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R E V I E W A R T I C L E

Novel Routes of Insulin for Diabetic Treatment

Sk. Salma Sultana*, A. Kiran, G. Komala, D. Aruna, G. Pravallika, Sk. Mahaboob Masthan, U. Ramakrishna

Jagan's College of Pharmacy, Jangalakandrika, Muthukur, Nellore, Andhra Pradesh, India

A B S T R A C T

The discovery of insulin is considered to be one of the greatest breakthroughs in medical history. Before this, for thousands of years a diagnosis of diabetes meant certain death. Working at a university of Toronto laboratory in 1921Drs Frederick banting and Charles Herbert best succeeded in making a pancreatic extract which had anti- diabetic characteristics, later this extract became known as insulin, a hormone that is secreted by the beta – cells of the islets of langerhans and regulates the serum level of glucose. Estimates show there are more than 15 million diabetics living today, who would have died at an early age without insulin modern science and technology have deviced several innovative insulin delivery systems to meet the needs of diabetics.[1]

Keywords: Inertsil islets of langerhans, serum glucose, diabetics, anti- diabetic.

A R T I C L E I N F O

Corresponding Author
Sk. Salma Sultana
Jagan's College of Pharmacy,
Jangalakandrika, Muthukur,
Nellore, Andhra Pradesh, India

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1. Introduction

Developments in insulin delivery

In early days of insulin therapy, many patients found it inconvenient to receive multiple injections a day. Therefore, researchers began look for a way to prolong the action of insulin. In 1936 Drs hans Christian hagedorn and B norman Jensen, investigators at nor disk insulin laboratories, discovered that the effects of injected insulin could be prolonged by the addition of protamine obtained from the sperm of a species of American trout. Scott and fischer of Toronto university reported that the addition of zinc to insulin prolonged its effect and ensured its stability, and later ZPI insulin, protamine and porcile insulin, was produced.in 1946, nor disk formulated the first crystalline (protamine –isophane) insulin, known as neutal protamine

hagedorn (NPH), which could produce stable mixture s with fast- acting insulin.

In the mid – 1950s, the lente insulin formulation, with different ratios of amorphous and crystalline zinc insulin, were introduced. By then, patients had a wide choice of fast-and long acting insulin preparations to choose from. However, most patients developed antibodies to the forein bovine or porcine insulins, and so development of purified monocoponent (MC) insulin, and subsequently of human insulin, was a significant advancement. In 1973, purified MC insulin from animal pancreas was introduced, which, as far as possible, eliminated pro insulin and other immunogenic peptides from the preparation.

The advent of genetic engineering has allowed the biosynthesis of recombinant human insulin .in 1978 genentech produced synthetic human 'insuline. In Escherichia coli bacteria using recombinant DNA technology. The introduction genetic engineering of human insulin not only safeguarded future insulin supply, but also made it possible to restructure the insulin molecule to surmount some of the therapeutic limitation of the conventional molecule [2-5]

Insulin devices used

Insulin delivery systems that are currently available for the administration of insulin include syringes, insulin infusion pumps, jet injectors and pens. The insulin delivery systems are given below.

Insulin Syringe

This is the most commonly used, and the most eco-nomical of all the delivery devices. It consists of a vial or a small bottle and insulin syringes. The needles of the syringes are short and thin, making them less pain-ful. Recent advancements have given rise to coated needles that further reduce the pain. The syringes have gradations to help draw the correct dosage of insulin. Insulin syringes are characterized by three factors, i.e. needle gauge, needle length and syringe capacity. The manufacturers of the syringes offer a wide array of sizes and styles. The proper selection of an appropriate syringe is based on many considerations, like chemical composition of the material from which syringes are made, syringe capacity. Insulin syringes that were in-troduced initially were large and heavy with reusable glass plungers and barrels with a long, large bore needle. Today, many insulin injection syringes are available in the market that is derived from plastics being light in weight, disposable and versatile in use of variety of micro fine needles.

Advantages

- It is cheap.
- Its usage is easy to understand especially by the less educated people.
- It can be used by the blind too. This can be done by someone filling the syringes and the patient inject-ing it at the desired time.
- These syringes increase patient comfort and offer convenience, thus better patient compliance.

Disadvantages

- It is uncomfortable to use in parties or get-togethers
- It is more painful to use when compared to other devices such as insulin pens as the syringe needles are slightly thicker than pen needles.
- The procedure is slightly elaborate and time con-suming when two types of insulin are required to be mixed and taken.
- It includes their bulky construction and the re-quirement of time and practice to learn optimal sy-ringe technique.

2. Insulin Infusion Pumps

An 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.

Mechanism

The pump itself (including controls, processing module, and batteries) a disposable reservoir for insulin (inside the pump) 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. Conti-nuous subcutaneous insulin infusion (CSII) is a way to simulate the physiology of daily insulin secretion. The first CSII pump was introduced in the market in 1974.

By design, an insulin pump typically consists of a reser-voir filled with insulin (e.g., Velosulin® BR), a small bat-tery operated pump and a computer chip that allows the patient to control the insulin delivery. The pump is designed to provide a continuous supply of insulin in-fusion around the clock and can be adjusted as per the specific needs of the patient. Appropriate amounts of insulin are delivered into the body by the pump through a thin plastic tube known as an infusion set. Most of the factors that affect the variability of subcu-taneous injections such as depth of injection and change of injection sites are avoided with pump sys-tems. In these pumps, the insulin reservoir is con-nected to a subcutaneous catheter, which is changed every two to three days. Thus, advantageous for people who do not like injections as it is only necessary to insert a needle once every three to four days. These are relatively easier to operate than the earlier ones and can be carried conveniently in a shirt pocket. How-ever, some patients may not like the idea of wearing a pump constantly or disconnecting the catheter before bathing or swimming.

Insulin pumps provide accuracy and greater flexibility in insulin delivery for patients according to their individual requirements, especially during travel. Some of the available infusion pumps have the ability to accurately deliver micro doses (0.1 units) of insulin. The newer devices are easy to use and carry and pro-vide a small subcutaneous depot of unabsorbed insulin. The pump devices allow a patient to achieve a very tight control of

plasma glucose levels and enhance the overall quality of life. However, if and when insulin delivery is interrupted by infusion set malfunction, needle displacement, pump dysfunction or lack of insu-lin in the reservoir, circulating insulin concentration drops rapidly causing problems. This may be a great concern for some patients. However, patients who experience many hypoglycemic episodes may benefit from infusion pumps.When compared with optimized multiple daily insulin injections.

Advantages

- The use of rapid-acting insulin for basal needs offers relative freedom from a structured meal and exercise regimen previously needed to control blood sugar with slow-acting insulin. The alternative basal insulins, such as the long lasting insulins injected once a day, often release their insulin at a very unpredictable rate.
- Many pumpers feel that blousing insulin from a pump is more convenient and discreet than injection.
- Insulin pumps also make it possible to deliver more precise amounts of insulin than can be injected using a syringe. This supports tighter control over blood sugar level and reducing the chance of long-term complications associated with diabetes.
- It provides more freedom, flexibility, and spontaneity in the person's daily life.

Disadvantages

- 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 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.
- Possibility of insulin pump breaking and having to resort back to multiple daily injections until new pump arrives.

Insulin Jet Injectors

A jet injector (Introduced into 1980) is a type of medical injecting syringe that uses a high-pressure narrow jet of the injection liquid instead of a hypodermic needle to penetrate the epithelium

It is powered by compressed air or gas, either by a pressure hose from a large cylinder, or from a built-in gas cartridge or small cylinder. Some are multi-shot, and some are one-shot. The use of force on a fluid un-der considerable pressure through a very small open-ing allows such systems to deliver insulin without using a needle to pierce the skin. The dose is controlled by a dial-a-dose operation through a single component de-sign in comparison to the conventional multi compo-nent syringe and vial method. The available jet injec-tors allow a dose range of two to 50 units of insulin and can deliver insulin in half-unit increments. Insulin that is administered by the jet injector method is absorbed rapidly without the risk of subcutaneous infection. In gestational diabetes, jet injection therapy is associated with less anti insulin antibody (AIA) production and better postprandial glycemia

Disadvantages

- Force of the spray breaking the skin
- Most people report more pain with injectors than with a syringe
- It is time consuming to prepare and clean the injec-tor (some newer models have disposable injection chambers but they are expensive)
- The potential for a decreased amount of absorbed insulin over repeated administration with jet injec-tors.
- The size and the cost of these jet injectors are con-sidered unfavorably and often limit their routine use in patients with diabetes.
- Until the recent approval of inhaled insulin, insulin jet injectors were the only insulin delivery device available that did not use a needle or a sharp can-nula (needle-like tip to tubing used in an insulin pump).

Insulin Pens

Pen devices are novel in that they combine the insulin container and the syringe into a single modular unit. Insulin pens eliminate the inconvenience of carrying insulin and syringes. The first insulin pen (NovoPen®) was introduced by Novo Nordisk in 1987. Many pens are available since then in a variety of types and shapes. There are two main types of pens, one that is reusable and the other a prefilled device. In the former case, the patient must load an insulin cartridge prior to use. Regardless of the type, both pens hold cartridges containing from 1.5 ml to 3 ml of U100/ml insulin. The number of steps required to change an insulin car-tridge with reusable pens varies between the different pen device manufacturers. Prefilled devices are well accepted in a bedtime insulin regimen for type 2 pa-tients. Reusable insulin pens offer a wide range of ad-vantages such as their durability, eliminating the need of cartridge refrigeration and flexibility in carrying three to five day supply. The refilled insulin pens are smaller in size and lighter in weight. They cause minim-al pain due to the finest and shortest disposable insulin needles. They resemble the fountain pen; they are considered to be discreet. The manufacturers of the pen devices recommend keeping the needle separate and attaching only when ready to use. A study has shown that reus-ing insulin pen needles could help in reducing the eco-nomic burden of diabetes without leading to needle tip deformity and increased pain. The needles for pens are available in varying lengths (from 8 mm to 12.7 mm) and varying gauges (from 29- to 31-gauge; the larger the gauge number, the smaller the diameter of the needle bore).The devices can add lifestyle flexibility and may result in better glycemic control. Many newer generation pens are able to deliver 60 U at a time for type 2 patients. Insulin pens have become very popular in

some countries such as France where over 50 per-cent of insulin-treated patients are using insulin pen.

Advantages

- More convenient and easier to transport than traditional vial and syringe
- Repeatedly more accurate dosages
- Easier to use for those with visual or fine motor skills impairments
- Less injection pain (as polished and coated needles are not dulled by insertion into a vial of insulin before a second insertion into the skin)
- Insulin pens are smaller in size and lighter in weight.

Disadvantages

Unlike the traditional syringe, pens are usually restricted to full or half unit dosing. You are also not able to mix two different insulins in the same pen.[6].

Inhaled insulin system

Inhalation powder has been approved in both the u.s and the European union for adults with type 1 and type 2 diabeties . the dry powder is rapid acting, human insulin that is inhaled through the mouth into the lungs prior to eating, using the handeled inhaler. Dry powder aerosol compose of large, porous particles (5-30 micron metersin diameter)of spray-dried human insulin an exciepient matrix effecitently to the deep lung and exert systemic effects.

Pulmonary delivery of an encapsulated drypowder of human insulin.these powder is mild acidic conditions.insulin can be loaded on to these particals by combining a mildly acidic solutions os the drug with suspension is converted into dried powder. Which is incorporated into electronic dose conter to encourage adherence and allow for monitoring of insulin delivery. Pulmonary surfactant,a complex mixture of mainly phospholipids and protein nano particls was prepared and used as absorption enhancers in insulin dry powder delivery.

The large porous particles of poly (lactide-co-glycolide)(PLGA)-insuline complex for pulmonary delivery were developed with the aid of hydroxyl propyl –beta-cyclodextrin (HPβCD).insulin delivered through PLGA-HPβCD-insulin porous particles significantly reduced blood glucose levels,with controlled release of insulin to the lungs.(7).

3. Physiology of insulin secretion

Circulating, monomeric insulin is composed of two polypeptide chains (the A and B chains consisting of 21 and 30 amino acids, respectively) and two disulfide bridges, which create the quqternary assembly of the molecule.

Human insulin synthesizedvas preproinsulin (110amino acids)in the rough endoplasmic reticulum.removal of the first 24 amino acids (sinle peptide)and packaging in the golgi apparatus , insulin is stored in proinsulin in the immature secretory granules. The conversion of proinsulin into active insulin and c- peptide is catalysed by the proteoytic activity of proinsulin convertase.

Insuin is secreted by the beta cells. Every beta cell contains 10,000- 13,000 secretory granules and single insulin granule contains ~10 molecule of insulin.[8]

Pharmacokinetics of inhaled insulin

Comararision of the different systems, the inhaled insulin is difficult because their properties varied widely from devices, to dosing, to insulin formulation. inhaled insulins are absorbed more rapidly than subcutaneous route.the T max of the inhaled insulin ranged from 7-80minutes compared with subcutaneous(42-274 minutes).bioavailability of inhaled insulin 9 percet to 22 percent. To potential dose increases up to 10 times than subcutaneous injection.

Glucodynamics of inhaled insulin

- Glucodynamics is measured by determing the infusion rate of glucose neccessaaary to maintain euglycemia.
- Glucodynamics parameter determines the hypoglycemic effects of therapy.
- In healthy males receiving inhaled insulin, rates of glucose infusion were higher in the first hour after dosing than the receiving regular insulin by injection, correlating with the more rapid rise in serum insulin levels.
- Total glucose consumption was comparable for bioequivalent doses of inhaled versus regular insulin.
- Individuals with TIDM, the glucose infusion rate profile showed an early peak rate with inhaled insulin vs regular insulin with similar glucose consumption.

Equivalence dosing of inhaled insulin

- Pharmacokinetic and glucodynamic studies have been performed to determine the equivalence of each inhaled insulin formulation relative to sub cutaneous insulin.
- In order for patients to receive the appropriate amount of insulin to cover carbohydrate ingestion, they must perform a series of inhalations using the doses available for each delivery system.
- For example, a patient normally requiring 10 units of regular insulin could inhale either 3 one mg blisters (9 unit equivalents) or 1mg blister and 3 mg blister (11 unit equivalents) of exubera to achive a comparable insulin dose.[9]

Adverse effects of inhaled insulin

- Low blood sugar(hypoglycemia)
- Cough
- Sore throat
- Headache
- Diarrhea
- Fatigue
- Nausea
- Bronchitis
- Urinary tract infection

Advantages

- Easy to cary
- Painless and easy intake. thus , no hindrance multiple doses

- Short and rapid action
- Specified temperature not essential to store
- Inhaled insulin shows equivalent glycemic control
- Reduces number of insulin injections
- Can be used immediately before meal

Dis-advantages

- Non productive cough is common said effect.
- No available long term safety data.
- Contra indicated in patients with respiratory problems, lung cancer or smokers.
- Multiple inhalations for higher insulin doses.
- Risk of lung function decreased.
- Most addictive route of administration because it heals the brain so quickly.
- Pulmonary secretions.

4. Novel routes for the insulin administration

1. Buccal delivery of insulin

Mucosal membranes of the inner lining of cheeks can acts as excellent sites for insulin delivery. The area is robust, rich in blood supply, as expensive smooth muscle and provides short cellular recovery following damages are injury. Visability and accessibility of buccal mucosa also makes it an idea site for delivery. The insulin sprayed into buccal mucosa cannot enter deep lungs because of its size and hence it is safe for lungs . Insulin which is administrate through buccal route is called buccal mucosa.The main dis advantage of this route is low bioavailability due to the relatively low passage of active agents across mucosal epithelium. Bioadhesive polymers can be used as an alternative. They adhere to the biological substrate to provide contenude contact of the agent with the site delivry. The various bioadhesive formulations include gels,fims ,tablets , vesicles , nano paricles and sponges.they are retained for longer time and hence show improved pharmacokinetic as well as absorption properties.

2. Oral delivery of insulin

An oral dosage form is the prefered form of delivery because of the easy administration, patient compliance and economical issues. No oral preparations of insulin are available till date. The advantages this route is capability insulin to mimic normal physiological role. The difficulties encountered in the oral delivery of insulin include Degradation of protein at lower ph of stomach and by defferent digestive enzymes in stomach and small intestine. this cause decreces bioavailability. Gastrointestinal patches system are available today the provide bioadhesion, and undirectional release of protection for the drug from ph variations and also from enzymes. protection of insulin gastric environment has been achieved by coating nanoparicls with Ph sensitive polymers, which dissolves in mild acidic environment of the intestine.

3. Transdermal delivery of insulin

It is a needle free technique, which is convenient with good patient compliance and prolonged therapeutic applications. It bypasses first pass metabolism and escapes degradation by gastric enzymes. Lontophoresis is a technique that improves the transdermal delivery of compounds through skin by applicatiojn of small amount of microdermabration is an another method that improves the permeability of insulin through skin. It is achieved by mildly damaging or removing the outer layer of skin and stratum corneum.

4. Rectal delivery of insulin

Insulin enters through the lymphatic system. These are porto-systemic anatomoses in rectal vessels. These vessels connect the potal system to systemic system, hence allowing absorbed drugs to directly enter the systemic circulation. advantage of this system passes to proximal areas that are actively involved in digestion, avoids the local enzymatic degradation and independent of intestinal motility,a gastric emptiying time and diet. Lower bioavalability, potential adverse effects of using increased permeability of rectal mucosa to toxic substances present in the GIT lumen.[10]

5. Ocular delivery of insulin

Topical administration for ocular therapeutics is ideal because of smaller doses required compared to the systemic use, its rapid onset of action and freedom from systemic toxicity topical applied ocular drugs have to reach the inner parts of the eye and trans corneal penetration is belived to the major route for drug absorption. Corneal absorption is much slower process than elimination. ideal ophthalmic drug delivery must be able to sustain the drug release and to remain in the vicinity of front of the eye fo prolong period of time.

6. Insulin aerosols

Inhalable insulin is powdered form of insulin, delivered with an inhaler into the lungs where it is absorbed. In general inhaled insulin have been more rapidly absorbed than subcutaneous injected insulin, with faster peak concentration in serum and more rapid metabolism. The common side effects of inhaled insulin are low blood sugar, a cough, and sore throat. If you have type 1 diabetes, you‘ll still need to take long acting insulin, to help control to help control your blood sugar. If you smoke or you have lung disease, such as asthma or COPD.

7. Intranasal insulin delivery

The nasal administration of drugs for systemic effect has been widely investigated for protein and peptide delivery because of the high permeability of the nasal epithelial membrane, avoidance of first pass metabolism and improved patient compliance. Cell-penetrating peptides (cpps)are useful tool for delivering therapeutic macro molecules across cell membranes .L-or D forms of penetratin,or the L-or D forms of octaarginine (L-orD-R 8),were used for nasal insulin delivery.cpps dramatically increased nasal insulin absorption. The results demonstrated that L penetrating was the most effective promoterof insulin absorption with bioavailability up to76.7%.it significantly increased the permeability of insulin across the nasal membrane without causing detectable damage to the integrity of cells in the nasal respiratory mucosa.[11,12].

8. Vaginal or intra uterine insulin delivery

Insulin delivery through the vaginal mucosa can also prevent pre systemic degradation. Attempts were made with lysophosphotidylcholine- containing insulin as an aqueous solution and as lyophilized powder with bioadhesive starch micro spheres administrsted intra vaginally to sheep. Insulin as also been administered through intra uterine delivery in

rats and found to be absorbed in abiologically active form in the uteruses of rats.[13]

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