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INSULIN DRUG DELIVERY: STRATEGIES AND TECHNOLOGIES

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ABSTRACT

In today's era, most of the pharmaceutical companies are investing and doing workout on developing non-invasive routes for insulin delivery. Insulin delivery by non-invasive route is an area of current interest. All patients with type 1 and many with type 2 diabetes are treated with insulin. Future possible methods and routes of insulin delivery are reviewed. Delivery of insulin by injectable is only successful route in acute diabetes. New milestones had have been achieve in research for insulin delivery by peroral, nasal, pulmonary, transmucosal, buccal, ocular, rectal and vaginal routes. Bioavailability of insulin by non-invasive routes is less compared with subcutaneous insulin. This view will no longer sustain because in next few years several novel delivery devices and dosage forms could be launched that may result in improved and easy control of diabetes in patients.

Keywords: Alternate insulin delivery systems, nasal insulin delivery, non-invasive insulin delivery, diabetes

INTRODUCTION:

For over 88 years patient have been reliance on parenterals as the main route of insulin administration. For most patients with type I diabetes, the tedious part of the treatment is to tolerate needle after needle, both for glucose measurement and for insulin delivery. A rigorous research effort has been undertaken worldwide to replace subcutaneous route by a more accurate and non-invasive route. The therapeutic insulin era began on 11th of January in 1922 with the first clinical use of insulin by Banting and Best which is miracle of 20th century medicine.⁽¹⁾ Insulin is the only

known pharmaceutical example where greater reactivity is observed in the crystalline state relative to its amorphous phase.⁽²⁾ Most of protein based drugs such as monoclonal antibodies, growth hormones, vaccine etc. are still being developed as injectable for initial market launch.⁽³⁾

This is because non-invasive routes are suitable for small molecules and may require transport enhancers. Diabetes mellitus is the third leading cause of death after heart disease and cancer in developing countries. WHO report estimated that by 2030, number of people affected will be around 366 millions. Normal blood glucose is around 90 to 120

mg/dL.⁽⁴⁾ Food and Drug administration in 1996 provides approval for subcutaneous delivery of insulin and its sale.⁽⁵⁾ Insulin is polypeptide hormone produced by the β -cells of islets of Langerhans of pancreas and is main key for metabolism of carbohydrate, fats and proteins. It is anabolic

hormone and promotes synthesis of glycogen, tricylglycerols and proteins. Human insulin has molecular weight 5734 and contains 51 amino acid in two polypeptides chains. The chain A has 21 amino acids and chain B has 30 amino acids. These chains held together by two interchain disulfide bridges.⁽⁶⁾

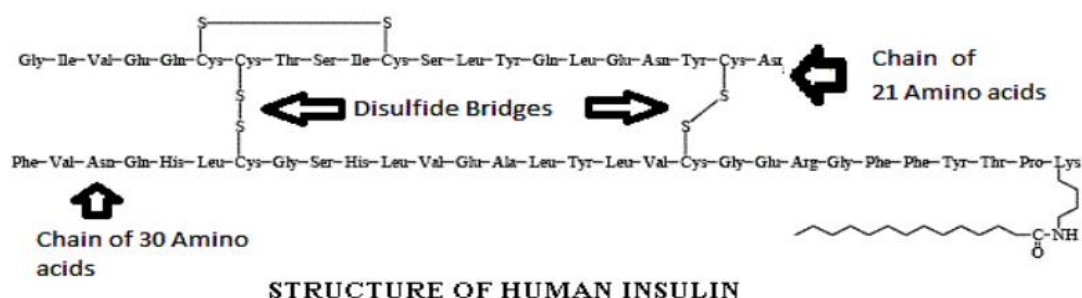


Figure 1: Figure represent structure of human insulin

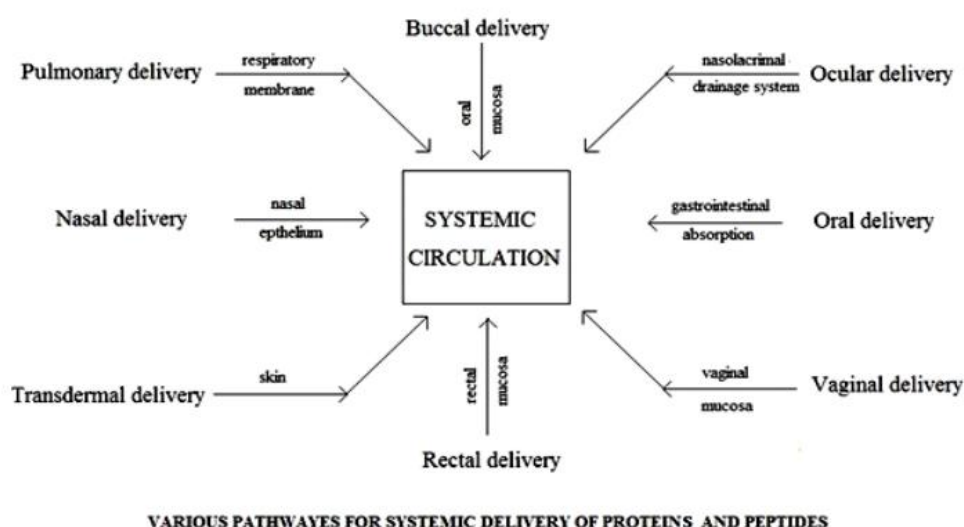


Figure 2: figure showing various pathways for systemic delivery of proteins and peptides.

Table 1: Comparison between type 1 and type 2 diabetes⁽⁷⁾

Parameters	Type 1 diabetes	Type 2 diabetes
Age at onset	Usually under 30	Usually over 40
Body weight	Normal	Obese
HLA association	Positive	Negative
Family history	Common	Nearly universal
Insulin in blood	Little to none	Some usually present
Islet cell antibodies	Present at onset	Absent
Prevention	0.2% - 0.3%	6%
Symptoms	Polyuria, polydipsia, polyphagia, weight loss, ketoacidosis	Polyuria, polydipsia, peripheral neuropathy

Control	Insulin, diet and exercise	Diet, Exercise and oral hypoglycaemic drug or insulin
Ketosis	Very common	Rare
Vascular and neural change	Eventually develop	Will usually develop

Absorption of peptide drug depends upon:

- A. Dosage form and formulation
- B. Physiological factors (e.g. food, intestinal motility, flow rate, transit time)
- C. Physicochemical factors (e.g. property of peptide pKa, molecular size, lipophilicity, stability, flow rate)

Main mechanism for insulin absorption were transcellular and paracellular.⁽⁸⁾

Table 2: Half life of various protein and peptides are:⁽⁹⁾

Protein/ Peptides	Half life(min)
YGGFM	15.1 ± 2.0
YGGFL	20.8 ± 1.5
YAGFM	226.5 ± 1.5
Substance P	5.8 ± 0.2
Insulin	98.1 ± 6.4
Pro-insulin	55.7 ± 7.0

Table 3: Percentage of dose absorbed from various routes after insulin administration.⁽⁹⁾

Routes	Insulin (Mw 6000)
Oral	0.05%
Nasal	30%
Buccal	0.5%
Rectal	2.5%
Vaginal	18%
Subcutaneous	80%

PULMONARY DELIVERY

In this the drug (insulin) is delivered through the airways. Advantage is that the blood stream can be reached from the alveolar epithelium without penetration enhancers, which facilitates a good bioavailability.⁽¹⁰⁾ Inhaled insulin therapy may be especially useful for patients with true needle phobia and those with extensive cutaneous

lipodystrophy at injection sites.⁽¹¹⁾ The pulmonary absorption of macromolecules decreases with increase in molecular weight of the macromolecule.⁽¹²⁾ For effective distribution in lungs of drug, required particle size should be in 1-5µm.⁽¹³⁾ In clinical trials, patients have been generally more satisfied with inhaled insulin than with subcutaneous insulin.⁽¹⁴⁾ The kinetics of absorption decreases significantly with increasing molecular weight.⁽¹⁵⁾ Exubera (Pfizer), the only device for insulin delivery that has been approved by the Food and Drug Administration is an inhaler that delivers a dry powder formulation of human insulin produced by means of recombinant DNA technology. After oral inhalation of a single dose of insulin by this device, approximately 40% of the dose reaches the deep lung and 10% dose is bioavailability.⁽¹⁶⁾ Use of inhaled insulin in patient with lungs diseases such as asthma or chronic obstruction pulmonary diseases is not recommended, since absorption of insulin in these patients is unpredictable.⁽¹⁷⁾ Active smoking increases the rate and extent of insulin absorption.⁽¹⁸⁾ Major drawback of inhaled insulin is that it is more expensive. Inhaled insulin causes a more rapid decrease of the bloodglucose concentration than subcutaneously administered insulin.⁽¹⁹⁾ A chronic administration of absorption enhancers (e.g., alcohol, bile acids, and cyclodextrins) can damage alveolar epithelium.⁽²⁰⁾ Human insulin microcrystals with

lactose carrier were produced for pulmonary delivery with average particle diameter was 2.3µm and a narrow, monodispersed size distribution.⁽²¹⁾

NASAL DELIVERY

The absorption is relatively small. For insulin bioavailability of the order of less than 1% have been reported.⁽²²⁾ The nasal mucosa offers direct access to the compartment of the central nervous system via the olfactory route.⁽²³⁾ The absorption of such molecules is dependent on the physicochemical and physiological factors, the most important of which are the site of deposition in the nasal cavity, the mucociliary clearance mechanism, passage through the mucus layer, transport across the epithelial membrane and enzymatic degradation of the peptide or protein.

Improved nasal bioavailability of the eel calcitonin and insulin by means of formulation employing carbopol 941 and carboxymethylcellulose (CMC) were investigated. The absorption of insulin was enhanced by the carbopol gel formulation but not by the CMC formulation.⁽²⁴⁾ Hyaluronate sodium (HAS) is a natural polymer and a major component of intestinal tissue. It improves the absorption of insulin and the effect was concentration dependent.⁽²⁵⁾ The pharmacokinetics and pharmacodynamics of intranasal insulin formulation Nasulin™ were studied. Intranasal formulation was generally well tolerated and relatively well absorbed.⁽²⁶⁾ It was found that after administration of the ethylhydroxyethylcellulose (EHEC) in combination with insulin to rats, the plasma glucose levels were found to be decreased slightly (12%). When EHEC was made hypotonic as compared with isotonic or hypertonic, the absorption of insulin was

improved.⁽²⁷⁾ Freeze dried insulin was investigated with bioadhesive powder dosage form for the administration in nasal cavity. Formulation tests give significant clearance in plasma glucose level in dog and rabbit models.⁽²⁸⁾ Chitosan based nasal insulin gel have been investigated. The required for the nasal gel to attain the lowest serum glucose levels was around 1.5 hr to 2 hr where for subcutaneous formulation it was 3 hr.⁽²⁹⁾ Thiolated polymers have been demonstrated to show a strong permeation enhancing effect for the uptake of drugs from the nasal mucosa.⁽³⁰⁾ Reshma D'Souza et al. formulated nasal gel and performed preclinical and clinical studies. It was observed that insulin rapidly passes into systemic the circulation and this formulation is not feasible for chronic patients in the long run.⁽³¹⁾ Large surface area of nasal mucosa facilitates absorption.

Various factors effecting nasal absorption are:⁽³²⁾

1. Physiological factors
 - a. Speed of mucus flow
 - b. Change in physiological state
 - c. Atmospheric conditions in the nasal cavity.
2. Dosage form factors
 - a. Physicochemical properties of the active drug
 - b. Concentration of the active drug
 - c. Physicochemical properties of the pharmaceutical excipients used.
 - d. Density, viscosity and pH characteristics of the formulation
 - e. Toxicity of the dosage form
3. Administration factors
 - a. Size of dose
 - b. Site of deposition

- c. Mechanical loss posteriorly into the oesophagus
- d. Mechanical loss to other regions in the nose
- e. Mechanical loss anteriorly from the nose

- 3. Growth hormones
- c. Horseradish hormones
- d. Pancreatic hormone
 - 1. Insulin
 - 2. Glucagon
- e. Posterior hormones
 - 1. Oxytocin
 - 2. Vasopressin

List of proteins and biological products being studied for nasal delivery

- 1. Amino acid
- 2. Peptides
 - a. Calcitonin
 - b. SS-6
 - c. Cholecystokinin
 - d. Enkephalins
 - e. Kyotorphin
 - f. Pentagastrin
 - g. Secretin
 - h. Substance P
- 3. Polypeptides and proteins
 - a. Albumins
 - b. Anterior pituitary hormones
 - 1. Adrenal corticotropic hormones
 - 2. Gonadotropin releasing hormones

Disadvantage or barrier to nasal absorption of insulin is due to mucociliary transport mechanism, enzymatic activity and low permeability nasal epithelium.

Chitosan salts such as chitosan glutamate and chitosan hydrochloride have been used in-vivo as absorption enhancers for peptide drugs. The nasal application of insulin with chitosan glutamate led to a significant reduction in blood glucose levels of rats and sheep.⁽³³⁾ Glutaraldehyde cross-linked microspheres showed better reduction of blood glucose level than citric acid cross-linked microspheres in albino rabbit.⁽³⁴⁾

Table 4: List of various non-invasive insulin products and their status.

NAME	NATURE OF PRODUCT	OF	ADVERSE EFFECT	COMPANY	STAGE OF DEVELOPMANT
Generex lyn™	Oral- Oral spray		Not Available	Generex	In market
Exubera	Inhaled powder	insulin	Shortness of breath, sore throat and dry mouth ⁽³⁵⁾	Pfizer	FDA approved (in market)
PassPort™ System	Transdermal insulin patch		Not Available	Alter Therapeutics	In FDA clinical trials
ORMD-0801	Oral capsule	insulin	Not Available	Oramed	Phase 2b non-FDA clinical trials completed
AEERxIdms	Inhaled solution	insulin	Not Available	Aradigm and Novo Nordisk	In clinical phase III
IN-105	Oral insulin		Not Available	Biocon	In clinical phase III
HIIP (Air®)	Inhaled powder	insulin	Not Available	Alkermes and Eli Lilly	In clinical phase III
NIN-058	Tablet		Not Available	Nobex corporation	In clinical phase II

VIAtab	Oral sublingual prandial insulin	Not Available	and GlaxoSmithLine	
Cobalamin (TM)	Nanoparticle for oral delivery of insulin	Not Available	Biodellnc	In clinical phase I
Technosphere®	Inhaled insulin powder	Not Available	Access pharmaceutical Inc.	Preclinical studies
MedTone®	Inhalation device	Not Available	Aerogen	Phase III trials FDA- new drug application (36)
			Mannkind Crop.	Not Available (37)

ORAL DELIVERY

The major problems involved with the oral administration of insulin are acid and enzymatic decomposition by the gastric medium and poor absorption in small intestine due to its macromolecular structure. Number of strategies had been designed to overcome the barriers for absorption through gastrointestinal tract.⁽³⁸⁾ Little success has been achieved in this direction. Only very small fraction of an oral insulin dose becomes available for absorption through the gastrointestinal membrane.⁽³⁹⁾ The absorption of insulin from the intestine was shown to be feasible if it is delivered directly into the ascending colon with sodium deoxycholate and achieved a 50% reduction in blood glucose levels.⁽⁴⁰⁾ The silica-phatidylcholine-insulin formulation found to be effective in reducing glucose level.⁽⁴¹⁾ Tests are performed on enhancing ability of two absorption enhancers, sodium glycocholate and sodium salicylate in different parts of rat's gastrointestinal tract.⁽⁴²⁾

Various approaches used for oral delivery of insulin are:

1. **Entrapment in liposomes:** An interesting approach that was development and applied to the oral delivery of peptide is through liposomes. 50% reduction in blood glucose

levels in normal rats by an insulin containing liposome has been achieved.⁽⁴³⁾ An extensive study on the delivery of insulin-entrapped liposome on the dogs had conducted in the duodenal region via a catheter.⁽⁴⁴⁾ The degradation of macromolecules can be avoided by encapsulation of sensitive molecules in protective carrier systems such as stabilized liposomes and nanoparticles. A reduction of glycemia in diabetic rats by 50-60% after intragastric administration of insulin in polyalkylcyanoacrylatenanocapsules was observed.⁽⁴⁵⁾

2. **Encapsulation in Azopolymer coating:** The feasibility of using encapsulation in azopolymer coating as a potential oral delivery system for the systemic delivery of therapeutic peptides and proteins. This involves the coating of peptides with polymers with azoaromatic groups and the cross linking of azopolymer to form an impervious film to protect the orally administered peptide molecules from metabolism and degradation in the stomach and small intestine.⁽⁴⁶⁾
3. **Emulsion formulation:** water-in-oil-in-water type multiple emulsion formulation has been developed to deliver insulin orally to rabbits

and diabetic rats to the jejunum and reduction in urinary glucose level in the diabetic rats have been observed.⁽⁴⁷⁾

4. **Encapsulation in erythrocytes:** Erythrocytes have been investigated as a drug carrier for the intravenous sustained delivery of drug. In-vivo studies have been performed.⁽⁴⁸⁾
5. **pH-responsive complexation gels:** In this technology, pH-responsive carrier were designed to protect the insulin from acidic environment of stomach before releasing drug in the small intestine. Lowman et.al. prepared and stud a delivery system consisting of insulin containing microparticles of cross-linked copolymers pf poly(methacrylic acid) which are grafted by ethylene [PPA-g-EG]. During studies strong hypoglycaemic activity was observed.⁽⁴⁹⁾
6. **Microspheres:** Insulin has been incorporated into microspheres of poly[bis(p-carboxyphenoxy)propane] anhydride and sebacic acid [PCPP-SA] 50:50. The loading of insulin was 15% in these microspheres, which were between 850 and 1000µm in diameter. Much of the insulin is released over the first 24-48 hr and continues to release for 120hr.⁽⁵⁰⁾ Albumin microspheres of insulin were also investigated⁽⁵¹⁾
7. **Microbeads and Pellets:** Insulin has been formulated in controlled release microbeads and pellets. A solvent evaporation microencapsulation procedure was used to produce microspheres with up to 20 % by weight of insulin. Solvent casting techniques were used to prepare pellets. No deactivation of the micro molecule or inflammation at the

implant site or other adverse effect was observed.^(52, 53)

8. **Emisphere:** Delivery of insulin in form of emisphere was investigated in late 1990s and clinical studies were performed in between 2001-2004 by U.S. base company. Further research was stopped by company as per the statement on their web homepage.⁽⁵⁴⁾
9. **Gel-Core-solid lipid nanoparticle (SLN):** Gel-Core-solid lipid nanoparticle (SLN) of insulin with the hydrogel core and lipid shell were prepared by double emulsion and thermal sensitive gel technology, with the intention to improve the entrapment efficiency. Pluronic F127 and Glycerylpalmitostearate were selected as hydrogel material and lipid material, respectively.⁽⁵⁵⁾
Hexyl-insulin monoconjugate 2 (HIM2) is recombinant insulin with a small polyethylene glycol 7-hexyl group attached to protein 828 amino acid lysine. The results of phase I/II clinical trials suggests that oral HIM2 was safe and may prove effective in controlling postprandial hyperglycemia.⁽⁵⁶⁾

PARENTERAL ROUTE

Most protein and peptides used for systemic therapeutic purpose have high molecular weights and are hydrophilic and there for only suitable mean of administration is injection.⁽⁵⁷⁾ Due to enzymatic degradation insulin is administer parentally there for its absorption depends upon injection site, injection depth, concentration used and massage at site of injection.⁽⁵⁸⁾ Absorption of insulin followed this order, abdomen region >

arm > buttocks > thighs.⁽⁵⁹⁾ If the injection is too deep and does not distribute the insulin solution or suspension in the subcutaneous tissue solution or suspension in the subcutaneous tissue but rather in the muscle, absorption is faster due to the greater vascularisation of muscles with respect to subcutaneous fat. If the injection is too superficial then process is slower and incomplete. Injection of high volume of insulin has poor absorption as compared to smaller volume of solution. Massage with cotton wool soaked with disinfectant should be avoided.

Various approaches used for parenteral delivery of insulin are:

1. **Long acting insulin injectables:** For long acting insulin preparations complexation of insulin with zinc salt and base protein were made. For example protamine -Zn-insulin suspension. The amorphous Zn-insulin complex, which has a rapid onset (0.5 – 1.0 hr) and have 12- 16 hour action.
2. **Infusion pumps for insulin delivery:** A continuous, subcutaneous insulin infusion device had been developed. Intraperitoneal delivery of insulin using an implantable micropump has been investigated.⁽⁶⁰⁾
3. **Self regulating delivery system:** In this approach, development of an artificial beta cell that consist of glucose sensitive hydrogel membrane for the feed back controlled delivery of insulin.
4. **Implants (vapour pressure activated drug delivery):** The drug reservoir is in solution form and is contained inside an infusate chamber which is physically separated from the vapour

chamber. The vapour chamber contains a vaporizable fluid which vaporizes at body temperature and creates vapour pressure. Due to this pressure the drug to move out of the infusate chamber into the blood circulation at a constant flow rate.⁽⁶¹⁾ An implantable infusion pump for the constant infusion of insulin for antidiabetic medication had been developed.⁽⁶²⁾

5. **Transferosomes:** These are lipid vesicles made of soybean phosphatidylcholine loaded with insulin that are flexible enough to pass through pores smaller than themselves. Transferosomes transport the insulin with at least 50% of the bioefficiency of a subcutaneous injection. The application of insulin-laden transferosomes over a skin area 40 cm²(square) would provide the daily basal insulin needs.⁽⁶³⁾

TRANSDERMAL DELIVERY

Poor oral availability has generated need of focusing the attention on non-oral route for routine and effective drug administration. Skin permeability enhancers and other excipients, which promote skin permeation have to be considered as an integral part of the most of transdermal formulation because of the barrier properties of the stratum corneum. The penetration enhancers have been classified into three categories, i.e. lipophilic solvents, surface active agent and two component systems. Basic components of transdermal devices are polymer matrices that regulate the release of drug, the drug absorption/permeation enhancer, excipients

and adhesives.⁽⁶⁴⁾ Many attempts were made to overcome the skin barrier to allow insulin transfer. This includes techniques such as sonication, iontophoresis, transfersomes.⁽⁶⁵⁾ Tropical formulations based upon liposomes may offer some opportunities for polypeptide and protein drug delivery.⁽⁶⁶⁾ Studies have been performed with highly deformable liposomes containing insulin after application to intact skin. Hypoglycemia is observed after 90-180 minutes, depending upon the carrier composition. The decrease in the blood glucose concentration is about 35% of that of subcutaneously administered insulin but the cumulative effect significantly larger.

Various approaches used for transdermal delivery of insulin are:

1. **Iontophoresis:** Iontophoresis facilitated transdermal delivery was investigated to deliver insulin. It is a concept through which delivery of protein (i.e. insulin) is facilitated by direct electric current by enhancing the delivery of drug ions into the skin and surrounding tissues. Transport of hexameric insulin by iontophoresis across mouse skin is poor, but smaller, monomeric sulfated insulin and insulin analogues with increased negative charge are transferred more efficiently.⁽⁶⁷⁾ Glucose levels in diabetic rabbits can be effectively controlled by insulin delivered transdermally by a DC- producing iontophoretic delivery device.⁽⁶⁸⁾ In study using diabetes rats, iontophoresis of bovine insulin (10-200 IU/ml) was not effective in decreasing the plasma glucose level when given alone, but application

of a depilatory cream for hair removal followed by iontophoresis of bovine insulin produced a concentration dependent fall in plasma glucose level, indicating the necessity of permeation enhancers.⁽⁶⁹⁾ Novartis animal health signed an agreement with Australian pharmaceutical company Phosphagenics Ltd to develop a transdermal insulin delivery system for pet.

2. **Patches:** The Altea therapeutics Passport™ system was the first product in development shows in US FDA clinical trials to provide a non-invasive, controllable and efficient way to deliver insulin via a patch on the skin. The passport™ system enables fast, controlled drug delivery without the pain of an injection or the possible complications associated with inhaled medications.⁽⁷⁰⁾
3. **Jet type injector device:** jet injectors are new devices that administered insulin without needles by delivering a high pressure stream of insulin into subcutaneous tissues, example Precijet-50. It is suggested that jet injectors should be advised to those patients who develop problems with injection route.⁽⁷¹⁾ This device have advantages of simple design, can mix two type of insulin and small in size.
4. **Sonophoresis:** Low frequency ultrasound has been investigated to enhance permeation of insulin macromolecules through human skin by several folds. The had be studied that permeability achieved by 1 hr of sonophoresis performed three times daily would allow a typical daily would allow a typical daily dose of insulin of 36 units.⁽⁷²⁾
5. **Patch type infusion pump (IIP):** Patch type infusion pump technologies has been created

by Matthew J Skladany et al. It is comprise of an insulin reservoir, delivery system and a cannula.⁽⁷³⁾

RECTAL DRUG DELIVERY

Many experiments have been conducted to investigate the renal delivery of insulin formulation. Absorption is enhanced by use of absorption promoting agents. Bioavailability in humans remains very low (4-10%) and appears not to be dose related.⁽⁷⁴⁾ Microenema has been formulated to deliver insulin. On addition of 4% gelatine in formulation enhance the absorption of insulin.⁽⁷⁵⁾

VAGINAL DELIVERY

The vaginal preparations in market are for tropical action, e.g. vaginal infections, spermicidal agents and labour inducing agents etc. Reduction in blood glucose levels have been observed in dog when insulin is administered intravaginally.

Advantages:

1. The possibility of prolonged retention of delivery system.
2. Avoid first pass metabolism.
3. Minimal proteolytic degradation.

BUCCAL DELIVERY

Thick multilayer barrier and the constant flow of saliva are the main problems for insulin delivery through this route.⁽⁷⁶⁾

CONCLUSION

Subcutaneous route provides maximum insulin bioavailability. Pulmonary delivery appears to be most feasible non-invasive route. Ongoing phase 3

studies will determine its safety, tolerability and feasibility. Coming few year promises a major change in the delivery of insulin, which will be beneficial for the billions reliant on subcutaneous administration.

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