

Review Article

Recent Developments In Insulin Delivery For The Treatment of Diabetes Mellitus

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ABSTRACT

Diabetes mellitus is a chronic lifelong condition which affects millions of people in the world. The main cause of this disease is the pancreas will not producing insulin, "a hormone which regulates blood glucose level in the body", will leads to severe vascular complications and leads to death. The one and only way of survive against this disease is to provide exogenous insulin in our body. The conventional mode of delivering the exogenous insulin is by subcutaneous route by needles or injections which produces painful and invasive therapy leads to poor patient compliance. So various methods are developed for delivering the exogenous insulin in our body like inhaled insulin (Exubera), transdermal patch, insulin infusion pump and insulin sprays and insulin pills are available which uniform maintain blood glucose level in the body for several hours leads to increased patient compliance, So in present review we highlighted the novel methods of insulin delivery for the treatment of diabetes mellitus.

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INTRODUCTION: Diabetes mellitus is a metabolic disorder or chronic life condition in which there is high blood sugar level for longer period of time which leads to hyperglycemia, glycosuria or sometimes ketonaemia resulting in severe vascular complications which leads to death. The main causes of diabetes mellitus are either the pancreas not producing insulin or the cells of the body will not respond properly to insulin produced.¹⁻³ Current status of diabetic patients in world is predicted to be 171.2 million (2.8%) in 2000 and 366.2 million by the year 2030 (4.4%).⁴⁻⁶ Diabetes mellitus is of two types, Type-1 diabetes or simply called insulin dependent diabetes mellitus (IDDM), that are characterized by destruction of β -cells in pancreatic islets result in the pancreas failure. Type-2 diabetes or simply called non insulin dependent diabetes mellitus results in insulin resistance either due to abnormality in the gluco-receptor of β -cells or reduced sensitivity of peripheral tissues to insulin.^{2,3}

Insulin was discovered by Benting and Best, is a peptide hormone synthesized by β -cells in the pancreas as a single chain peptide known as preproinsulin (110 AA"s) from which 24 AA"s are removed to form Proinsulin. (figure1) Insulin basically contains two polypeptide chains made up from 51 amino acids; the A chain has 21, while B chain has 30 amino acids.⁷ The role of insulin in our body is to facilitate glucose transport across cell membrane and regulates the metabolism of carbohydrates and fats by increasing the glucose absorption from the blood to skeletal muscle. Failure, with respect to these functions will cause serious complications. Conventional insulin preparations are available and are given in table 1, but the resistance will develop due to lifelong treatment. So it is essential to modify the delivery of insulin in body to improve the efficacy and also to prevent from severe diseases like diabetes mellitus. So in present review, we highlighted some novel strategies to deliver insulin for the treatment of diabetes mellitus

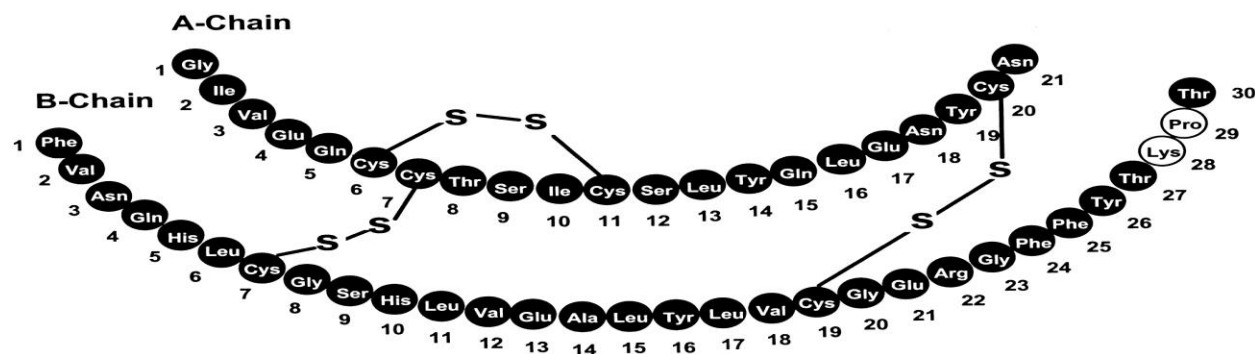


Figure1: The A chain (21 AA"s) and B chain (30 AA"s) are linked with a disulfide linkage and form two polypeptide chains.⁷

Type	Insulin Preparations	Physical properties (Appearance)	Duration (hrs)	Can be mixed with
Rapid Acting	Insulin lispro	Clear	3-5	Regular, NPH
	Insulin aspart	Clear	3-5	Regular, NPH
	Insulin glulisine	Clear	1-2	Regular, NPH
Short Acting	Regular (soluble) insulin	Clear	6-8	All Preparations will mixed except insulin glargine
Intermediate acting	Insulin zinc suspension or Lente insulin	Cloudy	8-10	Regular

	Neutral protamine Hagedron (NPH) or isophane insulin	Cloudy	8-10	Regular
Long acting	Protamine zinc insulin (PZI)	Cloudy	24-36	Regular
	Insulin glargine	Clear	24	None

Table1: Available insulin preparations in the market.³

There are number of drugs (oral hypoglycemic) available in the market are given in table 2, for the treatment of diabetes mellitus, but its only provide symptomatic relief, instead to providing permanent relief because the pancreas will fail to produce insulin in the body which control glucose level in blood. It is more worsen in fed conditions, where blood sugar level rises steeply and then difficult to control.

ORAL HYPOGLYCEMICS				
Sulfonylureas	Biguanides	Meglitinide/Phenylalanine analogues	Thiazolidinediones	α -glucosidase inhibitors
First generation Tolbutamide Chlorpropamide	Metformin	Repaglinide	Rosiglitazone	Acarbose
Second generation Glibenclamide Glipizide Gliclazide Glimipride	Fenformin	Nateglinide	Pioglitazone Troglitazone	miglitol

Table 2: Oral hypoglycemic for treatment of Type-2 diabetes mellitus.²

Oral hypoglycemic are also categorized into two groups. Group-1 drugs reduce plasma glucose by stimulating insulin production, also known as insulin secretagogues. Examples are first and second generation sulfonylureas and meglitinide/D-Phenylalanine analogues. Group-2 drugs reduce blood glucose without stimulating insulin production, also known as non insulin secretagogues. Examples are biguanides, thiazolidinediones and α -glucosidase inhibitors

Problems in current insulin delivery

Exogenous insulin is the one and only method to maintain blood glucose levels in body, but due to frequent administration and short duration of action will lead to inadequate blood glucose levels. Recent findings suggest that if a person suffering from diabetes mellitus, he will take insulin injections 60000 times throughout his life.⁸ Also the subcutaneous route for insulin delivery will more painful will lead to decrease patient compliance. Such non invasive and intensive technique will motivate researchers to develop novel methods for insulin delivery that will lead to increase patient compliance. Table 3 shows summary of current available techniques for insulin delivery.⁹⁻¹¹

Insulin delivery devices	Delivery mechanism	Advantages	Disadvantages
Insulin syringes and needles	Injection (subcutaneous route)	Less expensive, microfine needles is available	Painful treatment, poor patient compliance

Insulin infusion pumps	Insulin delivered into the body by the pump through a thin plastic tube	Greater accuracy and flexibility, tight control of blood glucose levels	Very expensive
Insulin jet injectors	Insulin delivered as fine stream transcutaneously at high pressure	No needles involved, Painless treatment	Insulin levels is decreased with frequent administration
Insulin pens	Contains insulin container and syringe into a single unit that provide continues infusion	Greater flexibility, better glycemic control, improved patient compliance	Not available for all insulin types
Mouth spray	Deliver insulin through an aerosol spray	Continues infusion and better glycemic control	High cost, Only selective preparations are available
Transdermal patch	Deliver insulin through skin via stratum corneum with the aid of ultrasound	Faster and uniform insulin delivery	Technology is very costly, Skin irritation

Table 3: Currently available insulin devices¹⁰⁻¹³

MODIFICATION OF CURRENT INSULIN PREPARATIONS

- 1. Pegylated insulin lispro:** The main limitation of exogenous insulin is excreted through glomerular filtration leads to increased renal clearance and short half life. Insulin lispro is modified by bound to Polyethylene glycol (PEG) chain resulting in large bulky molecule which hinders its excretion through glomerular route. Pegylated insulin having less renal excretion which leads to more insulin stays in the body for longer period of time (>36 hours). Studies shows that Pegylated insulin lispro has wide duration of action as compare to insulin glargine.¹⁶ In comparison to exogenous insulin, Pegylated lispro has less concentration in peripheral tissues which leads to lesser side effects. Researchers also finds that PEG-lispro gives morning produces uniform blood glucose levels similar to insulin glargine. In Phase 2 trials, Patient receiving PEG-lispro will have 12% higher risk of hypoglycemia than other insulin analogs.¹⁴⁻¹⁶
- 2. Ultra-rapid acting insulins:** These rapid insulins are quickly absorbed over a short duration of time and provide faster glycemic and blood glucose level controlled as compare to conventional formulations. Currently available preparations are Insulin aspart, Insulin lispro and Insulin glulisine. Insulin aspart is a novel molecule that is under evaluation in Phase 3 clinical trials but provide good results in Type-1 diabetes mellitus. Another rapid acting insulin is under clinical trials is BIOD-123, is a formulation of recombinant insulin and magnesium sulfate which gives faster absorption rates as compare to other analogues.^{17,18}
- 3. Co-administration of Insulin with Incretin:** Combining insulin analogue with incretin will provide controlled diabetic conditions as compare to other combinations. The synergistic nature of this

combination will provide less risk of hypoglycemia and weight gain. Studies find that combining insulin detemir to liraglutide and metformin leads to improved glycemic control as compare to metformin and liraglutide alone.¹⁹

4. **Addition of Hyaluronidase:** Hyaluronidase is a molecule produced from recombinant technology. Addition of Hyaluronidase will significantly increase the speed of absorption of insulin to provide better glycemic controls. Studies find that hyaluronidase combines with insulin lispro, aspart or glulisine shows ultra rapid action profile in healthy subjects.^{20,21}
5. **Insulin glargine/lixisenatide fixed combination:** This combination is the agonist of glucagon –like peptide-1 agonist developed by sanofi. The dose of both the combination is set flexibly according to patient need and severity of the disease in which one of the dose of this combination will controlled by other drug to provide therapeutic effect.²²

RECENT ADVANCEMENTS IN INSULIN DELIVERY

The current insulin delivery techniques will provide better glycemic controls in type-2 diabetes mellitus but these techniques have also some limitations which hinder its efficacy. So researchers are focused on more advanced techniques for insulin delivery orally as well as topically. Techniques like polymeric and chitosan nanoparticles, Pluronic micelles, liposomes, Self nanoemulsifying drug delivery system are served as effective drug delivery system for oral delivery of insulin. Table 4 gives summary of all of these techniques used for oral and topical insulin delivery

Table 4: Studies shows novel methods for insulin delivery

Method for insulin delivery	Delivery mechanism	Significance	Reference
Microneedles (Transdermal delivery)	Microneedles creates small holes from which topical formulation will be administered	Faster absorption rates as compare to oral insulin and provide better glycemic controls	23
Closed loop insulin delivery	Automated insulin delivery through computer chip in the form of closed loop	Automation provides better glycemic controls	24
Modified chitosan nanoparticles	Drug loaded particles will efficiently deliver insulin into blood vessels	Improved targeting with reduced toxicity	25
Self-nanoemulsifying drug delivery system	Drug encapsulate into the globules leads to improved bioavailability	Improved encapsulation efficiency and <i>in-vitro</i> drug release	26
Chondroitin-sulfate capped gold nanoparticles	After loading into CS nanoparticles leads to improve targeting	Improved glucose levels with reduced cytotoxicity	27
Pegylated starch acetate nanoparticles	The hydrophobic polymer provides controlled drug delivery by releasing the drug in sustained manner	Enhanced encapsulation efficiency	28
Pluronic P-85/Poly (lactic acid) vesicles	Insulin loaded P-85-PLA vesicles deliver insulin in a controlled manner	The blood glucose concentration increasing slowly to	29

		31.8% at 10.8 hrs	
Biotinylated liposomes	Biotin conjugated phospholipids deliver insulin in a time specific manner	Increased cellular uptake and enhancer gastrointestinal transport	30

Table 5: List on insulin formulation or dosage forms patented

Insulin Product/dosage form patented	Route of Administration	Manufacture or research institute	Reference
Computer chip controlled insulin pump	Implantable type	Researchers from Delaware university	31
Oral formulation (Liposomal)	Peroral	Stefanov and others	32
Insulin capsule	Peroral	Unigene lab.inc.	33
Ocular insert	Ocular	Lee and others	34
Aerosol delivery	Pulmonary	Aradigm Corporation	35
Oralin	Transmucosal	Generex biotechnology	36
Buccal formulation	Transmucosal	Del Rx	37
Nasal technology	Internasal	West pharmaceutical services	38
Suppositories	Rectal	Honsy and others	39
Lingual spray	buccal	Flemington pharmaceutical corporation	40
Electrophoresis	Transdermal	Cygnus pharmaceuticals	41
Transdermal patch	Transdermal	Vector medical technologies	42
Sonophoresis	Transdermal	Encapsulation systems	43
Micropor™	Transdermal	Helix Biopharma corporation	44
Transfersulin	Transdermal	Ima Rx technologies	45

Novel developments in insulin delivery

Oral insulin capsule for Type-2 diabetes mellitus: Diabetic patients will struggle everyday for maintain their blood sugar level daily. Injectable insulin will have poor patient compliance for their painful and invasive treatment. So luckily, Oramed pharmaceuticals just receive approval from the U.S food and drug administration to ship their experimental drug ORMD 0801 (Oral insulin capsule), given orally for the treatment for the treatment of Type-2 diabetes mellitus. This drug has a potential to delay progression at earlier stages of treatment and also effective for late stage complications.⁴⁶

Insulin smart patch: Researchers at the University of North Carolina will create a smart patch is another alternative to injectable insulin. This smart patch work smartly in releasing the high dose of insulin whenever

body needs. This patch tested on preclinical trials found that it maintains the blood sugar level for several hours. Also it is non toxic and high biocompatible, will give the promising insulin delivery for diabetic patients.⁴⁷

Tresiba (a long acting insulin drug): FDA just accepted the resubmitted application of tresiba, a long acting insulin drug known as degludec. Data generated from clinical trials found that it has an predictable annual sale of 2.2 billion by 2020. Tresiba is suitable for treating patient of 18 years or upper age. It is taken subcutaneously for once a daily. Tresiba will maintain blood glucose level lasts up to 42 hours due to the presence of hexadecanedioic acid which will form soluble insulin hexamers which will provide slower release and main long lasting glucose level, will make this drug more versatile to conventional insulin therapy.⁴⁸

Insulin Pills: Insulin pills or tablets, will be the another alternative to conventional injectable insulin for the treatment of diabetes mellitus. These pills will in clinical trials produce satisfactory results and several companies will racing to establish as a novel technology for patient compliance, as compare to injectable delivery.⁴⁹

Insulin Vaccine: Type 1 diabetes occurs when the defense mechanism of the immune system attacks itself on the cells of the pancreas which produces insulin, a hormone which maintain blood sugar level in the body. The conventional therapy will focus on exogenous insulin to maintain blood glucose level, which the patient will take for a lifetime. Type-1 diabetes is more pronounced genetically when the immune system start attacking the normal cells of pancreas, so scientists will understand the concept of Type-1 autoimmunity that produces high risk of Type-1 diabetes mellitus and produces novel vaccine which triggers immune response and produces auto antibodies that produces self defense mechanism for protection against Type-1 auto immunity attack. Researchers led by Professor Mark Peakman and Professor Colin Dayan are currently conducting a multi-centre trial of a vaccine which they hope will trigger an immune response to protect against Type 1 diabetes.⁵⁰

Insulin Exubera: A revolution to insulin delivery

Insulin exubera is a type of inhaled insulin in the form of dry powder that will specially design to deliver the powdered insulin to human alveoli. It is also known as “Titanic of NDDS” and is first marketed by Eli-lily and Pfizer. This concept of inhaled insulin delivery was successful in terms of efficacy and patient acceptability, but after some time, USFDA will withdraw this product in market forcefully due to many reasons like poor bioavailability, dose dumping and cost is 5 fold higher then subcutaneous injections.⁵⁰



Figure 2: Exubera inhaled drug delivery system.⁵⁰

In patients with Type 2 diabetes, exubera insulin works successfully in maintaining blood glucose level up to several hours in a day. A 6 months, randomized study was conducted for insulin exubera to evaluate the reduction in HbA_{1c} count as compare to oral agents. The results (figure 3) were indicated 10 fold reduction in HbA_{1c} count in exubera insulin therapy.

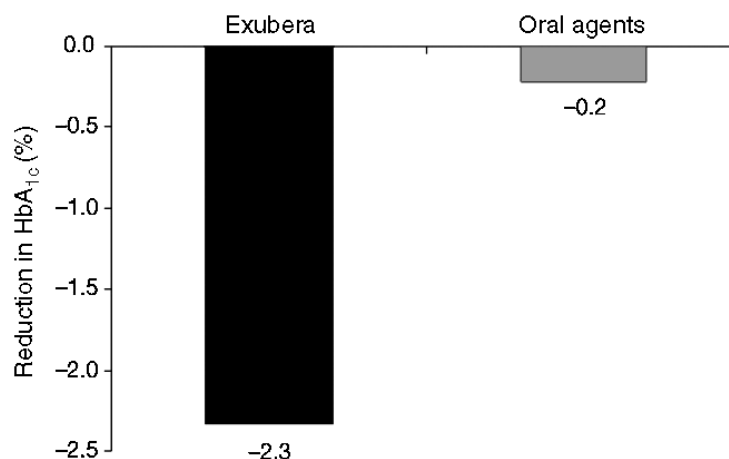


Figure 3: Better glyceic controls in Exubera insulin as compare to oral agents in a randomized study. Reproduced from 50

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