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REVIEW ARTICLE

Recent Approaches in Insulin Delivery

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ABSTRACT

Insulin remains indispensable in the management of diabetes mellitus since its discovery in 1921. The foreignness of early available porcine and bovine insulin led to the development of human insulin by transpeptidation and biosynthesis in microorganisms. Needle phobia and stress of multiple daily injections led to the investigation and exploitation of all promising routes, ranging from nasal to rectal, by a wide variety of devices and delivery systems. This article describes the development of human insulin, various routes for delivery of insulin (including oral, nasal, buccal, rectal, and pulmonary), and various devices for regulated, safe, and convenient insulin delivery. The article reviews some recent advances in insulin delivery such as the bioresponsive and self-regulated insulin delivery system.

INTRODUCTION

The history of the galenic pharmacy of insulin represents a unique chapter in the therapeutics. Insulin remains indispensable in the management of diabetes mellitus, since its discovery in 1921 by Banting and Best (1). For more than a decade, that is, from 1921 to 1936, unmodified, short-acting ordinary insulin was the only preparation available. The treatment of diabetes with one injection of this type of insulin was not sufficient and therefore stress and discomfort of multiple daily injections prompted numerous attempts to prolong the subcutaneous absorption of insulin. This led to the discovery of the lente insulins.

The most unpleasant thing about insulin is that it needs to be given through an injection and therefore a search for a noninjectable preparation of insulin which could be administered by oral, nasal, rectal, or inhalated routes continues with some promise of a breakthrough in the future.

SOURCES OF INSULIN

Insulin is a hormone secreted by the beta cells of islets of langerhans of the pancreas. When this supply of (or response to) insulin is inadequate, diabetes mellitus results. The person with diabetes mellitus has to be supplemented with insulin obtained from other sources.

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Earlier insulin was obtained by extraction of the pancreas of the cow, pig, or sheep. Bovine and porcine insulins were very impure. They had to be purified by either repeated crystallization, HPLC, or ion-exchange chromatography.

Highly purified preparations (2) were commercially available for clinical use, such as single-peak or single-component insulins; monocomponent insulins; and chromatographically purified porcine insulin. Some major differences between the highly purified and conventional insulins are given in Table 1.

Production of animal insulin posed a major problem because a very large number of animals were needed to meet the worldwide requirements and therefore an alternative source of insulin was developed. A breakthrough occurred with the use of DNA recombinant technology and a DNA insulin preparation which was identical to human insulin was made available.

Human Insulin (3): Methods of Preparation (4–12)

Human insulin was produced by a genetic engineering process from a special laboratory strain of *E. coli*. It was the first human-type insulin to be approved by the FDA for marketing in 1982.

Human-type insulin is currently manufactured by three methods: (i) biosynthetic human insulin using genetically engineered microbes from *E. coli* and *bakers yeast*, (ii) semisynthetic human insulin, and (iii) proinsulin route.

Biosynthetic Human Insulin (4–8)

Biosynthesis is a process in which a synthetic gene sequence of DNA coded for a desired protein is inserted into a plasmid. This plasmid is then inserted into *E. coli* and cultured. For the A and B chains of insulin, fermentation is carried out separately. The DNA sequence's coding for A and B chains of insulin are synthesized chemically. The A-chain gene is linked to a large protein tryptophane synthetase gene by a methionine codon. This synthesized plasmid is inserted in *E. coli* culture. The B-chain gene is also prepared in a similar manner and inserted in a separate *E. coli* culture. The cells are harvested and insulin chains are cleaved by treatment with cyanogen bromide. A and B chains are then combined by air oxidation to produce human insulin. This insulin is described as "chain recombinant bacterial" (crb).

Semisynthetic Human Insulin (9,10)

Porcine insulin is produced by the usual acid–ethanol extraction and salting out methods. This crude insulin is then enzymatically converted by transpeptidation technique. Basically, porcine and human insulins differ only by a single amino acid, i.e., alanine in B-30 position. Alanine is replaced by threonine to produce human insulin. This insulin is designated as enzymatically modified porcine (emp) insulin.

Proinsulin Route (11,12)

Instead of separate fermentation of A and B chains, the entire proinsulin gene is inserted in a similar way into *E. coli* cultures and harvested to produce more proinsulin chains. Proinsulin is later cleaved by carboxypeptidase-B to yield human insulin and C-peptide, which is then further purified. This type of insulin is called "proinsulin recombinant bacterial" (prb).

Table 1

Differences Between Highly Purified and Conventional Insulins

Feature	Highly Purified Insulin	Conventional Insulin
Species	Porcine	Bovine or porcine
Purification Process	Chromatography	Recrystallization
Purity	Proinsulin free	Proinsulin
Immunogenicity	Less immunogenic	Immunogenic
pH	Neutral (7)	Acidic (2.5–3.5)
Miscibility	Mixing possible	Mixing not possible
Compatibility with body fluids	Compatible	Less compatible

Uses of Human Insulin

In the following cases, human insulin can be used:

1. All insulin-dependent diabetes mellitus (IDDM) patients who can afford it.
2. Patients who are on conventional insulin but show an allergy to it.
3. Insulin lipodystrophy.
4. Insulin resistance.
5. Gestational diabetes.

Human insulin can also be used for short-term cases such as infection, stress, surgery, and diabetic ketoacidoses.

INSULIN DELIVERY

Insulin has been given to diabetic patients exclusively by parenteral administration via the subcutaneous route. The usual duration of action is relatively short, i.e., 4–8 hr, and therefore 2–4 daily injections are required for proper control of severe diabetes.

An important advance in achieving the prolongation of insulin activity was made by complexing it with protamine. The protamine–insulin complex was found to be unstable but its stability was later improved by the addition of zinc chloride. Further investigations showed that controlled crystallization of zinc–insulin complex, without the use of proteins, formed an extremely long-acting insulin.

Three long-acting zinc–insulin preparations (13), i.e., semilente, lente, and ultralente insulin, have been formulated. These differ in their onset, intensity, and duration of action, and details are given in Table 2.

ROUTE OF INSULIN DELIVERY

Parenteral Route

Intramascular (i.m.) Insulin Delivery

Insulin delivery by the i.m. route is used in ketoacidosis and insulin is absorbed more rapidly than via the subcutaneous route, presumably because of higher capillary density in muscle. Absorption can be further accelerated by exercise or massage.

Intravenous (i.v.) Insulin Delivery

Insulin delivery by the i.v. route requires access to central veins. It is suitable only for short-term clinical use because of complications such as thrombosis and septicemia. The carefully regulated i.v. insulin infusion can achieve good blood glucose control and almost 100% bioavailability.

Table 2

Normoglycemic Activity and Duration of Action of Some Commercial Insulin Products

Insulin Preparation	Normoglycemic Activity		
	Onset (hr)	Peak (hr)	Duration (hr)
Regular Insulin[a]	0.5–1.0	2–3	4–8
Insulin–Zinc Complex[b]			
Semilente	0.5–1.0	5–7	12–16
Lente	1.0–1.5	8–12	24
Ultralente	4–8	16–18	>36
Insulin–Zinc–Protein Complex			
Globin–zinc–insulin injection	2	8–16	24
Isophane–insulin suspension	1–1.5	8–12	24
Protamine–zinc–insulin injection	4–8	14–20	36

[a]Regular: solution of porcine insulin.

[b]Semilente: suspension of amorphous bovine insulin–zinc complex; lente: suspension of 70% crystalline and 30% amorphous bovine insulin–zinc complex; ultralente: suspension of crystalline bovine insulin–zinc complex.

Intraperitoneal (i.p.) Insulin Delivery

The peritoneum is being considered as a possible site of insulin delivery for various reasons: The visceral peritoneal membrane has the same blood supply as the small and large bowel; the surface area of the peritoneum is large; and the peritoneum is suitable for long-term implantation of infusion cannula, without the thrombic risks of i.v. infusion.

Continuous Subcutaneous Insulin Infusion (CSII) (14–19)

The CSII mimics nondiabetic insulin delivery by infusing insulin from portable pumps at an adjustable rate with patient-activated boosts before meals. Pumps use only short-acting insulin which is delivered in two modes, basal and bolus. In the basal mode the pump delivers insulin continuously at a slow programmed rate for a particular time interval and provides the constant low level of plasma insulin during the basal and post-absorptive state. In bolus mode 15–30 min before each meal, the patient presses a button and the pump delivers a bolus to provide an additional quantity of insulin to cover the meal. An average of 40–60% of the total daily insulin is delivered in the basal mode with the remaining being given in three roughly equal boluses at meals. The total daily insulin requirements may be calculated using a Biostator or an i.v. insulin infusion system.

Nonparenteral Routes of Insulin Delivery

The stress and discomfort of multiple daily injections prompted numerous attempts to develop a safe and effective nonparenteral route for insulin delivery.

Potential routes for insulin administration are discussed below.

Oral Delivery of Insulin (20–31)

Oral administration of insulin is an attractive concept, but insulin is degraded by the strongly acidic environment in the stomach and by proteolytic enzymes in the intestinal tract as well as presystemic elimination in the liver. It has been reported that only a very small fraction of an oral insulin dose becomes available.

The following approaches have been evaluated as potential means to enhance the oral delivery of insulins.

Entrapment in Liposomes (20,22–24)

Stefanov et al. (24) investigated the feasibility of delivering insulin systemically by the oral route using liposomes prepared from phosphatidylcholine and cholesterol and reported that no change in blood glucose levels was noted in normal animals but a significant reduction was obtained with diabetic rats with the maximum effect observed within 3 hr. However, negative results were later reported.

The feasibility of delivery of insulin by oral liposome formulations needs further work with standardization of liposomes composition and improvement of physicochemical stability.

Encapsulation in Azopolymer Coating (21)

This approach involved the coating of insulin with polymers having azoaromatic groups and the crosslinking of azopolymers to form an impervious film to protect the orally administered insulin from degradation. When the azopolymers-protected insulin reaches the large intestine, the microflora reduces the azo bonds to break the crosslinking in the polymer film and hence releases the drug in the colon for absorption.

Nasal Delivery of Insulin (32–43)

As early as 1923, clinicians have attempted to administer insulin through the nasal mucosa. When insulin is combined with absorption enhancers and administered as an aerosol to the nasal mucosa, effective circulating levels of insulin can be achieved almost as rapidly as with an i.v. bolus.

Insulin requires the additional presence of absorption enhancers to cross the nasal mucosal barrier. Use of fusidic acid derivative, taurodihydrofusidate, as an absorption enhancer has been encouraging because insulin is absorbed across the nasal mucosa in an active, reproducible, and efficacious manner.

Nasal administration of insulin may become a promising route for insulin delivery. The rate of diffusion of a nasal preparation through the mucous blanket and its rate of clearance from the nasal cavity may be influenced by physicochemical properties of the formulation vehicle, particle size, or surface charge of the drug and/or additives.

Some absorption enhancers for transmucosal insulin delivery are saponins, disodium carbenoxolone, sodium caprylate, sodium laurate, polyacrylic acid, derivatives of fusidic acid, and bile acid salts.

Several factors should be considered in the optimization of nasal drug delivery: methods and techniques of administration, site of deposition, rate of clearance, and minimization of any pathological conditions.

Buccal Insulin Patch (31,34,44)

Efforts have been made to develop an insulin patch from which insulin would be absorbed through the lining of the mouth cavity. This would tend to mimic the basal insulin secretion.

By buccal delivery, drugs are absorbed rapidly into the reticulated veins, which lie under the oral mucosa and enter the systemic circulation directly, bypassing the liver.

A mucosal adhesive delivery system was developed for the buccal delivery of insulin. It was found that the systemic delivery of insulin through the buccal mucosa was significantly affected by the formulation composition used. Insulin could not be effectively absorbed by a simple disk-shaped dosage form prepared by the direct compression of insulin in a mixture of hydroxypropylcellulose (HPC) and carbopol 934. Buccal absorption was achieved by using a dome-shaped, two-phased mucosal adhesive device prepared by dispersing insulin crystals with sodium glycocholate, an absorption promoter, in an oleaginous core and then overlapping the medicated core with an adhesive dome.

Rectal Delivery of Insulin (45–48)

Despite its poor social acceptability, the rectal mucosa has also been investigated as a potential route of insulin administration. Insulin can be absorbed through this route in the presence of absorption-enhancing agents.

The coadministration of absorption-promoting adjuvants, such as sodium glycocholate, has been reported to enhance the rectal absorption of insulin. It was recently reported that a solid dispersion of insulin with sodium salicylate can produce a rapid release of insulin from the suppositories and achieve a significant reduction in plasma glucose levels.

The main problems associated with this route of administration are aesthetic unacceptability, poor bioavailability, erratic absorption, poor reproducibility in the amount of drug absorbed, and adjuvant-induced mucosal damage.

Pulmonary Insulin Delivery (by Inhalation) (49,50)

Delivery of medication to the respiratory tract for the localized therapy of respiratory diseases has been practiced for several decades.

The lungs are an attractive site for the systemic delivery of therapeutic proteins in view of the enormous surface area (70 m^2) that they offer compared to the other absorptive surface areas offered by other absorptive mucosa. Approximately 90% of the absorptive surface area offered by the lungs is attributed to the alveoli. Sufficient insulin can be absorbed through this route to produce hypoglycemia. The kinetics of insulin absorption across the respiratory mucosa tends to mimic the bolus insulin needs and peak levels are achieved in 15–20 min with return to baseline in 40–60 min.

The limitations of drug delivery by this route are that absorption and efficacy are not reproducible, and long-term administration may have other clinical implications and side effects.

Pancreatic Transplants (51)

Because insulin is secreted by the beta cells situated in the pancreas, efforts were made to try and transplant a pancreas in IDDM. The first pancreatic transplantation was performed in 1966, but it failed. This was due to poor surgical techniques at that time and graft rejection. Improvement in the surgical techniques along with the use of powerful immunosuppresants has led to much-increased survival rates for grafts—from 3% (1966–76) to 44% (1985–86)—and increased recipient survival rates for grafts from 42 to 83%. Unfortunately, in India there is a major drawback regarding the availability of cadaver donor organs. Efforts have been made to harvest a part of the pancreas from a live donor, but there is some evidence that the removal of half the pancreas would expose the donor to the risk of diabetes.

Thus, the only feasible current method seems to be to obtain pancreas from cadavers. This option is very rare in India for social, religious, and medicolegal reasons, and thus the feasibility of this mode of therapy in India would seem to be severely limited.

Islet Cell Implants (52–54)

With all the problems associated with pancreatic grafts and the fact that insulin is secreted by the beta cells, it was inevitable that efforts would be made to try and implant only the beta cells rather than the whole pancreas. Human fetal pancreas may be a source of islet cells.

The harvesting of the islet cells and the yield is quite good in quantity, viability, and purity. Thus, harvest is not a major limiting factor in islet cell implants. The major limiting factor is the immune rejection of the implants and the need of immunosuppressive drugs over a prolonged period, which may not be widely acceptable. To overcome this problem, the islet cells are microencapsulated with a special membrane made of materials such as alginate–poly-L-lysine.

DEVICES AND SYSTEMS OF INSULIN DELIVERY

Subcutaneous (s.c.) Injection Ports

These devices are simply modified needles or cannulae, implanted subcutaneously for some days, through which insulin is injected intermittently. The rationale is to make multiple insulin injections more acceptable or to help the patients with needle phobia.

Implantable Insulin Pellets

Implanted pellets of insulin are designed to release insulin steadily over a period of days or longer. They are normally placed in s.c. tissue, which is suitable for repeated implantation. A 12-month supply of basal insulin required for a diabetic patients is placed in a pellet and residual polymer can be removed or slowly biodegraded. These pellets are implanted in s.c. tissues.

Pen Injectors (55)

The first commercial model carried the barrel of a standard disposable insulin syringe within a casing which delivered a dose when a button was pressed. The disposable insulin injection pens offer a further advancement in portability and convenience.

Novolinpen is a pocket-sized apparatus that resembles a fountain pen. When fitted with a unit dose ampule of insulin, it becomes a portable, self-contained insulin syringe.

Injection Guns (56–59)

Injection guns are designed to penetrate the skin, either with a hypodermic needle or a jet of insulin, without direct effort being applied by the patient. Such devices are less painful; they also deliver a consistent amount of insulin and the depth and dispersion of injection depot is constant.

Mechanical Insulin Delivery Devices

Open-Loop Insulin Delivery (60,61)

In this system, there is no sensing device to measure the blood glucose level and no computer to determine the amount of insulin to be delivered. The patient has to monitor his or her glucose level in blood and set the pump's infusion dose based on the same.

The pump delivers the insulin through a tubing leading to a s.c. inserted needle. The infusion provides a basal insulin supply and an additional predetermined dose is delivered before each meal.

Indications of pump therapy are patients with diabetes with large fluctuations in glycemia; pregnant women with diabetes; patients with irregular working hours; and patients who suffer from dawn phenomenon.

Contraindications of the insulin pump are patients with poor cooperation; patients with repeated hypoglycemia; patients who are reluctant to wear the external device; patients with a tendency to develop infections at the infusion sites; and children under the age of 2 years.

There may be different complications of the open-loop insulin pump such as infection, hypoglycemia, malfunctioning of pump, and leakage of catheter with the wastage of insulin.

Closed-Loop Insulin Delivery (16,62,63)

This system consists of a continuous glucose sensor and a computer-controlled insulin infusion system which delivers insulin according to the blood glucose level so as to maintain normoglycemia. This type of system is also called bedside artificial pancreas or Biostator.

The blood glucose concentrations are displayed continuously and insulin, glucose, or both are infused intravenously by means of a constantly turning multichannel roller pump. This method of delivery is expensive and requires trained personnel.

Implantable Insulin Pump (64,65)

These are specially modified for implantation for very long periods into the patient's body. This is to avoid the problems associated with the use of an external device, such as infusion site infection and mechanical catheter damage.

The device has two chambers: the drug reservoir and metal bellows. Metal bellows is placed in a chamber containing liquid freon, which vaporizes at body temperatures, and by compression of the bellows, drug is expelled from the reservoir at a constant infusion rate. The advantage of this device is the lack of any rotating parts, as well as the automatic recharging of the power source by compression of the freon gas at each refill of the reservoir. The pump is usually implanted either in the upper left quadrant of the abdominal wall if the intraperitoneal route is chosen, or the pectoral position, when the catheter is placed in the vena cava. In due time, slowing of pump may occur because of obstruction in the catheter. Such devices should not be implanted in patients with brittle IDDM and patients with s.c. insulin resistance. This system requires constant immobilization of

patient and close supervision. Some complications have been reported such as inflammation and sepsis.

RECENT ADVANCES

Some of the latest advances in insulin drug delivery systems are discussed below.

Bioresponsive Insulin Delivery Systems (66–68)

Such a system consists of an artificial beta cell that consists of a glucose-sensitive hydrogel membrane for the feedback-controlled delivery of insulin. The glucose-sensitive membrane is fabricated by entrapping glucose-oxidase enzymes in a hydrogel polymer with pendant amine groups. As glucose diffuses into the polymer, glucose-oxidase catalyzes its conversion to gluconic acid (pK_a = 3.6), thereby lowering the microenvironmental pH in the membrane. The reduced pH results in increased ionization of the pendant amine groups. Electrostatic repulsion between the ionized amine groups increases the swelling and thus the permeability of the hydrogel membrane to insulin contained in the reservoir. Thus the membrane permeability to insulin is a function of the glucose concentration surrounding the membrane, and the release of insulin is accelerated by the increase in the glucose level.

Self-Regulating Delivery Systems (69–73)

Such a system is made by the preparation of biologically active insulin derivatives in which insulin is coupled with a sugar and this is formed into an insulin–sugar–lectin complex. The complex is then encapsulated within a semipermeable membrane. As blood glucose diffuses into the device and competitively binds at the sugar binding sites in lectin molecules, this activates the release of bound insulin sugar derivatives. The amount of insulin sugar derivatives released depends on the glucose concentration.

Thus, a self-regulating insulin delivery is achieved. Further development of a self-regulating insulin delivery system utilized the complex of glycosylated insulin–concanavalin A, which was encapsulated inside a polymer membrane.

Power Patch Applicator (74–77)

This is a body-wearable direct-current iontophoresis delivery device that uses a direct current of 0.4 mA applied continuously for 14 hr; insulin was successfully delivered transdermally through a negative reservoir electrode. A therapeutically useful serum insulin level was accomplished at 4 hr and beyond. The system was successfully applied to achieve the systemic delivery of human insulin and the control of hyperglycemia in albino rabbits with alloxan-induced acute diabetes mellitus.

Water-in-Oil Type of Emulsion (78)

Human insulin was incorporated into a water-in-oil (w/o) emulsion by high-pressure homogenization. A fine stable dispersion of the aqueous phase was achieved and the emulsion was able to protect insulin against gastric degradation in vitro without further encapsulation.

Biocarrier Insulin (79,80)

In this system insulin was first entrapped within ghost erythrocytes that were further entrapped in liposomes. The preparation was developed using ghost erythrocytes as biocarriers for intraduodenal administration of insulin because erythrocytes are broken by proteolytic enzymes in duodenal region. Such a system was able to protect insulin from acid and enzymes. From such a system insulin was absorbed and showed its glucose-lowering effects.

Encapsulation (81)

Insulin was encapsulated in a small soft gelatin capsule and coated with a polyacrylic polymer (Eudragit) with pH-dependent permeability properties. This type of system was able to protect insulin from a degradation as insulin was released after the duodenal region, where the pH can be above 7, so that insulin was not degraded.

Nanocapsules (82,83)

Nanocapsules are fabricated from biodegradable poly(isobutylcyanoacrylate). This system was able to protect insulin from proteolytic degradation and it has been shown that after intragastric administration of such a system in streptozotocin-induced diabetic rats, their fasting glycemia was normalized for a period of 1–3 weeks in a dose-dependent fashion. The interaction of encapsulated insulin with insulin receptors in vitro is similar to that of native insulin.

In addition, encapsulated insulin has a modified tissue distribution and a delayed urinary excretion.

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