IJMPR 2020, 4(3), 97-104

International Journal of Modern Pharmaceutical Research

www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article

SJIF Impact Factor: 5.273

NOVEL INSULIN DELIVERY METHODS FOR DIABETES MELLITUS

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Received on: 06/05/2020
Revised on: 27/05/2020
Accepted on: 17//06/2020

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ABSTRACT

Diabetes mellitus is a metabolic disease that causes high blood sugar level. Hyperglycaemia results when the pancreatic beta cells are unable to secrete enough insulin to maintain normal glucose level. Insulin therapy, which is the exogenous supply of insulin is highly effective in regulating blood glucose level in diabetes patients. Insulin is supplied conventionally through subcutaneous routes. In early days, impurities present in bovine insulin led to many immunological reactions. The disadvantage of subcutaneous insulin delivery has inspired the research for new delivery system and hence we have many different invasive and non-invasive delivery system available today. Oral, buccal, pulmonary, transdermal, rectal and ocular routes of insulin delivery, nanotechnology based and gene therapy-based insulin delivery system, implantable insulin pump, pen devices, insulin inhalers, etc are the recent advances in insulin therapy. An oral delivery system of insulin will have tremendous benefits in terms of a decrease number of injections for diabetic patients and a reduced incidence of side effects. The proposed review on novel insulin delivery for diabetes mellitus treatment revealed that traditional subcutaneous insulin causes pain and immunological reactions. Hence novel insulin delivery enables better compliance and pharmaceutical therapies.

KEYWORDS: Insulin, Diabetes mellitus, Novel delivery methods.

INTRODUCTION

Diabetes mellitus, commonly known as diabetes, is a metabolic disease that causes high blood sugar. The hormone insulin moves sugar from the blood into your cells to be stored or used for energy. With diabetes, your body either doesn't make enough insulin or can't effectively use the insulin it does make Diabetes mellitus (DM) is a chronic disease that caused by defective pancreatic insulin production-type 1 DM (T1 DM) early known as insulin dependent or juvenile-onset DM. Insulin resistance-type 2 DM (T2DM) early known as noninsulin dependent or adult onset diabetes mellitus or adult onset DM. This results in hyperglycaemia which leads to multi organ damage in prolong time e.g. neuropathy. DM causes important role in rates of morbidity and mortality to current population.[1] Diabetes control and complications trial (DCCT) confirms the relationship between diabetes control and the prevalence of chronic complications[2] Based on the trial, the main goal of diabetes treatment is to obtain plasma glucose level close to normal is currently possible with severe hypoglycaemic episodes.[3]

Insulin used to control the blood glucose level in DM patients. It is an important therapy for patients having T1DM and T2DM.It was discovered by Frederick Banting and Charles Best at 1921. First clinical use in 1922[4,5] Insulin is a hormone with intensive effects on metabolism and other body system. Insulin taken up glucose from the blood to body cells and store as glycogen in muscle and liver and stop used as glycogen in muscle and liver and stop use of fat as energy source. Its level has an important role in the central metabolic control mechanism. Its status is used as a control signal to other body systems (such as amino acid uptake by body cells). Insulin have some anabolic effects throughout the body. When the synthesis, release and control of insulin levels fails, diabete.[6,7]

The DM result in a defect of insulin function, the ideal treatment allows diabetics to regain normal insulin function the current research and technology (exogenous administration) has not being able achieve the DM therapy. The aim is achieved effective glycaemic control (i.e.; prevention of hyper and hypoglycaemia) and avoid DM complication.[8]

Injectable mode of administration is one of the demerits for current approved insulin regimen on the continuous administration it will lead to non-compliance parenteral administration bypasses the liver. Amount of circulating insulin produced by hepatic first pass metabolism. Hence hyper insulinemia prevented.[8,9]

The current alternatives for insulin therapy many different invasive and non-invasive delivery system. The articles intend to review and update available now, it reviews the oral, buccal, pulmonary, transdermal, rectal and ocular routes of insulin delivery, nano technology based and gene therapy-based insulin delivery system. Implantable insulin, pen devices, insulin inhaler, etc. This novel approach overcomes the undesirable effects of insulin during exogenous administration and enable better compliance.

Present mode insulin delivery and their problems

Insulin administration by subcutaneous route is the present mode of administration. The route of administration follows several challenges. Insulin injected subcutaneously at least twice a day having numbers of adverse reactions like pain, inconvenience of multiple injections, hypoglycaemia, itching allergy, hyperinsulinemia, lipodystrophy around the injection site. Due to the limitations novel drug delivery system approaches such as inhalational, transdermal, oral, rectal, vaginal, buccal, intranasal are explored.

Problems

[1] Enzymatic degradation of insulin

The environment of the gastrointestinal tract (GIT) causes insulin to undergo degradation. Due to the breakdown of proteins and peptides without any discrimination. Insulin undergoes enzymatic degradation by pepsin and pancreatic proteolytic enzymes like trypsin and αchymotrypsin. Insulin is subjected to acid catalysed degradation in the stomach, luminal degradation in the intestine and intracellular degradation. The cytosolic enzyme degrades insulin is known as insulin-degrading enzyme (IDE). Insulin is not subject to proteolytic breakdown by brush border enzymes.[10] Insulin can be presented for absorption only if the enzyme attack is either reduced or defeated.

[2] Intestinal transport of problems

Evidence of active insulin transport was negative. Morpho cytochemical and biochemical evidences for insulin absorption were demonstrated in the rat GIT. This result was achieved by direct instillation of an insulin solution into various parts of the GIT, followed by visualization with gold markers. Blood insulin immunoassay. There is no evidence for paracellular insulin transport. The researchers found that insulin is adsorbed on the apical plasma membrane and is internalized by endocytosis. It then reaches the basolateral plasma membrane via the small vesicle endosomal pathway and is secreted into the interstitial space. Whether internalization results from insulin receptors on the surface of epithelial cells is unclear. Presence of insulin receptors has been demonstrated in enterocytes on both the apical and basolateral sides.[11,12,13]

[3] Stability Problems

Protein activity depends on the three-dimensional molecular structure. During the development of the dosage form, proteins may be subject to physical and chemical degradation. Physical degradation involves the modification of the native structure to a higher order structure, while chemical degradation involving bond cleavage results in the formation of a new product. Proteins should be characterized for change in conformation, size, shape, surface properties and bioactivity in formulation processing. Changes in conformation, size, and shape can be observed by using spectrophotometric techniques, X-ray diffraction, differential scanning calorimeter, light scattering, electrophoresis, and gel filtration. The stability of insulin preparations has been documented in detail, and research data on protein solid state protein stability in dosage forms has been recently reviewed.[14,15]

Subcutaneous delivery method

[1] Needle and syringe

A common way to administer is with the needle and syringe. Syringes have various capacities (1 ml, 0.5 ml, 0.3 ml) with different types of needles. Needles have very thin tips and special coating to make painless injections.

[2] Insulin pens

Insulin pen injectors are a convenient and discreet way to administer insulin. They have a built-in knob that allows us to determine how much insulin to inject, a short needle at one end and a plunger at the other. Insulin particularly useful if we need to take premixed insulin.

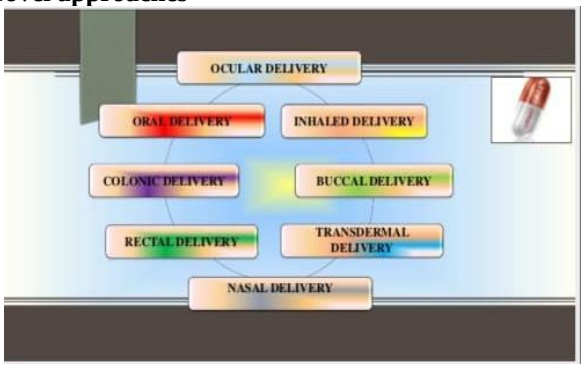
[3] Insulin jet injector

Insulin jet injectors offer an alternative to needles and work by sending a fine insulin spray skin using a pressurized air jet instead of a needle.

[4] Insulin pump

Insulin pumps are small pager-sized devices that can be strapped or put in a pocket. They consist of an insulin reservoir connected to a tube, ending in a cannula or catheter, which is inserted under the skin of our abdomen. They can be set to deliver insulin at a slow and continuous rate throughout the day or to release larger amounts at meals or when blood sugar is high. The main advantage of a pump is that it closely mimics the slow but continuous release of insulin by the pancreas.[16]

Novel approaches



Inhaled delivery

Development of inhaled insulin

Shortly after Banting and Best discovered insulin in the early 1920s, the first studies using inhaled insulin were performed. In these studies, it was reported that blood glucose decreased in response to insulin inhalation. In 1987, nebulized human insulin was shown to provide blood sugar control comparable to subcutaneous insulin in 6 children with type I diabetes mellitus. However, it was recognized that the bioavailability of inhaled insulin was significantly lower than that of subcutaneous preparations. Consequently, it was not until the development of better delivery devices and the understanding of particle pharmacology that inhaled insulin was ready for clinical study. Inhalable insulin was available from September 2006 to October 2007 in the United States as a new method of administering insulin, a drug used to treat diabetes, to the body. After withdrawal of the only inhaled formulation, all currently available insulin formulations are administered by subcutaneous or intravenous injection. New Inhalable Insulin Product Approved.[17]

Dose and administration

The dry powder insulin formulation described in this review is a mixture of human insulin (rdna origin), mannitol (stabilizing agent), glycine and sodium citrate. Insulin powder is available in 1 or 3 mg blisters. Instructions for use should be adequately explained to patients initiated with inhaled insulin to reduce administration errors. Insulin bubbles are placed in a slit in the inhaler device. Once perforated, the content is dispersed by compressed air into a visible aerosol cloud, which is captured in a holding chamber. The patient inhales in this chamber at the beginning of a deep and slow breath. If the insulin dose is not exactly 1 or 3 mg, the patient will need to inhale the contents of several blisters. Bioavailability does not appear to be enhanced by holding breath at the end of inspiration. As with other insulin products designed for meal use, the dosage of inhaled insulin should be titrated according to the needs of each patient. Any changes in insulin dose should be made with caution and under medical supervision. Due to the rapid onset of action, the dose should be administered 10 minutes before a meal to avoid hypoglycaemia. In patients with type 2 diabetes, concomitant antihyperglycemic therapy may need to be adjusted after initiation of inhaled insulin therapy. Finally, insulin dose adjustment may be necessary for changes in physical activity or meal plans.[18]

Mechanism of action

Most polypeptides used for therapy require parenteral administration, as oral administration results in loss of biopotency due to rupture in the stomach. Several non-oral routes of insulin administration have been studied including transdermal, buccal, nasal and inhaled delivery. Specifically, the lung offers an attractive option for therapeutic administration of polypeptides, given its accessibility and large alveolar-capillary network for drug absorption.[19]

Delivery system

Insulin to be delivered into the lungs, inhalation devices that provide dose accuracy and consistency are critical. Due to their inefficient absorption, higher doses of inhaled insulin compared to subcutaneous insulin should be administered to obtain an equivalent therapeutic response. The first inhaled insulin delivery system (Exubera), which is no longer available, involved the use of a bulky device to deliver human insulin as a dry powder formulation with little dosing flexibility. A different inhaled insulin formulation with a more convenient delivery system will be available in 2015. This new formulation (Afrezza) uses the Technosphere platform which contains recombinant human insulin dissolved in dry powder. Once inhaled, insulin is rapidly absorbed in contact with the surface of the lung. Both insulin and dust are almost completely eliminated from the lungs of healthy individuals within 12 hours of inhalation; Only 0.3 per cent of insulin and 0.4 per cent of powder concentration remain after 12 hours. In contrast, with Exubera's formulation, about 8 to 9% of the inhaled dose remained in the lungs 12 hours later.[20]

Advantages

Vast and well perfused absorptive surface, absence of certain peptidases that are present in the GI tract, the ability to bypass digestive enzyme and first pass metabolism, faster onset of action and longer glucose lowering activity.

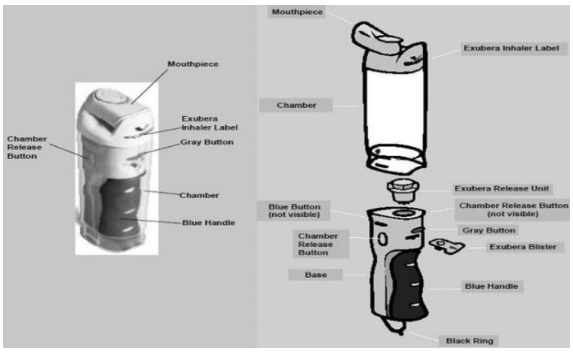
Inhaled human insulin

There are several forms of inhaled insulin, approved or under development. The only inhaled insulin approved is Exubera (human insulin [rDNA origin]). Other forms under development include AERx (NovoNordisk), AIR (Lilly), Spiro (Dura), Tecnosphere Insulin (MannKind) and Aerodose (Aerogen). Some are not powder but aerosol. Their excipients and drug delivery systems also differ.

Exubera: Exubera is dry insulin powder contained in small blisters of 1 mg and 3 mg of potency. After the blister is inserted into the base of the inhaler, a vacuum is established by engaging the lever on the base allowing aerosolization of the powder. The aerosol particles are

then inhaled. Each actuation of the Exubera inhaler produces 200 ml of a homogeneous powder. This powder contains human insulin(NA origin) and the excipients sodium citrate, glycine, sodium hydroxide (to maintain pH) and mannitol. None of these are known to be immunogenic. Mannitol has been used clinically as an agent in bronchial provocation tests, but its concentration in Exubera is lower than the lowest dose used in these test.[21]

The Exubera dose that reaches the alveolar level is the fine particle dose, which consists of particles with a diameter of 3.3 mcm or less. Filler mass is the most excipient amount of insulin in the individual insulin blister. For 1 mg Exubera blister, there are 0.7 mg of excipient and 1 mg of insulin. When the inhaler is triggered, 0.53 mg of insulin is emitted, of which 0.4 mg with a diameter of less than 3.3 mcm. Thus, of 1 mg insulin in the blister, 0.4 mg or 40% is deposited at the alveolar level. With 3 mg Exubera, the blister creates a dose of 1.0 mg of fine particles; therefore, 33% is deposited in the alveoli. Most of the insulin that reaches the distal lung is absorbed. There is no evidence of insulin accumulation in the alveoli. Unabsorbed insulin undergoes metabolic degradation or slow mucociliary clearance.[22]



Afrezza: It is based on technosphere dry powdered formulation. The onset of action of afrezza inhaled insulin is 15 minutes and duration is 2-3hrs, which is ideal for postprandial blood glucose control. Recombinant human insulin using technosphere concept where microparticles form microspheres which are lyophilised into a dry powder for inhalation. It is market for diabetes management in patients with T1DM. Currently is in phase3 trials. Transient non productive cough and modest reduction in lung function initially are the common Sid effects. Other pulmonary insulin delivery systems including AERx, proMaxx, AIR, spiros etc.[23]

Transdermal delivery

Transdermal administration of insulin eliminates the problems associated with needles and injections, and the large surface area of the skin makes it a convenient route for insulin administration[24] However, insulin penetration is interrupted by the stratum corneum, the outermost layer of the skin. Numerous methods have been explored to overcome the stratum corneum barrier.

There are several ways in which insulin can be delivered transdermally, such as:

A) Iontophoresis, the technique that uses small electrical currents[25]
B) Sonophereis or phonopheresis uses ultrasound waves[26]
C) Microdermal ablation by removing the stratum corneum[27]
D) Electroporation uses high voltage pulses applied for a very short period[28]
E) Transfersulin is transferosome-encapsulated insulin, a flexible, elastic vesicle that tightens itself to release drugs through the pores of the skin[29]
F) Insupatch ™, a device designed as a supplement to an insulin pump that applies local heat to the skin to increase insulin absorption.[30,31]
G) Recombinant Human Hyaluronidase (rhuph20) to Increase Insulin Absorption from Subcutaneous Tissue[32]

Advantages

- Good patient complaints
- Prolonged therapy
- Avoid first pass metabolism and degradation in the gastrointestinal tract.
- Bypasses first pass metabolism and also suitable for unconscious patients.

Drawbacks

- Insulin molecules are large enough to penetrate the skin at therapeutically useful rates
- Requires micro needles
- On administration in several patients makes irritation, itching, skin rashes etc.[23]

Insulin patches

Insulin patches are also currently under development, but it is difficult for insulin to be absorbed into the skin. The patch is designed to release insulin slowly and continuously. Additional dose can be administered by pulling of tab on the patch.

Rectal delivery

Rectal gels and suppositories showed fair results. However, this route is not commercially viable.[33,34]

Intra tracheal: Insulin administration was reported in 1924, but is not practical, so it is not necessary for further development.[35]

Buccal delivery

Oral administration of insulin has benefits similar to oral insulin, with the advantage of circumventing gastrointestinal degradation. In addition, the relatively large surface area results in better bioavailability. which is a short-acting liquid insulin formulation that is administered using the Generex metered dose aerosol

applicator (RapidMist ™). Eli-Lilly and Generex conducted phase 1 and phase 2 studies in patients with T1DM and T2DM with promising results[36,37] However, in 2004, both companies dissolved their development agreements[38] Phase 2 clinical trial is ongoing and further information is awaited. Another molecule being developed by Shreya Life Sciences Pvt. Ltd. in India is oral Recosulin® and the results of phase 2 and phase 3 assays are expected[39,40] Another method for administering insulin is fast dissolving films as an alternative to oral tablets for rapid drug administration[41] Monosol Rx (pharmaceutical film delivery technology), in collaboration with Midatech Company, developed the oral Midaform ™ insulin. No information is available on studies using this formulation. Another formulation "orally dissolved insulin films" is being investigated by PK / PD.

Nasal delivery

In theory, intranasal administration has several advantages over oral (GI peptidase derivation), subcutaneous (noninvasive and painless) and inhalation (no problems with pulmonary function), which makes this route attractive for insulin administration[42] However, intranasal delivery has deficiencies such as limited permeability of a large molecule across the nasal mucosa and rapid mucociliary clearance resulting in variable absorption[42] Historically, intranasal administration with early porcine and bovine insulins has been investigated in patients with T1DM[43,44] Two technologies are currently being investigated: Nasulin ™ (CPEX Pharmaceuticals) and Nasal Insulin by Nastech Pharmaceutical Company Inc. Both insulin preparations have about 15 to 25% bioavailability with onset of action. at 20 minutes[45,46] Results from phase 2 and 3 clinical trials are expected. Substances such as bile salt, surfactant and fatty acid derivatives are being investigated to increase mucosal insulin permeability but increase the risk of local irritation., nasal discharge, sneezing or burning sensation[46,47] Nasal insulin crosses the blood brain barrier, therefore, has a hypothetical effect on memory function[48] In a randomized placebo-controlled study of 104 adults with mild cognitive impairment or mild to moderate Alzheimer's disease, they were randomized to receive either placebo or 20 IU or 40 intranasal insulin. Intranasal insulin treatment improved memory, preserved caregiver functional capacity, and preserved overall cognition without any significant hypoglycemic event. These improvements in cognitive functions were correlated with changes in the level of Aβ42 and the ratio of tau protein to Aβ42 in cerebrospinal fluid[49] Based on this, large randomized controlled trials are underway to evaluate the usefulness of this agent in the treatment of Alzheimer's disease.

Ocular delivery

To date, no human studies have been reported with this route and one animal study has failed to achieve a significant plasma insulin concentration.

Advantages

Less development of immunological reactions in tissues, less side effects, no tolerance avoidance of hepatic first pass metabolism

Limitations

- Low bioavailability
- Irritations
- Loss of drug molecules via blinking, tearing and drainage

E.g.: Gel foam.[23]

Oral delivery

The oral route of insulin administration may be the patient-friendly way of taking insulin and may more closely mimic the physiological release of insulin (higher portal insulin concentration than the peripheral one).[50]

Hydrogels: They are crosslinked networks of hydrophilic polymers, capable of absorbing large amounts of water and swelling, maintaining their three-dimensional structure. Complexing hydrogels are suitable candidates for the oral administration of proteins and peptides because of their ability to respond to pH changes in the GI tract and to provide drug protection against the hostile GI tract environment.

Liposomes: Insulin-trapped liposomes cause dose-dependent hypoglycemia. The researchers prepared liposomes with variable composition by two methods: hydration by solvent evaporation and evaporation of the solvent bead. Lecithins containing 100 mg lecithin, 20 mg cholesterol, 150 units insulin and 1% v / v tween were the most effective.

Erythrocytes: Human red blood cells were developed as oral transporter systems for human insulin.

Nanospheres: Damge et al., Prepared insulin-loaded nanospheres by isobutyl cyanoacrylate (IBCA) polymerization in acid medium.[51] These nanospheres exhibited an average size of 145 nm and an association rate of 1 U insulin per milligram of polymer. These nanospheres were dispersed in oily medium (eg; Miglyol 812) containing surfactant (eg; Polox-amer 188 and deoxycholic acid) and evaluated for degradation in vitro and in vivo.

Nano cubicle: A liquid formula that can be easily dispersed in water to produce particles called "nanocubicles" was developed by Chung.[52]

Thiolated Chitosan Insulin Tablets: The efficacy of orally administered insulin was also improved using thiolated chitosan. Iminothiolane was covalently bound to chitosan and the resulting chitosan-TBA conjugate (chitosan-4oiobutylamidine) exhibited 453.5 ± 64.1 μmol of thiol groups per gram of polymer.

Oral insulin pill: The administration of insulin in pill form has always been an attractive concept in research. Due to the numerous limitations of this mode of insulin administration, efficacy has been difficult to demonstrate. Research has focused on overcoming these limitations by stabilizing degradation, improving permeability and adding absorption promoters to protect insulin as it passes through the stomach.

Future Trends For Insulin Delivery Systems

Insulin sprays for both the nose and mouth, and oral insulin (insulin pills) are methods of insulin administration that continue to be investigated. These options represent long-term possibilities for insulin delivery, as the difficulties in obtaining adequate amounts of insulin in the bloodstream have yet to be overcome.

Islet cell transplantation: This is a newly developed surgical procedure - called the Edmonton Protocol - whereby islet cells from a donated human pancreas are injected into the liver of a type 1 diabetes recipient. Transplanted cells begin to secrete insulin while the recipient needs to take immunosuppressive drugs. lifelong to avoid rejection of transplanted tissue. Clinical trials continue to establish the safety and long-term efficacy of this procedure as a means of providing insulin.

Insulin pump: Nanopump is a powerful device and has many possible applications in the medical field. The first application of the pump, introduced by Debiotech, is insulin delivery. The pump injects insulin into the patient's body at a constant rate, balancing the amount of blood sugar. The pump may also administer small doses of medication for a long period of time.[53]

Gene Therapy: Two recent reports describe research on gene therapy for different aspects of diabetes. These reports are at the forefront of what will undoubtedly be exciting and ongoing research arising from the decoding of the human genome.

CONCLUSION

The significant impact on novel approaches of insulin delivery system affected in the development of competing approaches. Continued study improves the ability to deliver insulin. The advanced technologies of insulin delivery in diabetics patient can reduce the multiple daily subcutaneous injection. It can also reduce or avoid the harmful effect due to subcutaneous injection like pain, inconvenience, overdose, itching, allergy etc and overcome the enzymatic degradation, instability, intestinal transport problems. Therefor we should give more preference to research work and investigation for the development of more effective and safe delivery system of insulin, Which gives rapid action with less side effects and patient improve patient comfortness.

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