 (ref. 13).

In vivo bioavailability study. An *in vivo* bioavailability study conducted on 12 healthy volunteers with sustained release tablets of the present invention containing 5 mg glipizide, shows well-sustained plasma levels of glipizide over 24 h with 50 to 60 ng/ml plasma concentration of glipizide after 24 h. The pharmacokinetic properties are depicted in Table 2.

Table 1. *In vitro* dissolution of glipizide extended release

Time (h)	Release (%)
1	2–4
2	9–13
4	23–29
6	37–45
8	48–59
10	59–69
12	72–85

In vivo bioequivalence study. The bioequivalence study was performed with the new extended release formulation of glipizide 10 mg in comparison with international reference formulation for all pharmacokinetic parameters, viz. maximum plasma concentration (C_{max}), time for C_{max} (T_{max}) and Area Under Curve [$AUC_{(0\rightarrow)}$]. The 90% confidence interval (CI) for test as well as reference formulation lies within the prescribed limits of 80–120% for all pharmacokinetic parameters. This shows that there may be less intra and inter-subject variations. This may improve the therapeutic response for this agent. Figure 1 shows the plasma drug concentration over time for test as well as reference formulation.

Extended release metformin. Metformin is a biguanide that has been used worldwide for the treatment of the Type 2 diabetes for last 4 decades. It improves glycemic control by enhancing insulin sensitivity in liver and muscle. It is not associated with hypoglycemia. Improved metabolic control with metformin does not cause weight gain and may lead to weight loss. Metformin also has beneficial effects on several cardiovascular risk factors such as dyslipidemia, elevated plasma plasminogen activator inhibitor, other fibrinolytic abnormalities, and hyperinsulinaemia and insulin resistance[14].

Metformin is not metabolized by the liver and excreted intact in urine. Elimination is characterized by a rapid initial phase during which ~ 90% appears in the urine within ~ 8–12 h and a slower elimination phase with a half-life of ~ 12–20 h (refs 15–17).

Table 2. Pharmacokinetic properties of glipizide extended release

Parameters	Glipizide extended release 5 mg	Immediate release glipizide 5 mg
C_{max}	415.7 ng/ml ± 22.75	310– 450 g/ml
T_{max}	5.67 h ± 1.37	1–3 h
AUC (0–24)	4181 ng/ml × min (± 380)	

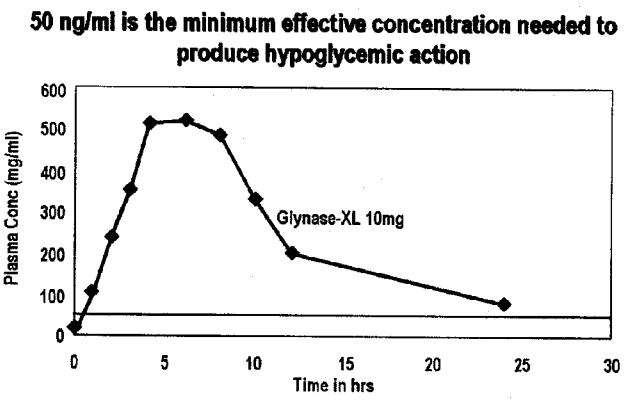

Figure 1. Plasma concentration vs time with glipizide extended release formulations.

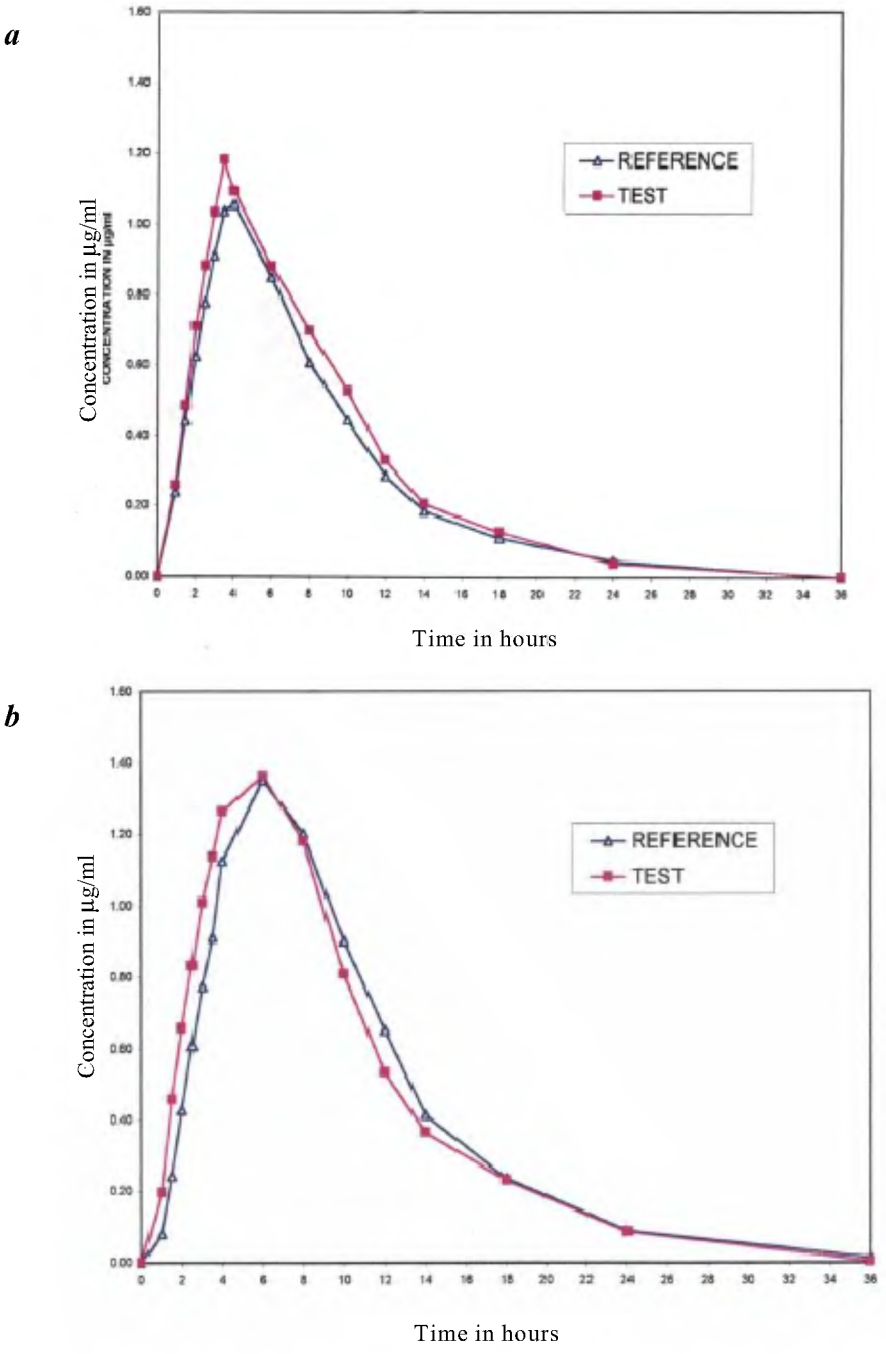

Figure 2. Plasma concentration vs time with metformin sustained release and conventional formulations in fasting as well as fed state. ***a***, Fasting state; ***b***, Fed state.

Metformin is generally given in divided doses two to three times a day. The usual starting dose is 500 mg twice daily. The dose should be increased or decreased by 250–500 mg/d every 2 weeks until the desired level of glycemic control is achieved or a maximum dose of 2000 mg/d is reached[18].

Taking into consideration its importance in therapeutics and its pharmacodynamic advantages over other agents, the sustained release preparation of metformin not only will offer improved patient's compliance but also may improve the path physiology of the disease. For many drugs it has been demonstrated that their pharmacodynamic action is related to their plasma concentration. Because of this critical relationship, the proof of bioequivalence of products is most important to assure equal therapeutic efficacy. This will also confirm the usage of the new formulation as therapeutic alternative to the reference formulation. The use of generic preparation of

therapeutically well established drug principle has to be justified by appropriate data as per the guidelines laid down by US FDA and other regulatory authorities.

A new sustained release formulation of metformin 1000 mg is manufactured and tested for its bioequivalence to international conventional metformin. The bioequivalence of metformin sustained release 1000 mg was performed against two tablets at a time of 500 mg of international formulation and found to be bioequivalent. This study was performed in accordance with USFDA guidelines for conducting bioequivalence[19]. The strict Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) was implemented as per guidelines[20].

The plasma metformin levels versus time of two formulations are depicted in Figure 2. This shows that the plasma levels over an approximate period of 18–24 h are maintained and are very similar. The C_{max}, T_{max} and $AUC_{(0\rightarrow)}$ are within CI interval limits of 80 to 120% and this is as per the acceptable criteria laid by USFDA.

Thus, it can be concluded that the plasma levels of sustained release metformin 1 g are similar to two tablets of 500 mg of conventional metformin in both fasting as well as fed state. Therefore, this formulation definitely can be used as a substitute for current 500 mg formulations. This might give same or improved efficacy and better compliance.

This will offer advantages like reduction in number of doses per day resulting in improved patient's compliance, sustained metformin levels which by reducing daily fluctuations may improve the pathophysiology of the disease (fasting hyperglycemia, hyperinsulinaemia and resistance of insulin action at liver and periphery) and it will be a good option for combination therapy along with other agents.

Conclusion

Though many new oral hypoglycemic agents are now available, there is difficulty of choosing the right medication for a longer period either because of their side effects and/or contraindication and non-responders during the management of such a chronic disorder. Sulphonylureas and biguanides are still the first preference of agents. Therefore, introduction of extended release glipizide and sustained release metformin will be very useful agents for the management of Type 2 Diabetes.

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