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Review Article

Narrative Review: A Rational Approach to Needle Free Insulin Technology

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ABSTRACT

Needle free injection techniques can be used to administer vaccines and medications in the pork industry. In this review we have discussed history of diabetes mellitus with its whole introduction, types of insulin, need for needle free insulin technology, insulin pumps, intraject drug delivery, current needle free devices in the market. Needle free injection offers a fast, effective route of administration. Needle free injection technology has been used widely in clinical practice for many decades and has been shown to be safe and effective for the administration of many different medications for a variety of applications, including immunization and mass inoculation of large populations. Diabetes mellitus is a chronic condition that has a major impact on the lives of people with diabetes and their families and may complicate family functioning. An insulin injection is always became a painful experience to a diabetic patient. It definitely affect the patient compliance of the diabetic patient. The needle free insulin technology is the best alternative to the pains and needles. With oral drug delivery there is one another drug delivery that is insulin drug delivery with osmotic pump and handheld controllable injections. The future work that would most benefit the controllable NFTI project would be to create a tissue model that would allow the correlation of jet power with depth of injection. This also has implications for a human market for this device. Future work in this area could drastically improve healthcare for animals and humans alike.

Key-words: NFIT, Diabetes mellitus, Insulin, Insulin pumps, Needle free devices.

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INTRODUCTION

The main goal for the delivery of any drug therapy is oral administration with once or twice daily dosing. However, there are large numbers of therapies protein based, gene-based and vaccine-based that cannot be delivered by this route for example insulin, growth hormones and other similar biologics. The pitfalls of needle-based injections are psychological resistances to self-injection or needle-phobia, awareness of serious problems has caused physicians and their patients to either delay therapy initiation or seek out less-invasive alternatives and even at some cost to clinical effectiveness. To overcome the problems related to needle based injections, there is one technology that has received considerable attention during the past few years and that offers all of the sought after benefits is Needle Free Injection Technology (NFIT). These technologies have been developed for injecting liquid formulations, as well as injecting drugs and vaccines in a solid dosage form[1].

Needle-free injection techniques can be used to administer vaccines and medications in the pork industry. Needle-free injection offers a fast, effective route of administration. Needle-free injection technology has been used widely in clinical practice for many decades and has been shown to be safe and effective for the administration of many different medications for a variety of applications, including immunization and mass inoculation of large populations. Needle-free injection technology works by forcing liquid medication at high speed through a tiny orifice that is held against the skin. This creates an ultra-fine stream of high-pressure fluid that penetrates the skin without the use of a needle. Needle-Free Injection Management System is a device that provides needle-free technology for the delivery of medications via the intramuscular, subcutaneous, or intra-dermal routes while eliminating or reducing complications associated with previous needle-free devices (e.g. cross-contamination from patient to patient, lacerations at the injection site, difficult device cleaning, cumbersome tanks)[2].

In fact majority of percutaneous injuries in health care workers are due to needles from the centers for disease control sharps safety workbook. As show in figure 1[3].

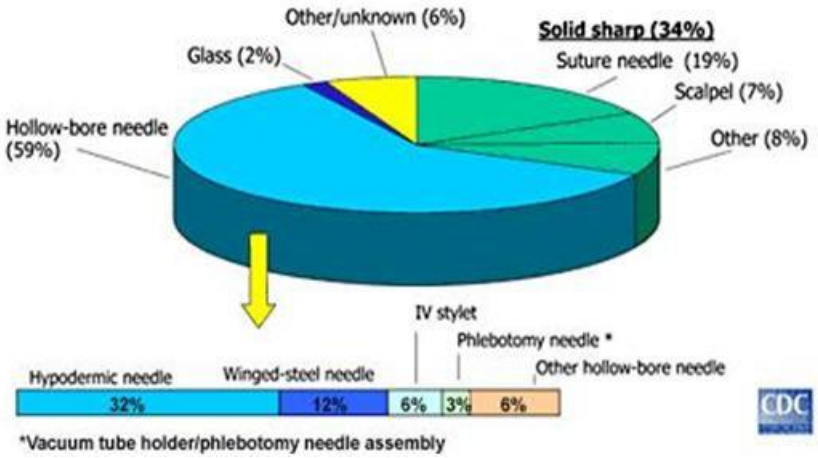


Figure. 1: Devices involved in percutaneous injuries, (n=13,731 healthcare workers).

HISTORY[4]:

As long as drugs have been known to cure diseases, people have searched for better methods of delivering them. During the early nineteenth century researchers made a series of discoveries that eventually led to the development of the hypodermic needle by Alexander Wood in 1853. This device was used to give morphine to patients suffering from sleeping disorders. In subsequent years, the hypodermic needle underwent significant changes which made them more efficient to use, safer, and

more reliable. However, needles still have significant drawbacks which prompted researchers to find needle-free alternatives. The first air-powered needle-free injection systems were developed during the 1940s and 1950s. These devices were gun-shaped and used propellant gases to force fluid medicines through the skin. Over the years, the devices have been modified to improve the amount and types of medicines delivered, and the efficiency and the ease of use.

DIABETES MELLITUS[5]:

Diabetes mellitus is a chronic condition that has a major impact on the lives of people with diabetes and their families and may complicate family functioning. Diabetes mellitus, often simply referred to as diabetes, is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced. This high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger)[6]. Regardless of the cause of diabetes mellitus, hyperglycemia is the main issue. The common hormonal defect in diabetes mellitus is insulin deficiency, which may be total, partial, or relative. Metabolic derangements are due to insulin deficiency and the complications of the disease are due to hyperglycemia[7].

Types of diabetes[8]:

- **Type 1 diabetes:** Results from the body's failure to produce insulin, and presently requires the person to inject insulin. (Also referred to as *insulin-dependent* diabetes mellitus, IDDM for short, and *juvenile* diabetes.)
- **Type 2 diabetes[9]:** Results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. (Formerly referred to as *non-insulin-dependent* diabetes mellitus, NIDDM for short, and *adult-onset* diabetes.)
- **Gestational diabetes:** It is when pregnant women, who have never had diabetes before, have a high blood glucose level during pregnancy. It may precede development of type 2 DM.

Other forms of diabetes mellitus include congenital diabetes, which is due to genetic defects of insulin secretion, cystic fibrosis-related diabetes, steroid diabetes induced by high doses of glucocorticoids, and several forms of monogenic diabetes. Globally as of 2010 it is estimated that there are 285 million people diabetes with type 2 making up about 90% of the cases.

Classification[7]:

The term "type 1 diabetes" has replaced several former terms, including childhood-onset diabetes, juvenile diabetes, and insulin-dependent diabetes mellitus (IDDM). Likewise, the term "type 2 diabetes" has replaced several former terms, including adult-onset diabetes, obesity-related diabetes, and non-insulin-dependent diabetes mellitus (NIDDM). Beyond these two types, there is no agreed-upon standard nomenclature. Various sources have defined "type 3 diabetes" as: gestational diabetes, insulin-resistant type 1 diabetes (or "double diabetes"), type 2 diabetes which has progressed to require injected insulin, and latent autoimmune diabetes of adults (or LADA or "type 1.5" diabetes).

Type 1 diabetes:

Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas leading to insulin deficiency. This type of diabetes can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated nature, where beta cell loss is a T-cell mediated autoimmune attack. There is no known preventive measure against type 1 diabetes, which causes approximately 10% of diabetes mellitus cases in North America and Europe. Most affected people are otherwise healthy and of a healthy weight when onset occurs.

Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Type 1 diabetes can affect children or adults but was traditionally termed "juvenile diabetes" because it represents a majority of the diabetes cases in children.

"Brittle" diabetes, also known as unstable diabetes or labile diabetes is a term that was traditionally used to describe to dramatic and recurrent swings in glucose levels, often occurring for no apparent reason in insulin-dependent diabetes. This term, however, has no biologic basis and should not be used. There are many different reasons for type 1 diabetes to be accompanied by irregular and unpredictable hyperglycemias, frequently with ketosis, and sometimes serious hypoglycemia, including an impaired counter regulatory response to hypoglycemia, occult infection, gastroparesis (which leads to erratic absorption of dietary carbohydrates), and endocrinopathies (eg, Addison's disease). These phenomena are believed to occur no more frequently than in 1% to 2% of persons with type 1 diabetes.

Type 2 diabetes[8]:

Type 2 diabetes mellitus is characterized by insulin resistance which may be combined with relatively reduced insulin secretion. The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. However, the specific defects are not known. Diabetes mellitus due to a known defect are classified separately. Type 2 diabetes is the most common type.

In the early stage of type 2 diabetes, the predominant abnormality is reduced insulin sensitivity. At this stage hyperglycemia can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce glucose production by the liver.

Gestational diabetes[9]:

Gestational diabetes mellitus (GDM) resembles type 2 diabetes in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2%–5% of all pregnancies and may improve or disappear after delivery. Gestational diabetes is fully treatable but requires careful medical supervision throughout the pregnancy. About 20%–50% of affected women develop type 2 diabetes later in life.

Even though it may be transient, untreated gestational diabetes can damage the health of the fetus or mother. Risks to the baby include macrosomia (high birth weight), congenital cardiac and central nervous system anomalies, and skeletal muscle malformations. Increased fetal insulin may inhibit fetal surfactant production and cause respiratory distress syndrome. Hyperbilirubinemia may result from red blood cell destruction. In severe cases, perinatal death may occur, most commonly as a result of poor placental perfusion due to vascular impairment. Labor induction may be indicated with decreased placental function. A cesarean section may be performed if there is marked fetal distress or an increased risk of injury associated with macrosomia, such as shoulder dystocia.

A 2008 study completed in the U.S. found that the number of American women entering pregnancy with preexisting diabetes is increasing. In fact the rate of diabetes in expectant mothers has more than doubled in the past 6 years. This is particularly problematic as diabetes raises the risk of complications during pregnancy, as well as increasing the potential that the children of diabetic mothers will also become diabetic in the future.

Other types[10]:

Pre-diabetes indicates a condition that occurs when a person's blood glucose levels are higher than normal but not high enough for a diagnosis of type 2 diabetes. Many people destined to develop type 2 diabetes spend many years in a state of pre-diabetes which has been termed "America's largest healthcare epidemic."

Latent autoimmune diabetes of adults is a condition in which Type 1 diabetes develops in adults. Adults with LADA are frequently initially misdiagnosed as having Type 2 diabetes, based on age rather than etiology.

Some cases of diabetes are caused by the body's tissue receptors not responding to insulin (even when insulin levels are normal, which is what separates it from type 2 diabetes); this form is very uncommon. Genetic mutations (autosomal or mitochondrial) can lead to defects in beta cell function. Abnormal insulin action may also have been genetically determined in some cases. Any disease that causes extensive damage to the pancreas may lead to diabetes (for example, chronic pancreatitis and cystic fibrosis). Diseases associated with excessive secretion of insulin-antagonistic hormones can cause diabetes (which is typically resolved once the hormone excess is removed). Many drugs impair insulin secretion and some toxins damage pancreatic beta cells. The ICD-10 (1992) diagnostic entity, malnutrition-related diabetes mellitus (MRDM or MMDM, ICD-10 code E12), was deprecated by the World Health Organization when the current taxonomy was introduced in 1999.

Signs and symptoms[9]**:**

The classical symptoms of diabetes are polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger). Symptoms may develop rapidly (weeks or months) in type 1 diabetes while in type 2 diabetes they usually develop much more slowly and may be subtle or absent.

Prolonged high blood glucose can cause glucose absorption in the lens of the eye, which leads to changes in its shape, resulting in vision changes. Blurred vision is a common complaint leading to a diabetes diagnosis; type 1 should always be suspected in cases of rapid vision change, whereas with type 2 change is generally more gradual, but should still be suspected. A number of skin rashes can occur in diabetes that are collectively known as diabetic dermadromes.

Diabetic emergencies[10]**:**

People (usually with type 1 diabetes) may also present with diabetic ketoacidosis, a state of metabolic dysregulation characterized by the smell of acetone; a rapid, deep breathing known as Kussmaul breathing; nausea; vomiting and abdominal pain; and altered states of consciousness.

A rare but equally severe possibility is hyperosmolar nonketotic state, which is more common in type 2 diabetes and is mainly the result of dehydration.

Complications[11]

All forms of diabetes increase the risk of long-term complications. These typically develop after many years (10–20), but may be the first symptom in those who have otherwise not received a diagnosis before that time. The major long-term complications relate to damage to blood vessels. Diabetes doubles the risk of cardiovascular disease. The main "macrovascular" diseases (related to atherosclerosis of larger arteries) are ischemic heart disease (angina and myocardial infarction), stroke and peripheral vascular disease.

Diabetes also causes "microvascular" complications—damage to the small blood vessels. Diabetic retinopathy, which affects blood vessel formation in the retina of the eye, can lead to visual symptoms, reduced vision, and potentially blindness. Diabetic nephropathy, the impact of diabetes on the kidneys, can lead to scarring changes in the kidney tissue, loss of small or progressively larger amounts of protein in the urine, and eventually chronic kidney disease requiring dialysis. Diabetic neuropathy is the impact of diabetes on the nervous system, most commonly causing numbness, tingling and pain in the feet and also increasing the risk of skin damage due to altered sensation. Together with vascular disease in the legs, neuropathy contributes to the risk of diabetes-related foot

problems (such as diabetic foot ulcers) that can be difficult to treat and occasionally require amputation.

Causes:

The cause of diabetes depends on the type[12]

Type 1: Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas leading to insulin deficiency. This type of diabetes can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated nature, where beta cell loss is a T-cell mediated autoimmune attack[13]. There is no known preventive measure against type 1 diabetes, which causes approximately 10% of diabetes mellitus cases in North America and Europe. Most affected people are otherwise healthy and of a healthy weight when onset occurs. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Type 1 diabetes can affect children or adults but was traditionally termed "juvenile diabetes" because it represents a majority of the diabetes cases in children[14].

Type 2: diabetes is due primarily to lifestyle factors and genetics.

It results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. It is also known as non-insulin-dependent diabetes mellitus, NIDDM for short, and adult-onset diabetes[15].

Following Table.1 is a comprehensive list of other causes of diabetes[5,12]:

Table. 1: *Causes of Diabetes*

• Genetic defects of β-cell Function
  • Maturity onset diabetes of the young (MODY)
  • Mitochondrial DNA mutations
• Genetic defects in insulin processing or insulin action
  • Defects in proinsulin conversion
  • Insulin gene mutations
  • Insulin receptor mutations
• Exocrine Pancreatic Defects
  • Chronic pancreatitis
  • Pancreatectomy
  • Pancreatic neoplasia
  • Cystic fibrosis
  • Hemochromatosis
  • Fibrocalculous pancreatopathy
	• Endocrinopathies
	  • Growth hormone excess (acromegaly)
	  • Cushing syndrome
	  • Hyperthyroidism
	  • Pheochromocytoma
	  • Glucagonoma
	• Infections
	  • Cytomegalovirus infection
	  • Coxsackievirus B
	• Drugs
	  • Glucocorticoids
	  • Thyroid hormone
	  • β-adrenergic agonists

Management[8]:

Diabetes mellitus is a chronic disease which cannot be cured except in very specific situations. Management concentrates on keeping blood sugar levels as close to normal ("euglycemia") as possible, without causing hypoglycemia. This can usually be accomplished with diet, exercise, and use of appropriate medications (insulin in the case of type 1 diabetes, oral medications as well as possibly insulin in type 2 diabetes).

Patient education, understanding, and participation is vital since the complications of diabetes are far less common and less severe in people who have well-managed blood sugar levels. The goal of treatment is an HbA1C level of 6.5%, but should not be lower than that, and may be set higher. Attention is also paid to other health problems that may accelerate the deleterious effects of diabetes. These include smoking, elevated cholesterol levels, obesity, high blood pressure, and lack of regular exercise.

Lifestyle[9]**:**

There are roles for patient education, dietetic support, sensible exercise, with the goal of keeping both short-term and long-term blood glucose levels within acceptable bounds. In addition, given the associated higher risks of cardiovascular disease, lifestyle modifications are recommended to control blood pressure.

Medications[10,16]**:**

Oral medications

Metformin is generally recommended as a first line treatment for type 2 diabetes as there is good evidence that it decreases mortality. Routine use of aspirin however has not been found to improve outcomes in uncomplicated diabetes.

Insulin[10]

Insulin is a hormone with intensive effects on both metabolism and several other body systems (eg; vascular compliance). Insulin causes most of the body's cells to take up glucose from the blood (including liver, muscle and fat tissue cells), storing it as glycogen in the liver and muscle and stops use of fat as an energy source[16].

Type 1 diabetes is typically treated with a combination of regular and NPH insulin, or synthetic insulin analogs. When insulin is used in type 2 diabetes, a long-acting formulation is usually added initially, while continuing oral medications. Doses of insulin are then increased to effect.

Types of insulin[10]**:**

Insulin types may refer to where the insulin comes from or how quick it acts .There are a number of types of insulin available. From rapid acting to long acting, from animal insulin through to analogue insulins. Insulin can be categorized by how the insulin is derived and how quickly it acts.

Forms of insulin[17,18,19]**:**

Animal insulin, as the name suggests, comes from animals. Human insulin is misleading as it doesn't, in fact, come from humans. Instead, human insulin is a laboratory made insulin.

Analogue insulin is a type of lab grown human insulin which is modified to affect how quickly or slowly it acts.

- Analogue insulin[18]
- Animal insulin[19]
- Human Insulin

Speed of insulins:

Each of these types of insulin can also be categorized by the speed at which they works. This is termed the action of the insulin.

- Rapid acting insulin
- Short acting insulin
- Intermediate acting insulin
- Long acting insulin

Insulins range from rapid acting insul

ins which can start to work almost immediately after being injected, through to long acting insulins which can keep working for up to a day, and some can last even longer. In between there are short acting and intermediate insulin's.

Mixed or combination insulins[17,19]**:**

Mixed or combination insulins are where a shorter acting insulin is combined with a longer acting insulin. On the plus side, this can mean less injections and can help to make dosages simpler. The disadvantage though, is that premixed insulins allow for less flexibility with tailoring your doses.

Common insulins[17]**:**

Common insulin products in the UK include the following:

- **Humalog:** Humalog is an Eli Lilly product, with the active ingredient insulin lispro. It is extremely rapid-acting, and will typically begin to work within 15 minutes.
- **Lantus:** Lantus is a long-acting analogue insulin. Typically Lantus is administered to the body once every day.
- **Levemir:** Levemir is also a long-acting analogue insulin. Levemir tends to have a slightly shorter duration than Lantus and therefore it is often taken twice daily.
- **Novorapid:** The active ingredient in Novorapid is insulin aspart. When novorapid is injected, it is extremely fast-acting, and works rapidly to normalise blood sugar levels. It typically begins working after 10-20 minutes, and will last for between 3 and 5 hours.
- **Actrapid:** Novo Nordisk did produce Actrapid preloaded pens, cartridges and vials for the UK insulin market. However, due to commercial reasons they have discontinued both the pens and cartridges as from January 2006.
- **Humulin:** Humulin insulins are human insulins made by Eli Lilly & Co. Short acting, intermediate acting and premixed humulin insulins are available.
- **Hypurin:** Hypurin insulins are animal insulins produced by Wockhardt UK. They make short acting, intermediate and long acting insulins and are available in beef or pork insulin forms.
- **Insuman:** Insuman is another insulin type that comes in several different forms. Insuman basal is an intermediate-acting insulin with the active ingredient isophane insulin.
- **Insulatard:** Insulatard, manufactured by Novo Nordisk, comes in preloaded pens (Novojet, InnoLet, Flexpen), penfill cartridges and vials based around the active ingredient human isophane insulin.

Analogue insulin is available in two main forms, rapid acting and long acting, as well as premixed combinations.

Examples of analogue insulin[19]:

- **Rapid acting:** Humalog, NovoRapid
- **Long acting:** Lantus, Levemir
- **Premixed analogue insulins:** Humalog Mix 25, Humalog Mix 50, NovoMix 30
- Premixed analogue insulins combine a ratio of rapid acting and long acting insulin.
- For example, Humalog Mix 25 consists of 25% rapid acting and 75% long acting insulin

Rapid acting insulins start to act immediately after injecting, with their peak action occurring within the first hour after injecting. The duration is up to 4 hours. The SQ-PEN is a needle free insulin injector, which delivers insulin to the subcutaneous tissue using a powerful spring to inject the insulin through a specially designed nozzle without the need for a needle. Since the nozzle is changed once every two weeks the SQ-PEN requires minimal maintenance.

Disadvantages of insulin injection:

- Some people suffer from a phobia of needles (Trypanophobia)
- Needle sticks are often painful
- Cross-contamination of patients

- Health care providers from accidental needle stick injuries make needle injections dangerous.
- The majority of percutaneous injuries in health care workers are due to needles
- A method of injection that does not involve needles or the pain and dangers associated with them could lead to improved healthcare across the planet.

Advantages of needle free insulin technology[2]:

- Needle-free injection technology offers a number of advantages over needle based injection methods.
    - Reliable, repeatable delivery of insulin into subcutaneous tissue.
    - Removes the danger of needle-stick injuries.
    - Ideal for those who dislike injecting with needles.
    - Removes the need for disposal of contaminated sharps.
    - May help avoid skin problems associated with using needles.
- The only maintenance needed for the SQ-PEN is to change the nozzle assembly once every two weeks.

Safety[10]:

Use of needle-free injections avoids risks of accidental needle stick injuries for friends, family and healthcare workers. Contaminated needles can transmit HIV, hepatitis, and other blood-borne pathogens, and pose a major risk to health.

NEED FOR NEEDLE FREE INSULIN TECHNOLOGY

Needle-based devices are tried and trusted delivery systems. However, for a small group of people such as those newly diagnosed with diabetes, those tired of using needles or children, consideration of a needle-free delivery system may be worthwhile.

Needle-based systems do have their problems. For example, in a study of 100 insulin-dependent diabetic patients, 65% of patients described trouble at the injection site. Whilst 31% sometimes missed their injections often, for example because they simply forgot. Another study looked at the responses to injection in 158 young people with insulin dependent diabetes in Sweden. The results suggested that most of this group only sensed minor pain when injecting although for a small minority, needle phobia and pain on injection was a significant issue.

In addition to the individual benefits of needle-free technology, there are community benefits. A greater uptake of needle-free delivery systems, would mean a lower needle disposal burden for the community. Needle-stick injuries are a common cause of injury to healthcare workers and it is not just the risks of transmission of infection (e.g. HIV Hepatitis B and Hepatitis C) but the emotional trauma when awaiting results of the various investigations. As many as 10% of all people have needle phobia. There is a view that 'mild needle phobia' within people with type 1 diabetes is possibly commoner than we think and this phobia could be associated with poorer outcomes

NEEDLE FREE INSULIN DELIVERY SYSTEM

Insulin Pumps[7]:

The insulin pump is a medical device used for the administration of insulin in the treatment of diabetes mellitus, also known as continuous subcutaneous insulin infusion therapy. The device includes:

- The pump itself (including controls, processing module, and batteries)

- A disposable reservoir for insulin (inside the pump)
- A disposable infusion set, including a cannula for subcutaneous insertion (under the skin) and a tubing system to interface the insulin reservoir to the cannula.

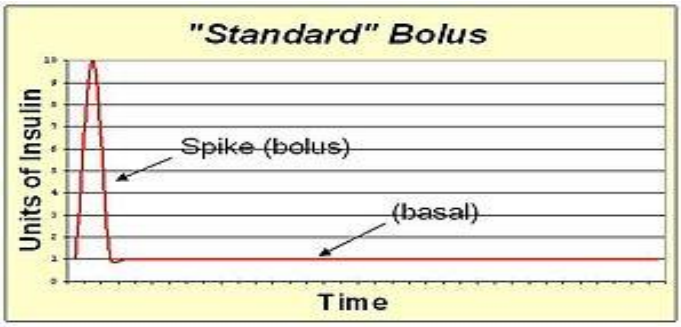
An insulin pump is an alternative to multiple daily injections of insulin by insulin syringe or an insulin pen and allows for intensive insulin therapy when used in conjunction with blood glucose monitoring and carb counting.

Dosing with insulin pumps[20,21,22]**:**

An insulin pump user has the ability to influence the profile of the rapid-acting insulin by shaping the bolus. While each user must experiment with bolus shapes to determine what is best for any given food, they can improve control of blood sugar by adapting the bolus shape to their needs.

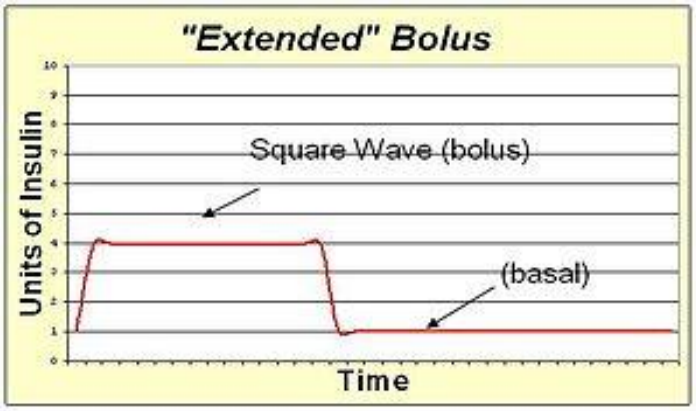
A standard bolus is an infusion of insulin pumped completely at the onset of the bolus. It is most similar to an injection. By pumping with a "spike" shape, the expected action is the fastest possible bolus for that type of insulin. The standard bolus is most appropriate when eating high carb low protein low fat meals because it will return blood sugar to normal levels quickly As shown in figure. 2,

Figure. 2: Standard bolus



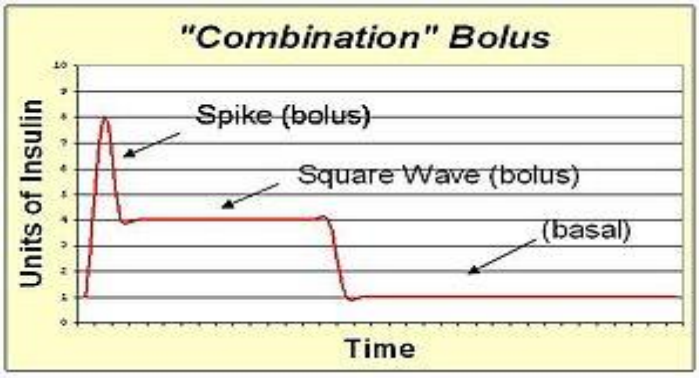
An extended bolus is a slow infusion of insulin spread out over time. By pumping with a "square wave" shape, the bolus avoids a high initial dose of insulin that may enter the blood and cause low blood sugar before digestion can facilitate sugar entering the blood. The extended bolus also extends the action of insulin well beyond that of the insulin alone. The extended bolus is appropriate when covering high fat high protein meals such as steak, which will be raising blood sugar for many hours past the onset of the bolus. The extended bolus is also useful for those with slow digestion (such as with gastro paresis or Coeliac disease). As shown in figure. 3,

Figure. 3: Extended bolus



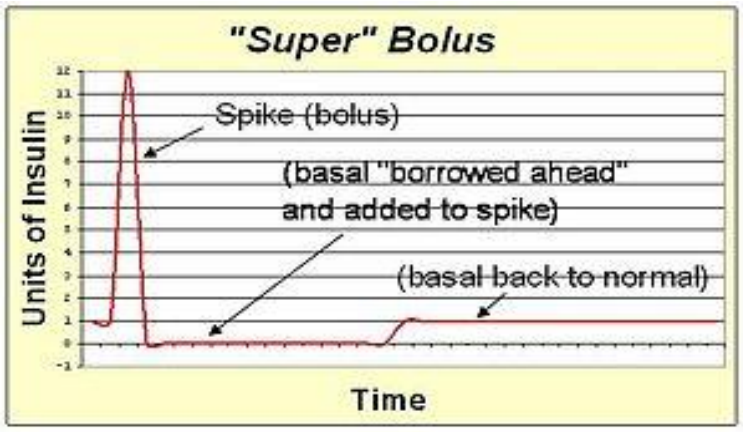
A combination bolus/multiwave bolus is the combination of a standard bolus spike with an extended bolus square wave. This shape provides a large dose of insulin up front, and then also extends the tail of the insulin action. The combination bolus is appropriate for high carb high fat meals such as pizza, pasta with heavy cream sauce, and chocolate cake.As shown in figure. 4,

Figure. 4: Combination bolus



A super bolus is a method of increasing the spike of the standard bolus. Since the action of the bolus insulin in the blood stream will extend for several hours, the basal insulin could be stopped or reduced during this time. This facilitates the "borrowing" of the basal insulin and including it into the bolus spike to deliver the same total insulin with faster action than can be achieved with spike and basal rate together. The super bolus is useful for certain foods (like sugary breakfast cereals) which cause a large post-prandial peak of blood sugar. It attacks the blood sugar peak with the fastest delivery of insulin that can be practically achieved by pumping. As shown in figure. 5,

Figure. 5: Super bolus

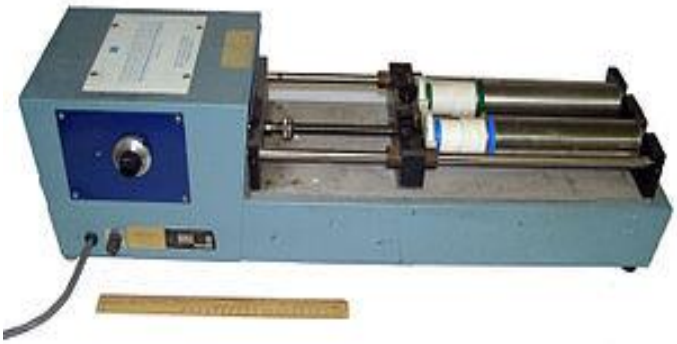


Types of insulin pumps[20,21]**:**

Insulin pump, showing an infusion set loaded into spring-loaded insertion device. A reservoir is attached to the infusion set (shown here removed from the pump) [20]. As shown in figure. 6,7,

Figure. 6: Insulin pump

Figure. 7: An early, large model of insulin pump, 78 x 12 x 22 cm[21]



Advantages of pumping insulin:

- Pumpers report better quality of life (QOL) compared to using other devices for administering insulin. The improvement in QOL is reported in type 1 and insulin-requiring type 2 diabetes subjects on pumps.
- The use of rapid-acting insulin for basal needs offers relative freedom from a structured meal and exercise regime previously needed to control blood sugar with slow-acting insulin.
- Programmable basal rates allow for scheduled insulin deliveries of varying amounts at different times of the day. This is especially useful in controlling events such as Dawn phenomenon.
- Many pumpers feel that bolusing insulin from a pump is more convenient and discreet than injection.
- Insulin pumps make it possible to deliver more precise amounts of insulin than can be injected using a syringe. This supports tighter control over blood sugar and Hemoglobin A1c levels, reducing the chance of long term complications associated with diabetes. This is predicted to result in a long-term cost savings relative to multiple daily injections.
- Many modern "smart" pumps have a "bolus wizard" that calculates how much bolus insulin you need taking into account your expected carbohydrate intake, blood sugar level, and still-active insulin.
- Insulin pumps can provide an accurate record of insulin usage through their history menus. On many insulin pumps, this history can be uploaded to a computer and graphed for trend analysis.
- Neuropathy is a troublesome complication of diabetes resistant to usual treatment. There are reports of alleviation or even total disappearance of resistant neuropathic pain with the use of insulin pumps.
- Recent studies of use of insulin pumps in Type 2 diabetes have shown profound improvements in HbA1c, sexual performance, and neuropathy pain.

Disadvantages of pumping insulin[22]**:**

- Cost of pumps and consumables is beyond the reach of the common individual.
- Insulin pumps, cartridges, and infusion sets are far more expensive than syringes used for insulin injection.
- Since the insulin pump needs to be worn most of the time, pump users need strategies to participate in activities that may damage the pump, such as rough sports and activities in the

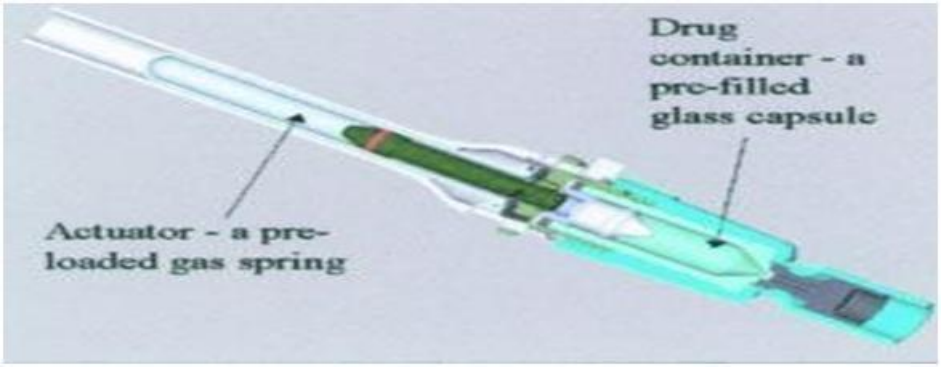
water. Some users may find that wearing the pump all the time (together with the infusion set tubing) is uncomfortable or unwieldy.

- An episode of diabetic ketoacidosis may occur if the pump user does not receive sufficient fast acting insulin for many hours. This can happen if the pump battery is discharged, if the insulin reservoir runs empty, the tubing becomes loose and insulin leaks rather than being injected, or if the cannula becomes bent or kinked in the body, preventing delivery. Therefore pump users typically monitor their blood sugars more frequently to evaluate the effectiveness of insulin delivery.
- Possibility of insulin pump malfunctioning, and having to resort back to multiple daily injections until a replacement becomes available. However most pump manufacturers will usually have a program that will get a new pump to the user within 24 hours or allow the user to buy a second pump as a backup for a small fee. Additionally the pump itself will make many safety checks throughout the day, in some cases up to 4,000,000 and may have a second microprocessor dedicated to this.
- Users may experience scar tissue buildup around the inserted cannula, resulting in a hard bump under the skin after the cannula is removed. The scar tissue does not heal particularly fast, so years of wearing the pump and changing the infusion site will cause the user to start running out of viable "spots" to wear the pump. In addition, the areas with scar tissue buildup generally have lower insulin sensitivity and may affect basal rates and bolus amounts. In some extreme cases the insulin delivery will appear to have no/little effect on lowering blood glucose levels and the site must be changed.
- Users may experience allergic reactions and other skin irritation from the adhesive on the back of an infusion set. Experience may vary according to the individual, the pump manufacturer, and the type of infusion set used.
- A larger supply of insulin may be required in order to use the pump. Many units of insulin can be "wasted" while refilling the pump's reservoir or changing an infusion site. This may affect prescription and dosage information.

INTRAJECT DRUG DELIVERY[23]:

The Intraject device comprises two parts: an actuator and a pre-filled glass capsule Intraject represents the world's first pre-filled, disposable, needle-free injection device for the delivery of liquid medicines. As shown in figure. 8:

Figure. 8: Intraject device



Invented by Terry Weston, the device is now being commercialised at Weston Medical Limited, a medical device company based in East Anglia, UK. To patients and healthcare professionals, the

device offers a simple form of self-injection and removes the growing risk of needle stick injury. Intraject is specifically aimed at meeting patient needs; being pre-filled and disposable, the system is designed for unobtrusive, contamination-free self-injection. With minimal training, a practitioner, patient or carer can deliver a reliable, virtually pain-free injection. Intraject offers pharmaceutical companies the opportunity to extend the product life-cycle and manage patent expiry. The system is designed for simple manufacture and, as a prefilled device, provides pharmaceutical licensees with the exclusivity which is critical for successful product differentiation at a low cost.

They are made up of three main pieces, the actual pen shaped injector device which powers the system, the disposable nozzle that injects the insulin and the disposable vial adapter.

The injector device is made to last for a considerable period of time (Bioject Corp claims over 3,000 injections for the Vitajet 3) but the nozzle and the vial adapters are disposable. They are not 'one time use' objects however. The nozzles can be used a number of times (Antares Pharma Inc claims 21 uses for the Medi-jector Vision). By forcing the insulin through a specially designed nozzle a very fine, extremely high pressure jet is produced. This jet is able to penetrate the skin without the assistance of a needle - I suppose one could say it does have a 'sort of' needle, just one made of insulin instead of steel! The opening at the end of the nozzle is really, really small, even compared to what we would consider the tiny opening in a fine insulin needle - around 0.006 inches as compared to 0.28 inches.

There are two different 'power sources' for achieving the pressure needed, either a compressed spring or a carbon dioxide or nitrogen cartridge. Springs have the advantage of being small, light, economical and durable, and do not need to be disposed of like a cartridge. If they have a disadvantage it is that you get a limited amount of force from a coiled spring but as we only want to get a reasonably small quantity of insulin into the subcutaneous layer, springs produce more than enough pressure for our needs.To use the device the spring needs to be compressed (charged) before each delivery. This is usually done by turning part of the device in one direction to wind the spring up.

Once it is fully wound the amount of required insulin is chosen by turning the dosing dial. The device is placed in the vial adapter (which holds the insulin vial) and the insulin is drawn into the nozzle. The nozzle is placed firmly against the skin, at 90 degrees to the body, at the chosen injection site and the actuator button is pressed which releases the spring. The insulin is injected through the skin to the correct depth.

Advantages[23]**:**

- No needle required. This is definite benefit to folk with a real needle phobia or who are just plain scared of needles, as many children, not to mention adults, are. Naturally it also removes the problems of bent and broken needles.
- Simple to use. Just wind, dial, fill, inject.
- Flexible. They can be used with all brands of U-100 insulin in standard 10 ml vials. You are able to mix insulins so eliminating the need for multiple injections that occur with an insulin pen. This is done by attaching a separate Vial Adapter to each insulin bottle, drawing in the first dose from the one bottle then changing to the second bottle and continue to fill until you have the correct dosage.
- No disposal problems because there are no 'sharps' involved.
- No needle removes the danger of needle-stick injuries to a person giving insulin to someone who is unable to do it for themselves.

- Versatility - Due to the ability in some brands to change nozzles a single device can be adjusted to suit different peoples needs in relation to skin thickness and body mass. Other manufacturers offer versatility by offering different pens for different situations.
- This method of delivery produces a better spread of insulin into the subcutaneous tissue. With a needle the insulin forms a round pool at the tip of the needle and absorption only takes place from the edge of this pool. With a jet injector the pressure causes the insulin to penetrate the tissue and flow through it via the easiest routes (like most of us it takes the path of least resistance). This results in a net like distribution of insulin over a large area of tissue.
- The insulin automatically goes to the correct depth, no more decisions needed on what length needle to use and no chance of intra-muscular injections.
- Speed of injection. From the time you depress the actuator the time taken to compl ete the injection is around 300 milliseconds. With a syringe or pen you have to keep the needle in place for at least 6 seconds to prevent the risk of insulin leaking back through the injector site.

Disadvantages[23]:

- Cost. This definitely tops the list. Compared to syringes the initial cost of these devices is high.
- Bruising. Just as one can get bruising from a needle puncture so one can get the same from these devices. However you look at it you are forcing a foreign substance into your body - you cannot blame it for fighting back!
- There is more to do in setting up the injector than there is in a syringe, so it takes more time.
- They are not widely used so the disposable bits can be more difficult to find. If you travel you will have to take sufficient supplies with you because it is likely you will not be able to find pieces for your particular injector in foreign countries.
- Sterilisation issues. This was a big problem with the older models and even some of the newer ones advocate cleaning every two weeks.
- Not as convenient as an insulin pen. You still have to carry around the device, the insulin vial, which needs to be kept refrigerated, the vial adapter and possible the disposable nozzle.
- Some people do not like the noise the injector makes when it delivers it's insulin.

CURRENT NEEDLE FREE DEVICES IN THE MARKET:

Biojector 2000[1]:

The Biojector 2000 is a durable, professional-grade injection system designed for healthcare providers. The Biojector 2000 is the only needle-free system in the world cleared by the FDA to deliver intramuscular injections. The system can also deliver subcutaneous injections, and is being used for intradermal injections in clinical trials.The Biojector 2000 uses sterile, single-use syringes for individual injections, which prevent the cross contamination that has been reported with fixed nozzle jet injection systems. More than 10 million injections have been administered successfully using the Biojector 2000, with no reports of major complications. Because there is no needle, the Biojector provides healthcare workers with an unparalleled level of protection against accidental needlestick injuries. In high-risk situations, such as delivering injections to patients known to be infected with HIV or hepatitis, the Biojector is an ideal injection system.

Mini-Ject[1]:

The Mini-Ject represents the next generation in needle-free injection systems by combining the features of accuracy reliability, a variety of pre-filled options, comfortable administration, and full disposability, all within a patient friendly easy-to-use design. The Mini-Ject can deliver a wide range of

drugs, ranging from small molecules to large proteins, fragile antibodies, and vaccines. Delivery can be targeted to intradermal, subcutaneous or intramuscular depending on the clinical need. No other single-use needle-free delivery technology provides the same level of performance as the Mini-Ject technology with the ability to target specific tissue layers over such a broad range of drug volumes (0.1 mL to 1.3 mL) and viscosities.

Iject[4]:

Bioject has developed a second-generation gas-powered injector known as the Iject, which is based on the design and performance of the B2000 and is intended to serve as a single-use pre-filled device. The pressure profile of the Iject has been documented by in vitro testing to be virtually the same as that of the B2000, and injection performance of the two devices is therefore predicted to be equivalent. The Iject is a pre-filled single-use disposable injection device (Figure 1) configured to administer 0.5 to 1.00 ml subcutaneous (Figure 2) or intramuscular injections. The device is distributed "ready to use." Thus, it requires no additional parts or modifications for function. The device is primed by rotating the trigger sleeve 180 degrees, and an injection is administered by advancing the trigger sleeve while the nozzle is held against the injection site (Figure 3) The Iject needle-free injection system is an investigational device, subject to the US Food and Drug Administration clearance for commercial distribution

Biovalve's Mini-Ject technology[24]:

The Mini-Ject represents the next generation in needle-free injection systems by combining the features of accuracy reliability, a variety of pre-filled options, comfortable administration, and full disposability, all within a patient friendly easy-to-use design. The Mini-Ject can deliver a wide range of drugs, ranging from small molecules to large proteins, fragile antibodies, and vaccines. Delivery can be targeted to intradermal, subcutaneous or intramuscular depending on the clinical need. No other single-use needle-free delivery technology provides the same level of performance as the Mini-Ject technology with the ability to target specific tissue layers over such a broad range of drug volumes (0.1 mL to 1.3 mL) and viscosities.

CONCLUSION:

An insulin injection is always became a painful experience to a diabetic patient. It definitely affect the patient compliance of the diabetic patient. The needle free insulin technology is the best alternative to the pains and needles. There are various alternative dosage forms are available for the needle free insulin technology which contains orally administered insulin therapy. In this therapy with advantages of painless and needle free technology it also have some disadvantages like enzymatic degradation and low absorption. With oral drug delivery there is one another drug delivery that is insulin drug delivery with osmotic pump and handheld controllable injections. A handheld controllable needle-free injection device was designed and manufactured using a voice coil as the controllable actuator. The device was capable of injections of different depths into tissue based on the driving voltage waveform given to the voice coil. The future work that would most benefit the controllable NFI project would be to create a tissue model that would allow the correlation of jet power with depth of injection. This model would probably vary based on the animal species, age, and perhaps even breed. However, this understanding would allow the user of a controllable NFI in the field to "dial in" the depth of the injection necessary and then have the controllable actuator deliver an injection with the appropriate jet power to produce that depth. This also has implications for a

human market for this device. By adjusting the depth of injection, it could be possible to minimize pain and deliver drug to the correct depth every time, unlike a needle where medical errors can result in incorrect injections. Future work in this area could drastically improve healthcare for animals and humans alike.

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