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Insulin Routes Of Administration

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Abstract

Diabetes mellitus is a chronic disease affecting a great number of the world's population. Insulinfor diabetes is most commonly delivered via subcutaneous injections, up to four times a day.
Using insulin therapy for long term adminstration is invasive in nature & has caused problems with patient compliance. New reasearch have been carried out to explore possible improvements to insulin therapy for diabetic patients, with some new products already available and FDA- approved. This review article highlight the various routes of insulin administration such as parentral , oral ,buccal, rectal, inhalation, artificial pancreas , transdermal and other new approaches of the insulin administration with their some insulin formulation.

Introduction

In 1921, the young physician Frederick Banting and the fourth-year medical student Charles Best - found the final link in a series of studies begun in 1916 by other researchers that guessed tg secretion of substance, already named "insulin", capable to decrease blood glucose concentrations [1]. The young researchers isolated this pancreas extract that "cured" hyperglycemia in diabetic dogs1-2

1922 they successfully administered it for the first time to a 14-year-old diabetic patient,Leonard Thompson.

1923, the company Lilly began marketing animal insulin.

In 1928, the hormone was identified to be a protein. Since the insulin of Banting and Best couldnot function for more than 6 h, much research went into finding ways of prolonging action

. In 1936, Hagedorn noted that addition of a basic protein, such as protamine, to the insulinpreparation, kept the hormone in suspension at the injection site, delaying absorption and prolonging its action.

In 1946, the first insulin "Isophane NPH" (Neutral Protamine Hagedorn), obtained combining insulin and

protamine in stoichiometric quantities at neutral pH, was marketed.

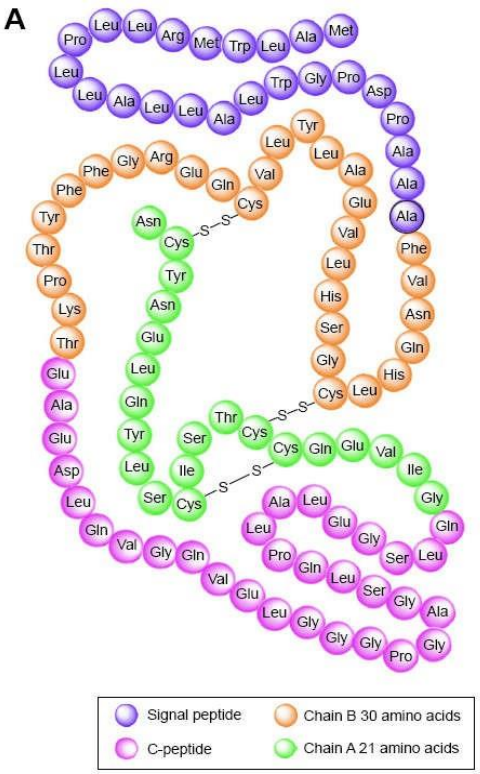
In 1952, the first Lente insulin, retarded with zinc and without protamine, was produced inDenmark.

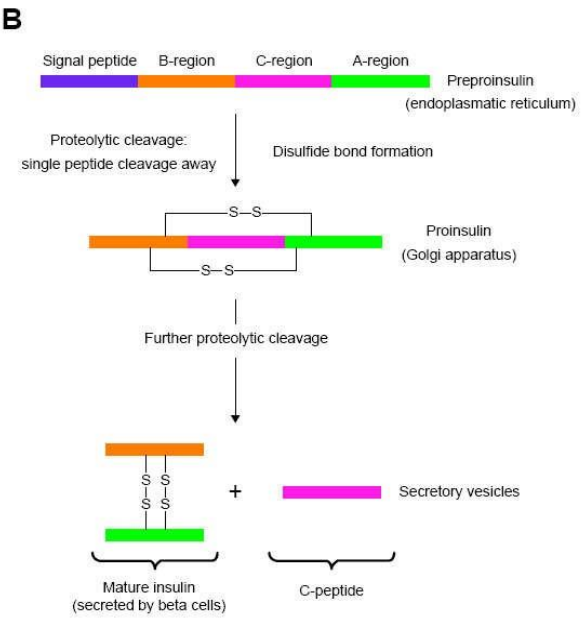
In 1955, Sanger determined the exact formula of bovine insulin

Diabetes mellitus (DM) is a chronic disease that is caused by defective pancreatic insulin production – type 1 DM (T1DM, previously known as insulin-dependent or juvenile-onset DM),or insulin resistance – type 2 DM (T2DM, previously known as non-insulin-dependent or adult- onset DM). The disease results in hyperglycemia which can lead to multi-organ damage in the long run, e.g., maculopathy, neuropathy, etc. DM causes significant rates of morbidity and mortality to the current population.[6]

Insulin is used to control the level of blood glucose in patients with DM. It is an essential therapy for patients suffering from T1DM, and T2DM (especially in late-stage disease). Since DM results in a defect in insulin function, the ideal treatment is to allow diabetics to regain normal insulin function. However, current research and technology has not been able to achieve this.
The current insulin treatment involves exogenous administration, with the aim of achieving effective glycaemia control (i.e., prevention of hyper- and hypoglycemia) and avoidance of the complications of DM. [7

• Type 1 diabetes 1. It is known as insulin dependent DM 2. Onset before age of 30 years, most often in childhood and adolescence 3. Destruction of beta cells. 4. Minor genetic susceptibility 5. Symptoms: Increase in thirst appetite, excessive urination and weight loss. Diabetic ketoacidosis	• Type 2 diabetes 1. It is known as non-insulin dependent DM 2. Onset after 35 years 3. Decrease in beta cell responsiveness for insulin. 4. Major genetic susceptibility 5. Symptoms: Postprandial Hyper-glycemia, appetite,





Synthesized in pancreatic cells as

Preproinsulin (110AA)

Proinsulin (86AA)

Insulin (51 AA)

Mechanism of action for insulin

Insulin acts through membrane kinase receptors which has enzymatic activity.

Insulin receptor (heteromeric receptors) consisting of alpha and beta subunits linked by disulphide bonds. Insulin binds with alpha subunit then activation of tyrosine kinase which is attached with beta subunit and then activation of tyrosine kinase takes place through phosphorylation.

Various routes of insulin administration

1. **Parentral**

The newly discovered parenteral insulin formulations include a different insulin glargine concentration of 300 U/ml, an

- ultra-long-acting insulin degludec
- ultra-short acting insulin Linjeta.

Both formulations show favorable characteristics that may replace or supplement currently available insulin injections

Two trail studies were carried to compare the efficacy of 2 different doses of insulin glargine, 300U/ml (IGlar-300) and 100U/ml (IGlar-100), on patients with T2DM.

First study: It involved T2DM patients using basal and mealtime insulin

Second study: It included the outcomes on T2DM patients using basal insulin and oral antihyperglycemics drugs.

Comparison of the studies showed that IGlar-300 is as effective as IGlar-100 in terms of HbA1C reduction, but the former is associated with a lower risk of nocturnal hypoglycemia. Trial one study found a 10% absolute and 21% relative risk reduction of nocturnal hypoglycemia, with noincrease in daytime hypoglycemia

Similarly, the trail 2 study demonstrated a 23% risk reduction in nocturnal hypoglycemia in addition to decreased risk of hypoglycemia at any time (24 hours) .

Insulin degludec (IDeg): A new preparation of modified human insulin with ultra-long action. This novel preparation has been compared with the insulin glargine (IGlar). Studies show that IDeg, when compared to IGlar, resulted in similar, or even better glycemic control, with less hypoglycemic episodes and lower risk of nocturnal hypoglycemia . In addition, IDeg resulted in a greater improvement in overall health status over 2 years ,with similar HbA1C control , and required lower doses for glycemic control , when compared to IGlar. Although IDeg may require less frequent injections (three times a week) compared to IGlar (once daily) in order to maintain effective basal insulin levels , more recent studies in T2DM patients do not recommend this thrice weekly IDeg regimen, as it may result in higher risk of hypoglycemia . However, the

time taken to recover from hypoglycemic episodes back to normal glucose levels was similar in both IDeg and IGlar . Compared to insulin detemir (IDet), IDeg also was better in terms of glycemic control, less nocturnal hypoglycemia and less frequent injections, when used in a basal bolus regimen with insulin as part .Due to the slow release and achieving a steady-state profile in once daily dosing, IDeg allows for flexibility in timing of doses, without affecting efficacy and safety. This is particularly important to patients who are elderly, with learning difficulties, or those depending on healthcare professionals for insulin injections .However, IDeg has not been approved by the Food and Drug Association (FDA) due to facts indicating an increase in the risk for major adverse cardiovascular events (MACE) associated with Ideg.

Linjeta™ (previously VIAject™): It is ultra-short acting with faster onset compared to human soluble insulin and insulin lispro (LIS) and showed less variability within subject compared to regular human insulin (RHI).

When compared to RHI and LIS, Linjeta™ exhibited less postprandial glycemic excursions and oxidative stress, as well as improved endothelial function

.

2. Oral

The oral route is the most widely used for insulin administration. Oral medication for diabetic patients treated throughout their lives represents a crucial demand in order to improve their quality of life and to assure adherence to the treatment regimen. Moreover, oral insulin is delivered directly to the liver via portal circulation and could generate a high portal-systemic gradient replicating the endogenous secretion of insulin. Nevertheless ,effective oral insulin delivery remains challenging because of poor bioavailability. In the gastrointestinal tract, the absorption of protein and peptide molecules is hampered by physical and biochemical barriers such as epithelium, variable pH, enzymatic proteolysis, effluxpumps, and first-pass elimination by liver ,

solubility, molecular weight, and partition coefficient are the major physicochemical concerns dictating drug dissolution and permeability through the gastrointestinal barrier. The pharmacokinetic and pharmacodynamics properties of oral insulin formulations change as a function of the site (along the gastrointestinal tract) and pathway (cellular or Para cellular) of absorption. The fast absorption has been attributed to Para cellular pathways, whereas the slow absorption to cell pathways (endocytosis via enterocytes or M-cells).

The application of nanotechnologies in drug delivery is expected to achievemultiple goals

: I) shielding the entrapped drugs from the gastrointestinal environment so that they can reach intact the site of absorption;

ii) enhancing drug water solubility

; iii) enhancing the intestinal permeability of drugs once carried by nanoparticles(NPs) that are chiefly taken up by M-cells, known for their high transcytotic capacity and low lysosomal hydrolase activity; and

iv) reducing dosing frequency because of the controlled and sustained release of the Nano encapsulated drugs, and thus improving treatment adherence.41

Oral bioavailability of insulin have been improved by different types of delivery systems and functional excipients such as: capsules, tablets, micro particles, micelles, liposomes, solid lipid NPs and NPs of biodegradable polymers, hydrogels, film patches, super porous matrices, intestinal patches, charge-coupled micro magnet micro particles, polymeric adhesives, protease inhibitors, insulin aggregation inhibitors, permeation enhancers, etc. Depending on their constitutivematerials and physicochemical characteristics, NPs may allow formulators to design different release profiles and to achieve local or systemic targeting of the encapsulated drug.41 Patents published on oral insulin delivery formulations havebeen recently reviewed.47

Carriers for oral delivery system.

Most materials used in the formulation of oral insulin NPs and tested in animals were polymers. Hydrophilic or hydrophobic polymers often were synthesized as micro particles or NPs. Polymers such as poly(lactase-co-glycoside (PLGA), poly(lactase) (PLA), poly(ε-caprolactone) (PCL), chitosan (CS) and its derivatives, dextran, solid lipids, poly(allyl amine), and poly(acrylic acid) have been used due to their well-established safety. Using various polymeric

materials and formulationprocesses allows to modulate the physicochemical properties of NPs, extent of drug loading, and drug release profile.

Gold nanoparticles (AuNPs) are being investigated as novel carriers for oral insulindelivery . They have excellent biocompatibility and low cytotoxicity. AuNPs are stable metal NPs with unique physical, chemical, optical, and electronic properties:

- large surface-to-volume ratio for easy conjugation of a variety of ligands,
- practical nanoscale assembly, inert nature,
- extreme resistance to oxidation, enhanced permeability and retention effect,
- surface plasmon resonance phenomenon, size- and shape-dependent electronic, and optical properties. To use the AuNPs in vivo for a long retention time avoiding the action of the reticular endothelial system, their surface can be modified with antibiofouling agents, such as polyethylene glycol, and more stable bonds can be created by self-assembling molecules with thiol groups onto gold surfaces.

Buccal route

Buccal route is highly accessible and have large surface area around 100-200 sq. . It has little proteolytic enzyme and the tissue is well vascularized. However continuous and variable saliva flow and robust structure of oral epithelium constitute a barrier to penetration of drugs. The drug delivery system requires intimate contact with buccal mucosa in order to maintain its position in mouth for longer period.

Various methods have been developed to improve drug delivery to buccal mucosa

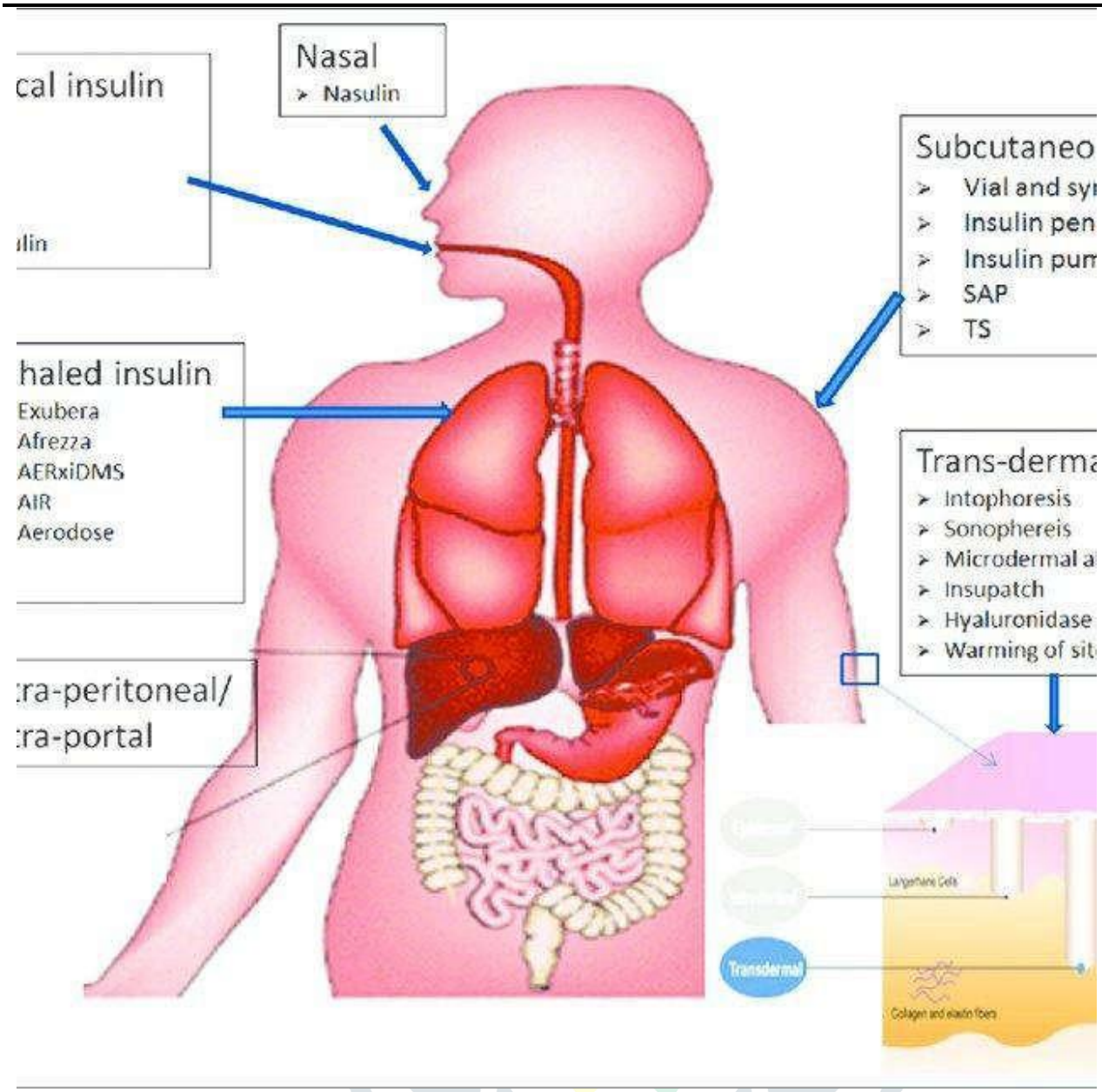
- Use of absorption enhancers such as bile salts , surfactants, fatty acids, alcohol, chelators.
- Protease inhibitors.
- Bio adhesive delivery system (gels , films , patches).
- Lipophilic modification (conjugation with polymer).

The device for delivery should be such that it must protect it from environmental degradation and promote permeation of macromolecule across mucosa

Insulin reaching the systemic circulation by absorption through the buccal mucosa is called buccal insulin. Buccal mucosa lines the inner cheek and buccal formulations are placed in the

mouth between the upper gingivae (gums) and the cheek (sometimes referred to as the buccal pouch) both for local and systemic delivery. The absorption potential of the buccal mucosa is influenced by molecular weight, hydrophilicity, electrostatic charge, conformation, stereospec- ificity, immunogenicity, solubility and partition coefficient of the peptides and proteins includinginsulin .. The experimental observations led to the conclusion that insulin could not permeate through buccal mucosa in the absence of absorption enhancers. Buccal administration of insulin with absorption enhancers showed a maximum 12% pharma- cological activity. In another study, it was found that a certain amount of time is required for insulin molecules to be taken up by the buccal mucosa and the absorption profile of plasma insulin was found to be dependent upon the time of application of dosage form (36). Therefore, the most successful approach for buccal mucosal delivery of insulin has been a bioadhesive formulation.

E.g. : generax biotechnology corporation (Toronto Canada) developed a preparation containing liquid formulation (oral – lynx) of recombinant human insulin and absorption enhancers and propeller and rapid mist ® device which sends small particles from aqueous spray into oral cavity.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Aerodose
Trans-derma
Intophoresis
Sonophereis
Microdermal a
Insupatch
Hyaluronidase
Warming of sit
ra-peritoneal/
ra-portal
Transdermal

4. Inhalation

Inhalational route of has advantage of rapid absorption due to the large surface area and close proximity of air and blood compartment. It also includes absence of peptides that breaks inulin and has ability to bypass first pass metabolism. This drug delivery system follows trancytotic and Para cellular mechanism.[49] In this route deep lung delivery of insulin influenced by several factors such as aerodynamic particle size, particle speed and ventilator parameters. Biopharmaceuticals with with mass median aerodynamic diameter of 1-3 micrometer reach he alveolar surfaces where they undergo different fates such as clearance by alveolar microphages , binding to surfactant and enzymatic degradation; high molecular weight proteins shows slow alveolar absorption . Moreover patient ability to perform an appropriate inspiration maneuver is another determinant for reproducible delivery of the drug to distal part of the lung. Inhalers for this delivery system belong to four categories metered dose inhaler ,spacer and holding chambers ,dry powder inhaler and nebulizer. EXUBERA by Pfizer was first inhalational insulin preparation introduced in market in 2006 and withdrawn of this takes place in 2007 because of 1) high cost 2)bulky delivery device 3)concern related to pulmonary function and 4) less preference by patient.[53] Exuberate was a dry powder inhalation which has similar properties to insulin apart and has fast onset of action(10-15) min. It reduces post prandial glucose level significantly.Exubera contradicate in smoker and it also required pulmonary function test before treatment with it.

AFREEZA, This is another inhalational preparation depend on techno sphere . It controls post prandial glucose level with onset of action of 15 mins and duration 2-3 hrs. Techno sphere technique shows side effect such as change in pulmonary function but this is small , occurred early and non progressive for 2 yrs.

Inhalational insulin as compared to other routes such as subcutaneous is good for short duration of action . On large scale it is accepted for T1DM patient. Tis route is limited by factors such as bioavailability , high cost, technical issues associated with inhaler and long term safety.

5. Artificial pancreas

They also called as integrated close loop control (CLC), This system utilizes real time feedback from continuous glucose monitoring (CGM), To continuous adjust insulin administration via an insulin pump. The medical equipment approach involves combining a continuous glucose monitor and an implanted insulin pump that can function together with a computer controlled algorithm to replace the normal function of pancreas . The development of continuous glucose monitors has led to the progress in artificial pancreas technology using this integrated system. This method mimics physiology of beta cells to certain extent an limited by delays in both insulin action and blood glucose sensing .First continuous glucose monitor (CGM) approved in 2016 developed by Dexocom. It requires pricking of finger twice a day for calibration of the device and it show notification on their device or on mobile app if glucose level fall under certain level. In 2018 next g6 model CGM by Decoma which last upto ten days and does not need finger prick caliberartin.IN SEP 2016 FDA approved the Medtronic MINIMED 670G , which was the first hybrid closed loop system .It senses a diabetic persons basal insulin requirement and automatiacally adjust its delivery to the body. This not for patient under 7 yrs and not for those required less than 8 units of insulin. Insulin like linjeta which raoid acting and absorption enhancers my help in improving response time of CLC sytem. This sytem used for T1DM patients. This system is less costly , more accessible and easily upgradable. With more advancements in technology, even better outcomes can be expected in future.

6. Transdermal

Although skin is easily accessible and has large surface area , it is impermeable to large hydrophilic peptide due to intracellular lipid layer of stratum cornim. There are ways to break down lipid layers and deliver insulin transdermal . This ways are as follows:

1) Iontophoresis, uses small electric current

2) Sonophorosesis uses ultrasound waves

3) Microdermal ablation by removing stratum cornium.

4) Eectroporation utilizes high voltage pulses that are applied for very short time [88]

5) Transfersulin is the insulin encapsulated in tanseferosome an elastic , flexible vehicle which squizze by itself to deliver drug through skin spores.

6) Insupatch , a device developed aa an add-on to minsulin pump that allpies local heat to skin in order to increase3 the

absorption of insulin.

Additionally microneddles of 1 micrometer diameter and of various engthcan deliver insulin in effective , accurate and precise manner. Transdermal drug delivery limited by skin injury , burn or blister .

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