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ENHANCING INSULIN EFFICACY FOR DIABETES TREATMENT: A CRITICAL REVIEW OF ITS NOVEL ADMINISTRATION ROUTES

SUMATHI A*[1], NEENU ANNA THOMAS[1], GOKULRAJ S[1], HARISH R[1], SIVAKUMAR T[2]

[1]Department of Pharmaceutics, Nandha College of Pharmacy, Koorapalayam Pirivu, Pitchandampalayam (P.O.), Erode, Tamilnadu, India, Pin – 638 052.

[2]Department of Pharmaceutical Chemistry, Nandha College of Pharmacy, Koorapalayam Pirivu, Pitchandampalayam (P.O.), Erode, Tamilnadu, India, Pin – 638 052.

ABSTRACT

Insulin, a pivotal hormone in glucose metabolism, has undergone significant scientific scrutiny since its discovery in 1921. This review article aims to encapsulate the advancements in our understanding of insulin's molecular mechanisms, therapeutic applications, and emerging trends in diabetes management. The review delves into the evolution of insulin therapies, from animal-derived formulations to modern recombinant DNA technologies, and the advent of biosimilar insulins. We discuss current innovations such as ultra-rapid-acting insulins, inhalable insulins, and the development of closed-loop insulin delivery systems. Additionally, the review addresses challenges in insulin therapy, including hypoglycemia management, insulin resistance, and the socioeconomic barriers impacting accessibility. By examining the integration of personalized medicine and digital health tools, this article underscores the future directions in insulin research and diabetes care.

KEYWORDS: Diabetes, Ultra-rapid-acting insulins, Inhalable insulins, Hypoglycemia management, Insulin resistance

INTRODUCTION

Insulin is a body's metabolite that produced by the pancreas which causes serious pathogenic issues like diabetes mellitus. Type I DM (previously known as insulin-dependent or juvenile-onset DM) or insulin resistance type II DM (previously known as non-insulin-dependent or adult-onset DM). Increased level of glucose in the body probes a way for diabetes mellitus in human body. It can be also characterized by the improper function of β-cells that fails to manage the insulin production in the body. Currently diabetes mellitus is treated using anti- diabetic drugs like metformin, DDP-4 inhibitors, thiazolidinedione and sulfonylurea. But these medicines are unable to control this condition completely. When the blood glucose level increases, the β-cells releases the insulin that reaches its receptors and regulates the glucose level in body. On considering the novel route of insulin administration, there are various forms of insulin like Inhaled insulin, oral, colonic, nasal, rectal, ocular, vaginal, buccal insulin delivery systems.

TYPE I DIABETES

Type I diabetes, often referred to as juvenile diabetes, is a chronic autoimmune condition characterized by the body's inability to produce insulin. Unlike type II diabetes, which is often linked to lifestyle factors, type I diabetes is primarily a result of genetic and environmental factors. Type I diabetes needs insulin replacement otherwise it will be life threatening. This condition requires lifelong management and impacts on individuals of all ages, but it is most commonly diagnosed in children and young adults.

Type I diabetes is primarily caused by the immune system mistakenly attacking and destroying the insulin-producing beta cells in the pancreas. This autoimmune response is not fully understood, but it is believed to result from a combination of genetic and environmental factors. Viral infections and certain toxins may trigger the immune system in genetically predisposed individuals.

Diagnosis is usually based on blood tests measuring blood glucose levels. A high fasting blood sugar level and the presence of glucose in the urine are key indicators. Often, additional tests, such as the glycated hemoglobin (HbA1c) test, are used to monitor long-term blood sugar control. [1,2]

TYPE II DIABETES

Type 2 diabetes is a chronic metabolic disorder characterized by elevated blood sugar levels resulting from the body's impaired ability to use insulin effectively or produce enough of it. Unlike type I diabetes, which is primarily an autoimmune condition, type II diabetes is often associated with lifestyle factors, genetics, and age, and it typically develops in adults, though it is increasingly affecting younger individuals. Understanding this condition is essential, as it affects millions of people worldwide and requires lifelong management to prevent potentially severe health complications[2]

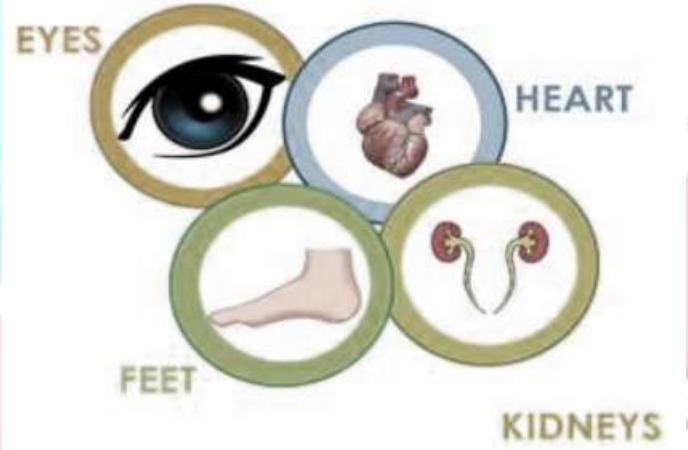

Figure 1. Complications of Diabetes

MECHANISM OF ACTION OF INSULIN

Insulin directly bind to the receptors present on the cells like hepatic cells and adipocytes. Insulin is an heterotetrameric glycoprotein. It has two subunits called alpha and beta. The alpha subunit is an extracellular subunit and beta is transmembranous unit. When insulin binds with the alpha subunits it activates the tyrosine kinase activity present in the beta subunit. The tyrosine kinase activates the translocation of glucose transport from the cytoplasm to the cell surface. These glucose transporters help the influx of glucose from blood to the belonging cells and reduces the glucose level.

Insulin promotes the glycogenesis in the hepatic cells the inhibit the gluconeogenesis and also promotes lipogenesis in adipocytes the inhibit lipolysis that helps regulating the blood glucose level.[3]

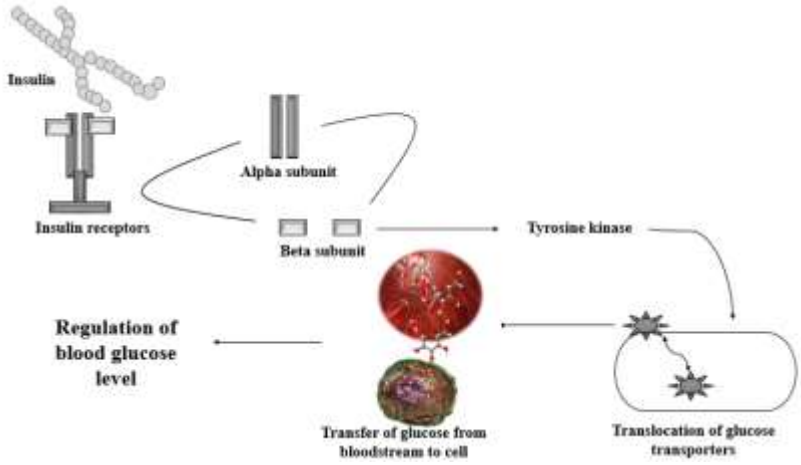

Figure 2. Mechanism of action of Insulin

TYPES OF INSULIN

Insulins are the substance that used to regulate the blood glucose level in the body. In that, rapid and short acting insulins helps in regulating the blood glucose level. There are five types of insulin like long acting, short acting, intermediate acting and long acting insulins.

a) Rapid acting Insulin

Rapid-acting insulins are a category of insulin medications used in the treatment of diabetes. They are designed to mimic the body's natural insulin response and have a quick onset of action, allowing for better control of post-meal blood sugar levels. These insulins are typically administered via injection or insulin pump and are an essential part of managing diabetes, particularly for individuals with type I diabetes and some with type II diabetes.

- Insulin Lispro, aspart, glulisine are some of the examples of rapid acting insulin.
- Insulin Lispro (e.g., Humalog) - Begins working within 15 minutes and peaks in about 1-2 hours.
- Insulin Aspart (e.g., NovoLog/NovoRapid) - starts acting within 15 minutes and peaks in 1-3 hours.
- Insulin Glulisine (e.g., Apidra) - Onset of action is about 10-15 minutes, with a peak effect in 1-1.5 hours.

b) Short acting Insulin

Short-acting insulins, also known as regular or fast-acting insulins, are a type of insulin medication used to manage blood sugar levels in people with diabetes. These insulins have been in use for many years and have a relatively slower onset of action compared to rapid-acting insulins. They are typically administered via injection and are essential in diabetes management, particularly for individuals with type I and some with type II diabetes.

- Regular Insulin is a classic short-acting insulin that has been in use for decades. It has a slower onset compared to rapid-acting insulins and a longer duration.

Short-acting insulins are often used in combination with longer-acting insulins or other diabetes medications to create a comprehensive insulin regimen tailored to an individual's needs. They are especially useful for individuals who have a consistent meal schedule and need insulin to cover their meals.

c) Intermediate acting Insulin

Intermediate-acting insulin is a type of insulin medication used to manage blood sugar levels in people with diabetes. These insulins have a moderate duration of action, longer than rapid-acting or short-acting insulins but shorter than long-acting insulins. They are typically used in combination with other types of insulin to provide both basal (background) and mealtime (bolus) insulin coverage. Some examples are,

- NPH Insulin (Neutral Protamine Hagedorn) is one of the most well-known intermediate-acting insulins. It is available in various brands and is typically cloudy in appearance. NPH insulin is often mixed with rapid- or short-acting insulins to provide both basal and mealtime insulin coverage.

d) Long-acting Insulin

Long-acting insulins, also known as basal insulins, are a category of insulin medications used to provide a steady and consistent level of insulin in the body to help control fasting blood sugar levels over an extended period. Unlike rapid-acting or short-acting insulins, which are used to address mealtime spikes in blood sugar, long-acting insulins primarily serve as a foundation for a person's overall insulin therapy and can often be administered just once a day.

- Insulin Glargine (Lantus) is a popular long-acting insulin that provides a consistent basal insulin effect and is typically administered once daily.
- Insulin Detemir (Levemir) is another long-acting insulin that offers a more predictable and consistent effect and is also usually taken once daily.[4]

COMMONLY USED DRUGS FOR DIABETES TREATMENT

Sulfonylureas, Biguanides and Thiazolidinediones are the categories of drugs that are mostly used for the treatment for Diabetes in pharmaceutical industries.

a) Sulfonylureas:

- First generation Sulfonylureas
  - Chlorpropamide – Diabinese
  - Tolazamide – Tolinase
  - Tolbutamide – Oriniase
  - Acetohexamide – Dyemelor
- Second generation Sulfonylureas
  - Glyburide – Glynase

- Glimepiride – Glimestar
- Glipizide – Glucotrol

b) Biguanides

- Metformin – Istamet

c) Thiazolidinediones

- Troglitazone – Rezulin
- Rosiglitazone – Avandia
- Pioglitazone – Actos[6]

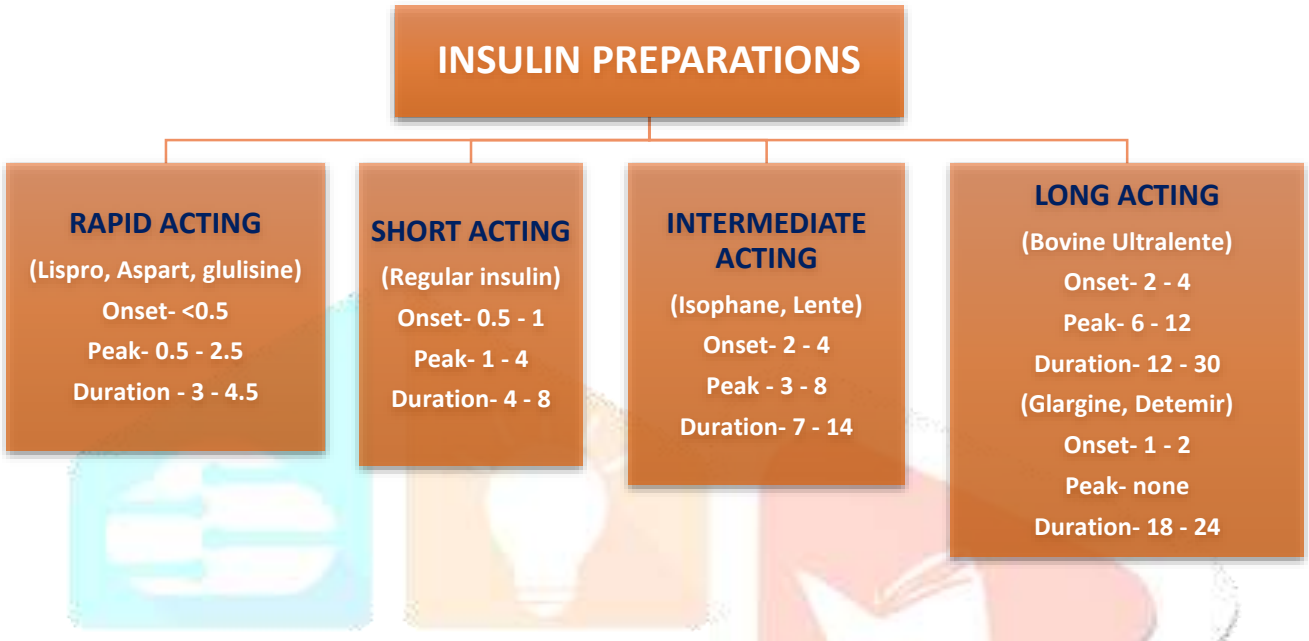

Figure 3. Classification of Insulin preparation[5]

NOVEL ROUTES OF INSULIN DELIVERY

a) Oral insulin

Comparing to other route oral route is more convenient and preferable way of patients. It have more advantages like higher compliance, conveniences and low risk if infections and injuries by needles. Nanoparticles, hydrogels, microspheres, mouth dissolving strips, sprays, liposomes are the oral way of administration of insulin. Some of the oral insulin preparations are Capsulin, ORMD – 0801, IN – 105 have passed Phase 2 trails.[7,8]

- Insulin pills
- Insulin capsules
- Insulin tablets

Figure 4. Novel routes of Insulin Delivery

b) Colonic insulin delivery

Colonic insulin delivery is another experimental approach to insulin administration, focusing on delivering insulin to the body through the colon, which is the lower part of the large intestine. This approach is being explored as a potential alternative to traditional subcutaneous insulin injections for people with diabetes. Colon has a large surface area that also rich in blood circulation provide better absorbance rate than other routes. But the challenges of formulation of colonic release insulin is difficult. And gastric irritation and side effects are there secondary concerns of these kind of dosage forms. These formulations are still in experimental stage and not a standard or approved method of insulin delivery. The development of these colonic oral route will provide significant convenience in the insulin intake.[9,10]

c) Vaginal insulin delivery

Vaginal route of insulin administration is a theoretical concept that helps to apply the insulin directly into the vaginal region or uterus. Some attempts are made with lyso- phosphatidylcholine containing insulin as aqueous solution and as lyophilized power along with bioadhesive starch microsphere to sheep. And also it has been done to rats and shown biologically active forms in the system. Further researches are in progress to attain such dosage forms.[11,12]

d) Rectal insulin delivery

The bioavailability of proteins and peptides are less compared to intramuscular, intravenous and subcutaneous route due to the absence of permeation enhancers. But the utilization of enhancers and sodium salicylate proved effective results in rectal absorption of insulin. Insulin suppositories are made to treat post prandial glycaemia and provide better action than conventional form, because it absorbed from the rectum and enter directly into the portal vein.[13,14]

Rectal gels and suppositories show good response on insulin delivery but these are not commercially viable.[15]

e) Ocular insulin delivery

Ocular insulin delivery shows various scope of researches like administration of regular porcine insulin eye drops with different absorption enhancers. This study shows that short acting insulin is systematically absorbed in dogs shows good therapeutic results.

This ocular route shows better action due to rapid absorption and it bypasses the gastrointestinal and hepatic metabolism. The absorption of ocular drugs are takes place at the nasal meatus or the conjunctival sac.

Further progress of the research are in ongoing process will succeed in the following projects.

Till date there is no human trails on ocular insulin delivery and animal studies are failed to achieve significant plasma insulin concentration.[16,17]

f) Inhaled insulin

It is modern way of delivering insulin before meal. Insulin inhalers are used for this drug delivery method. These inhalers works as like as the asthma inhalers, it delivers a dry powdered insulin into the lungs that get absorbed and passes to the blood stream. This method is used to administer only fast acting and long acting insulin. And large doses are required because only 10 per cent of the actual dose reaches the blood circulation on administration.[18]

Exubera is developed by Nektar Therapeutics and Pfizer collaboratively. It deliver the insulin in powder form which is available in blister packages of 1g and 3 g of conventional human insulin. This product is approved by FDA and EMA in 2006 for both type I and II diabetes. Due to its cost, it is not widely accepted by patients and physicians.[19]

Afrezza is a dry powder inhaler system with prefilled cartridges of powdered recombinant human insulin developed by Mankind Corp and pharmaceuticals which is approved by USFDA but rejected due to insufficient glycemic efficacy and remarkable adverse outcome.[20]

g) Nasal insulin delivery

Theoretically intranasal insulin delivery is more advantageous than other oral, subcutaneous and some other routes by better patient compliance.

But it also shows some cons like rapid mucociliary clearance that shows short time of contact in the nasal region results in low permeation into nasal membrane. [21]

h) Buccal insulin delivery

Buccal insulin delivery are made using aerosols that delivers the drug into oral cavity where the absorption occurs in the inner surface of the buccal mucosa and reaches the blood circulation.[22]

Buccal delivery eases the way by large surface are for absorption, easy way of administration and bypass of gastric and hepatic first pass metabolism. But it has limitations like ununiformed absorption at various region of buccal mucosa leads to irregular absorption of insulin into the systemic circulation. Oral

Recosulin is being developed by Shreya Life Science Pvt. Ltd., awaiting for Phase 2 & 3 results. Monosol Rx and Midatech Company in collaboration developed Midaform insulin delivered through oral route.[23]

i) Transdermal insulin delivery

Transdermal patches are employed for the transdermal delivery of insulin for large molecule delivery system like proteins through skin and into the bloodstream. The skin acts as a barrier for the inner system from external factor, to employ these action various barriers are like active and passive transports are employed. So to attain transdermal delivery slow and regular release of drugs, various techniques are used like ultrasounds, iontophoresis, microneedles a so on.

These challenge of transdermal release of insulin is ineffective passive absorption through skin due to large molecular weight of the protein drugs. [24]

Insupatch is a device used as an add on to insulin pump that applies local heat to skin in order to increase the absorption of insulin.[25]

Recombinant human hyaluronidase are developed to increase insulin absorption from subcutaneous tissue.[26]

APPROCHES OF INSULIN DELIVERY

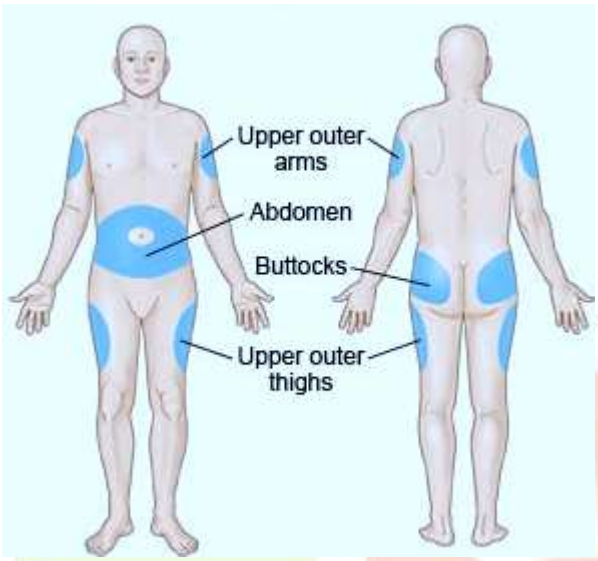

Figure 5. Injection Sites for Insulin Delivery

a) Needle and Syringe

Nowadays needle and syringe is a common way of administration. Syringes comes in various ranges like 0.3ml, 0.5ml, 1ml. Each dosage syringes requires different needle type. Needles have very fine points and special coating to make injections pain free.[26]

Administration of this type of dosage form requires special care like disinfection and careful handling of needle.

Advantages:

- Syringes allows accurate measurements and helps in dose precision that effectively control blood sugar level
- Syringes can be useful for administering all kinds of insulin like short acting, long acting, intermediate acting and rapid acting insulins
- This is so cost efficient and more affordable than other insulin delivery devices
- With proper training it is easy to use and also self-administering
- The dose taken in the syringes is easily visible and helps in measuring the amount of insulin taken transparently
- Does not require any additional components lime batteries and metering device used in insulin pens and pumps
- Syringes are portable, compact, and easy to carry
- Shows minimal waste of insulin during measurement and delivery

Disadvantages:

- Some patients may experience anxiety or fear for injections that will exert discomfort
- Some patients less convenient on carrying syringes and vials than other delivery system
- Repeated injection on same site may leads to localized skin problems lime lipodystrophy[27]

Figure 6. Approaches of Insulin delivery

b) Insulin pens

Insulin pens are most convenient way of administering insulin. They includes an inbuilt regulator that helps to adjust the dose of the insulin to be injected. It consist of a short needle in one end and a plunger at the other end that injects the dose of insulin into the body. These are usually used to administer premixed insulins.[27]

Advantages:

- Insulin pens are compact and easy to carry
- This device eliminated the need of vials, syringes and the preparation of insulin
- Insulin pens are user friendly and more convenient to use
- This device provide dose accuracy more than syringes
- This device is more discreet and less noticeable while administering in public compared to syringe
- Available for different insulin types like long, short, intermediate and raid acting insulins
- Use of fine needles in this insulin pens shows minimal pain compared to syringes

Disadvantages:

- Insulin pens more expensive than syringes and vials
- Some patients requires highly customized Insulin doses that is very challenging to achieve with insulin pens
- Generate more insulin waste than syringes particularly the left over insulins in the cartridges
- Mechanical failure such as jamming and dysfunction of pen may cause frustration and inconveniency
- Insulin pens are not available for all concentrations of insulins, so it gives limited choice for patients[28]

c) Insulin jet injectors

An insulin jet injector is a medical device designed to deliver insulin subcutaneously (under the skin) without the use of needles. It works by forcing a high-pressure stream of insulin through a tiny opening, creating a fine, high-velocity jet that penetrates the skin and delivers insulin into the subcutaneous tissue. This device consist of various components that helps to spray the metered dose of insulin into the system at a regular interval of time.

- Device Body
- Insulin Reservoir
- Nozzle
- Power Source
- Dose Regulator

Advantages:

- Jet injectors are needle free, so individuals experiencing fear using needles can appeal for this device delivery
- This device is painless and make comfortable for people fear for needles due to pain
- It delivers the insulin so quick that make more comfortable for use
- And also no risk of needle injuries on continuous administration

Disadvantages:

- More expensive than pens and syringes
- Jet injectors are large and less portable than insulin pens
- Jet injectors are inconsistent on depth of delivery of insulin, that affect the effectiveness of insulin
- May cause localized skin issues like bruising or hematomas if it not used correctly

- Not compatible with all type of insulin and some might require special designed cartridges
- Proper training required is required for handling the device
- Some jet injectors may be noisy
- This device requires regular cleaning and maintenance to make sure it works properly and free form trouble in the device
- Have limited customization for insulin doses that is not suitable for patients with varying insulin dose requirements[29]

d) Insulin pump

Insulin pumps are small devices that attached to a belt or kept it in a pocket. These contains a insulin reservoir connected to a tube which is connected under the skin of abdomen. It helps to release the insulin at a slow rate throughout the day. And also to release a large quantity when sugar level is high.

Advantages of this method is that it release the drug at slow rate and also provide continuous release of insulin like mimic the pancreas.[31]

Advantages:

- Insulin pumps provide precise and continuous release of insulin that mimics that natural activity of pancreas
- It can be programmed to individual insulin dose requirements
- Pumps allows easy bolus dosing , so user can calculate the precise bolus doses as needed
- With insulin pumps repeated injections in a day are avoided
- Insulin pumps are convenient and able wear it on belts and cloths
- Insulin pumps are equipped with Continuous Glucose Monitoring(CGM) which continuously tracks and analyses their blood sugar level

Disadvantages:

- Insulin pumps can be more expensive including supplies and maintenance of device
- Some people may find it challenging to adapt to this technology
- May experience some instrument malfunctions that disturbs the therapy

Need to change the infusion sites to avoid skin problems like irritation and lipodystrophy[32]

Figure 7. Symptoms of Insulin Resistance

e) Insulin port

Insulin ports are the device that directly channel the insulin into the subcutaneous tissue. On administration of this route, a inserting needle has a soft cannula under the skin. After application the needle is gently removed and the cannula still attached in the skin.

For injection of insulin, needle or injection pen is used. This system shows little disturbance over the region of inoculum and also has ease mode of administration.[33]

Advantages:

- Insulin ports are designed to remain in ports for several days that makes less requirements of needle sticks
- It remain in place for several days so easy administration of insulin makes more convenient for the patient

- Insulin ports offers flexibility in the injection site making it rotate while needed avoids skin irritation and lipodystrophy
- And also provide precise delivery insulin[34,35]

Disadvantages:

- Insulin ports leaves a small opening in the skin may leads to chances of skin infection
- And also some more cons like cost, device malfunction, maintenance, allergic reactions on skin, limited availability makes it inconvenient[36]

f) Insulin patches

Insulin patches are currently under development, it is designed to release the insulin slowly and continuously for desired period of time. Additional doses are added by pulling off a tab on the patch.

The design of these patches displays a adhesive patch consist of device that applied to the skin. The device consists of a insulin reservoir which contains liquid air solid form of insulin. And it contains a control mechanism that regulates the release of insulin.

This mechanism uses techniques like micro fluids, osmotic pumps or other methods to ensure controlled and consistent release of insulin.[33]

Advantages:

- It eliminates the need of injections and needle males it more comfortable
- Provide consistent and steady release of insulin
- Easy application on skin that makes it convenient and comfortable
- Reduces the injection site issues like irritations, pain or lipodystrophy
- It is so discreet and unnoticeable

Disadvantages:

- Limited insulin types are available in this delivery system
- Oil skin types, sweating or skin irritations can affect the adherence property that reflects on the efficacy of insulin delivery
- Costlier than needle and pens
- It took some time to provide action after delivery which is not suitable for patient requiring rapid action([33-35])

g) Insulin sprays

Insulin sprays are buccal delivery of insulin contains a wide range of absorbance of insulin in the buccal region. It consists of a reservoir that contains a suspended insulin that eject through the nozzle on pumping the spray. The device comprises a reservoir, pump, nozzle and a mouth piece where the insulin in up taken. The deposition of the insulin at the buccal region helps to avoid lung tissue damage by the insulin pumps. High speed sprays help the medication to enter into the quickly than other sprays.[36]

Advantages:

- Insulin sprays are non-invasive like inhalers which does not bother the people doesn't like needles
- Absence of needle provide infection free way of insulin therapy
- Provide precise dosing that helps maintaining proper glucose level[37]

Disadvantages:

Limited insulin options are available in the market and expensive

- Effectiveness of insulin sprays vary from one another
- Dose adjustments are more challenging in this device
- Insulin sprays are sensitive to temperature that might affect their stability[38]

h) Insulin inhaler

Insulin inhalers are new way of delivering pre-mealtime insulin. These devices can deliver particulate insulin to the alveolar space. These dosage forms get absorbed at the epithelium of lungs. The lungs have a wide surface area that leads to improved absorbance of the insulin into the circulatory system.

This instrument complies a nebulizer that converts the particulate into gaseous suspension that get pumped through the nozzle of the instrument. The patient should inhale the dosage form through the mouth piece of the instrument.[39]

This style of equipment provides a continuous release of insulin into the system. This is mostly used for pediatric and geriatric patients, and also for the patient who cannot ably swallow oral dosage form of insulins.

Mostly these patches are applied on the abdomen, upper arm and thighs. These are easy to remove the patches and reusable by refilling if needed.[40]

Advantages:

- Noninvasive and produce rapid onset of action
- Convenient and can be administered anywhere without discomfort

Disadvantages:

- Less effective compares to other devices and have limited options of inulin type for specific need of patients
- Long term administration of inhalers may affect the lung function
- Costly and dose adjustments are challenging
- It is sensitive to temperature and environment that alter the stability and shelf life[41]

i) Insulin Nano pump

Insulin Nano pumps are a tiny pump to be mounted on the disposable patches that shows continuous insulin infusion. This form of insulin delivery mimics closely the natural release of insulin from the pancreas.

This Nano pump utilized a technology called Micro- Electro- Mechanical System (MEMS). This technology senses the need of insulin and react by releasing the insulin. These Nano pumps provide increased safety which identifies occlusion and air bubbles quicker than other pumps. At rest this Nano pumps has a closed fluid rest and an anti-free flow system.[42]

Advantages:

- It provides continuous insulin delivery that provide stable blood glucose level
- Compared to large insulin pumps, it is more comfort and convenient
- Eliminates the need of multiple daily injections
- These pumps have customizable basal rate which can allow to adjust for individual needs

Disadvantages:

- Like other electrical devices Nano pumps also shows some malfunctions and battery problems
- The needs to be changed every few days that leads to some risks of site irritations or infections
- Also, it is very expensive and has limited compatibility of insulin type[43]

j) Insulin pills

Insulin pills are most simple, effective, convenient form of insulin delivery that helps to improve patient compliance. Insulin injects multiple times per day are required to control postprandial glycaemia.

These pills get absorbs in the small intestine, so it is coated with special azopolymer or encapsulated to protect it from gastric detoriations. Some pills are coated with controlled or sustained release for gradual release of insulin in the systemic circulation.

Advantages:

- It is noninvasive and eliminates the need of needles and injections
- Convenient and can carry everywhere the patient goes
- It eliminates pain and discomfort and suitable for patients with fear for needles

Disadvantages:

- Effectiveness of this type of insulin formulation due to absorption of insulin after the digestion of the pill in the gastric region
- Limited availability of insulin pills in the market
- Some insulin pills can cause gastric side effects like nausea or diarrhea
- Insulin pills are expensive compared to needles
- Provide precise doses in forms of pills is challenging[46]

MODERN DEVELOPMENTS IN INSULIN DELIVERY:

a) Capsulin

Oral insulin provides a painless and convenient way of administering medications for the patients and in advantage over other injections by compliance. Capsulin is an oral insulin that are intended orally to control type 2 diabetes in patients.[44,45]

For a long period of time, there is no availability of insulin in capsule formulation. So Capsulin is an enteric coated size four capsule that readily passes the stomach and release in the small intestine. It contains insulin in a dry powder form with excipients like natural bile salts and antioxidants. These excipients protect the insulin form degradation by protease in the gut. Then the insulin penetrates the mucin membrane and through the intestinal cell it reaches the liver by portal veins.

Unmodified human recombinant insulin is used in this formulation, so it doesn't react with the excipients and reaches the liver in its native form. It does not show any hypoglycemic effect due to its absorption in small intestine and directs to the liver where the glucose control in regulated.[46]

Capsulin is developed by Diabetology limited which is in phase 2 studies of clinical trials that moves successfully in progress.[47]

b) ORMD-0801

ORMD-0801 developed by the company called Oramed was also and orally ingested insulin delivery dosage form which made of an enteric coated capsule that passes the stomach and release the insulin the small intestine. The insulin gets pass the mucous membrane and through the portal vein reaches the liver for action.[48]

These novel insulin formulations include soybean trypsin inhibitor which inhibits proteolysis of the active ingredients, disodium ethylene diamine tetra acetic acid which facilitates translocation of insulin to the basal side of epithelium and subsequent systemic uptake, colloidal silicone dioxide as a common stabilizer, tween 80 which assists the emulsion and crossing of lipophilic and hydrophilic barriers and fish oil derived omega 3 acid triglycerides to prolong shelf life.

This formulation has tested 16 phase 1 and 10 phase 2 clinical studies involving 884 subjects in total of healthy and both type1 and 2 diabetic patients.

It induced greater reduction in HbA1c level which is safe ad well tolerated in individuals with type 2 diabetes mellites. The efficacy and safety of finding support continued development of 8mg dose at bedtime which is currently being evaluated in two phase 3 trials.[49]

And the company also on early stage development on ORMD-0901, an oral glucagon like peptide 1 (GLP-1) analog capsule for the treatment of diabetes.[50]

c) Exubera

Exubera was first inhaled insulin approved by the US Food and Drug Administration in 2006 in efficacy with regard to A1C lowering in both type 1 and 2 diabetes compared to regular insulin. [51]

It is a dry powder formulation available in 1mg and 3mg doses. It is found to have similar pharmacodynamic properties as insulin Aspart with a faster onset of action about 10 to 15 minutes.[52,53]

Exubera reduces the blood glucose level and ALE level in T1DM AND T2DM patients on clinical trials.

It was contraindicated with smokers with increased risk of hypoglycemic condition due to greater absorption compared to nonsmokers. So, the patients are required to undergo pulmonary function tests before treatment, after six months and annually after treatment.

This product is also contraindicated with patients with unstable controlled lung disorders like asthma and COPD. These factors lead to increased monitoring of patients during and after thearapy.[54]

This product did not do well commercially due to high cost and concerning the reduced pulmonary function, it is less preferred to the patients. And this product is withdrawn from the market in 2007.[55,56]

d) Afrezza

Even though the Exubera product was a dropout, In 2014 Afrezza was launched by Sanofi and Mankind based on Technosphere dry powdered formulation for patient with T1DM and T2DM. It involves new Gen 2 inhalers that is very small and compact to use than Exubera.[57]

Clinical trials of Afrezza with MedTone inhaler device was done until 2010. Mannkind corporation developed as second-generation inhaler device which is approved by the FDA after two phase 3 trials on the inhaler system.[57,58]

When insulin is inhaled through this device, the powder is aerosolized and delivered into the lungs. Then the insulin controls the high blood glucose level by inhibiting the hepatic glucose production.

Then the trials of Afrezza, Affinity 1 study conducted in patients with type 1 diabetes receiving basal insulin, A1C reduction with Afrezza was non-inferior to insulin Aspart and significantly fewer rate of hypoglycemia. Affinity 2 study was made in patients with type 2 diabetes uncontrolled on oral agents. The addition of prandial Afrezza was effective in lowering the A1C.[60]

Afrezza have advantages over Exubera like small, sleek and dosed in units and simple dosing conversion chart. These modifications allow more discreet administration process and a dosing regimen.

Even though Afrezza is better, it resembles the safety profile of Exubera with decline in pulmonary function and slight incidence of lung cancer. New concerns are brought forward after Afreeza's approval like risk evaluation and mitigation strategies.

It also has a black box warning information contains 'Increased risk of acute bronchospasm and Chronic lung diseases".[61]

e) Insulin Tregopil (IN-105)

Insulin Tregopil is an ultra-fast onset short duration of action insulin that is intended orally. It has onset of action of 10-20 mins and shows an excellent control of PPG (Post Prandial Glucose). It restores the insulin deficiency in patients with T2DM who are on basal insulin. Because of short duration of action, the risk of post prandial hypoglycemia is reduced. [62,63]

Initially Nobex Corporation, one of the pioneers on oral insulin discoveries developed methoxy (polyethylene glycol) hexanoyl human recombinant insulin (HIM2). HIM2 is safe and effective on

controlling post prandial glucose level in patients with diabetes and adverse effects were reportedly mild and less concerns.(64,65)

Biocon developed an advanced generation HIM2, which is novel, short acting, ultra-fast oral insulin for control of PPG called Insulin Tregopil (IN-105). It is administered orally and absorbed in intestine. It mainly acts on liver and has clinical advantages like less hypoglycemic activity, lower peripheral hyperinsulinemia, weight neutrality and improved patient compliance.(66,67)

Insulin Tregopil is similar to that of activity of endogenous insulin secreted from the pancreas which believed to bounded to the insulin receptors in liver and inhibit the glucose output in liver, skeletal muscles and fat cells also facilitates the cellular uptake of glucose and reduces the blood glucose level.(68-70)

The Biocon has conducted Phase II & III trials shows significant effects on patients with T2DM. Its absorption has a significant effect with the meal. In studying the response of IN-105 with meal with T2DM patients. The insulin was given 10 – 20 mins before meal resulted in an optimal post meal exposure and shows better PGP lowering compared with 30 min administration group. (71,72)

This formulation on further improvement to overcome the challenges with advancements in oral insulin delivery provide active effective response in diabetic treatment.(73-,75)

CONCLUSION

In conclusion, the exploration of novel routes of insulin administration for diabetes treatment is an exciting frontier in medical research and patient care. Traditional subcutaneous injections have long been the standard method, but the development of alternative approaches offers promising possibilities.

From vaginal insulin delivery to colonic insulin administration, researchers are diligently working to refine and validate these innovative methods. These approaches bring several potential advantages, including improved insulin absorption, convenience, and a reduction in the discomfort associated with needle injections. However, they also come with their unique challenges, such as formulation, dosage, and safety concerns.

While these novel routes are still in the experimental phase and regulatory approval is pending, they hold the potential to significantly impact the lives of individuals living with diabetes. As research progresses, it is crucial for healthcare professionals, patients, and the broader medical community to remain vigilant, keeping an eye on developments and staying informed about the latest advancements in diabetes management.

Ultimately, the pursuit of alternative insulin delivery methods reflects a commitment to enhancing the quality of life for those with diabetes, offering new hope, and potentially transforming the way this chronic condition is managed. As we await further scientific discoveries and clinical trials, the future of diabetes treatment may be on the cusp of significant change, with more options for personalized, effective care.

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