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REVIEW

New Developments in Insulin Delivery

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ABSTRACT

A vigorous research effort has been undertaken worldwide to replace injectable insulin by a more comfortable and painless delivery method. Several routes have been explored for their suitability with respect to insulin degradation in the human body. Considerable progress has been made in achieving the common goal for a convenient and equally effective insulin delivery. This article reviews the different routes available for insulin administration and the many successful developments that have been made in recent years for improving that particular route for a much better insulin delivery.

Key Words: Insulin; Different routes; Delivery; Patents.

INTRODUCTION

The discovery of insulin by, Banting and Best in 1921, was one of the greatest triumphs of the century in the discovery of life-saving remedies.[1] Even after seven decades, since insulin was first used in the therapy of diabetes, we are still seeking an easy, painless, and effective insulin delivery.

The present complications of diabetes mellitus are thought to arise from poor control of blood glucose because of an inadequate supply of insulin by the pancreas. Currently, insulin administration requires subcutaneous (SC) insulin injections, which, even in their simplest form (Nova-Pen system) are cumbersome and unacceptable to many patients with diabetes. This has motivated the search for novel therapeutic approaches to replace the present parenteral insulin delivery. Insulin is probably the most frequently studied polypeptide with regard to delivery by routes other than parenteral. Currently, there are approximately 280 new peptide and protein drugs that are being actively investigated for an alternative nonparenteral delivery route.

It was in the early 1970s that researchers actively started looking for other options for a more safe and effective insulin administration other than the paren-

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teral route, but the search for an alternative administration route had been ongoing since the 1920s.[1,2] In the meantime, the foreignness of early available porcine and bovine insulin led to the development of human insulin by transpeptidation and biosynthesis in microorganisms. Eventually, human insulin has almost replaced animal insulin, but the problem of painful administration of insulin still exists.

Despite the tremendous efforts that have been devoted to solve this problem, only limited success has been achieved and only with certain routes. However, it is well documented that small quantities of dietary proteins can be absorbed, even though these absorbed proteins can have little or no physiological significance. The colon may provide an advantageous and substantial absorption site for peptides and proteins in general and insulin in particular.

Ideally, an oral insulin dosage form would be preferred over the currently available parenteral route of administration, but this novel approach is confronted by common biological and physicochemical problems. These problems include luminal degradation, particle aggregation, and polypeptide degradation in the absorptive area of the gastrointestinal tract (GIT). Hundreds of pharmaceutical scientists, polymer and material chemists, biomedical and chemical engineers, and gastroenterologists are working to overcome this problem as we have entered the next millennium.

Several new and alternative routes have been explored for this purpose. Many of them have produced some or little success. Peroral and nasal insulin administrations have demonstrated good potential for the treatment of diabetes mellitus. Facilitated transdermal delivery has also enjoyed success in promoting the systemic delivery of insulin to some extent. In addition, pulmonary, buccal, and ocular insulin administrations have been shown to decrease serum/plasma glucose concentrations in many studies. Some progress has also been achieved for other routes (such as rectal, vaginal, and uterine) for their potential in systemic insulin delivery.

Various Delivery Routes

SC/Intramuscular Administration

Subcutaneously, insulin is injected beneath the skin, whereas in cases of intramuscular administration, the drug is deep injected into a skeletal muscle. The extent of absorption is generally complete in intramuscular delivery, and the rate of absorption depends on the vascularity of the muscle site, lipophilicity, and degree of ionization of the drug. However, because of poor blood supply to the SC region, compared with muscle tissue, the insulin absorption may be slower from SC injection than intramuscularly. Protein engineering has enabled the development of new insulin analogs (monomeric insulin forms). These new forms of insulin have exhibited a three- to four-fold increase in absorption from the SC route than human insulin.[3] Lately, several of these SC insulin preparations (for basal use and rapid-acting analogs designed to use preprandially) have been introduced.[4]

External and Implantable Pumps

External insulin pumps have been shown to control Type I (insulin-dependent) diabetes in patients. However, the use of short-acting insulin in the pumps can result in insulin deficiency and other serious complications; so, this problem must be overcome. Implantable pumps have been under investigation for more than two decades to improve their applicability. Replacement of the external pumps is desirable to avoid any injury caused by their use, such as infusion site infection and mechanical catheter damage. Recently, a group of researchers have reported success in controlling blood sugar levels by putting mathematical commands in a microchip and then making them compatible with an implantable insulin pump (Table 1).[5]

Oral Delivery Through GIT Absorption

The GIT is the route of choice for the administration of most drugs, regardless of their molecular structure or weight. Endogenous insulin has an important place in drug therapy of insulin-dependent diabetes mellitus or type I diabetes, but generally it is still delivered through injections. It would be of great advantage if insulin could be administered orally, but most of the insulin is degraded by the highly acidic gastric fluid and by proteolytic enzymes present in the small intestines and in presystemic metabolism thus making insulin inaccessible to this route. For the past few decades, a great potential has been foreseen in the efficient delivery of insulin by nonparenteral routes, in particular via the GIT. Novel concepts are needed to overcome significant enzymatic and diffusional barriers by adding various adjuvant. Various studies to this effect have shown that intact insulin can be found in systemic circulation of rats, rabbits, and

Table 1. Some of the insulin formulations and technology patented (mostly under development).

Insulin product/ dosage form/technology patented (in pipeline)	Route of administration	Manufacturer or research institution (name of company or researcher)	Reference
Computer chip controlled pump	Implantable pump	Researchers from Delaware university	5
Oral formulation (absorption enhancers/ promoters)	Peroral	Researchers from academia and industry	12,13,14,19 and 20
Oral formulation (absorption enhancers/ promoters)	Peroral	Researchers from academia and industry	14,15 and 16
Oral formulation (natural polymers)	Peroral	Tozaki and others	17
Oral formulation (liposomal)	Peroral	Stefanov and others	21
M2 oral form	Peroral	Nobex corp.	24,27
AI-401	Peroral	AutoImmune/EliLilly	27
Macrulin	Peroral	Cortec	28
Oral form	Peroral	Elan	28
Oral product	Peroral	Endorex	28
MEDDS	Peroral	IMEDD	30
Insulin capsule	Peroral	Unigene lab. inc.	32
Ocular insert	Ocular	Lee and others	38
Aerosol delivery	Pulmonary	Aradigam corp.	45
Inhaleable technology	Pulmonary	Inhale therapeutics	45
ProMaxx™	Pulmonary	Epic therapeutics	45
Dry particle aerosol (AIR™ technology)	Pulmonary	Alkermes	45
Spiros	Pulmonary	Dura pharmaceuticals	47
Insulin/inhaler	Pulmonary	AeroGen, Inc.	48
Inhalation product	Pulmonary	ImaRx therapeutics	49
Oralin	Transmucosal	Generex biotechnology	28
Buccal formulation	Transmucosal	DelRx	51
Dry powder inhaler	Internasal	Vectura ltd./ML laboratories	55
Nasal technology	Internasal	West pharmaceutical services	56
Touch-spray	Internasal	Odem ltd./Pari GmbH	57
Suppositories (sodium salicylate)	Rectal	Hosny and others	59
Lingual spray	Buccal	Valentis, Inc./Flemington pharmaceutical corp.	65
Electrophoresis	Transdermal	Cygnus pharmaceuticals	69
Sonophoresis	Transdermal	Encapsulation systems/ Penn State Univ.	70
MicroPor™	Transdermal	Altea development corp.	72
BIPHASIX patch	Transdermal	Helix BioPharma corp.	28
Transfersulin	Transdermal	IDEA	74
Transdermal patch	Transdermal	Vector medical technologies	75
Transdermal patch	Transdermal	Noven pharmaceuticals	76
SonoDerm™ technology	Transdermal	ImaRx therapeutics	77
SonoPrep delivery system	Transdermal	Sontra medical	78

(*continued*)

Table 1. Continued.

Insulin product/ dosage form/technology patented (in pipeline)	Route of administration	Manufacturer or research institution (name of company or researcher)	Reference
Islet cells encapsulation	Living cells transplantation	Shapiro and others	80
Biocapsule encapsulated with silicone membrane	Living cells implantation	Univ. of Illinois–Chicago researchers (Dr. Desai and others)	82
Islet cells encapsulation	Living cells transplantation	DRI	83

humans.[6–11] However, on studying the extent of absorption of the insulin, it has been found that very low amounts or empirically nothing significant has been absorbed (less than 1–2%). The use of absorption promoters/enhancers (including different bile salts),[12–14] protease inhibitors (e.g., sodium glycolate, aprotinin, bacitracin, bowmam-birk inhibitor, soybean trypsin inhibitor, and chromostatin),[14–16] or bioadhesives alone or in combination can improve the oral bioavailability to a certain extent. However, the results obtained during the past decade using nonbiodegradable and biodegradable biopolymers (enteric-coated polymers, swellable hydrogels, and encapsulation of insulin in water-soluble polymer) were not very encouraging. Chitosan and alginates (natural bicompatiable polymers) have also been used as coating polymers, when capsules containing insulin with absorption enhancers and protease inhibitors were given to rats.[17] The coating of insulin with polymers cross-linked with azoaromatic groups is thought to protect insulin from intestinal degradation, releasing the insulin only on reaching the colon by the direct effect of intestinal microflora on azo bonds.[18] The encountered difficulties were mainly related to the physiological peculiarities of gastrointestinal mucus. The use of polyacrylic polymers (Eudragit L100 and S100) as pH-dependent material to coat the insulin capsules containing absorption promoters and/or protease inhibitors has revived some hope in achieving an oral insulin formulation.[19] The polyacrylic polymer helps in protecting the capsule contents through the stomach and duodenum, and then release the insulin on reaching a safer place in the small intestines (at higher pH). This combination of a pH-dependent Eudragit-coated insulin (L100 or S100) and sodium salicylate has recorded a bioavailability of 13–15% relative to the intraperitoneally injected insulin.[20] Research in this area has also shed new light on the potential use of mucoadhesive polymers. An important class of mucoadhesive polymers, poly(acrylic acids), could be identified as potent inhibitors of proteolytic enzymes. A specific interaction between epithelia and some mucoadhesive polymers induces a temporary loosening of the tight intercellular junctions, which is suitable for the rapid absorption of smaller peptide drugs, such as insulin along the paracellular pathway. Another study highlighted the feasibility of the systemic insulin delivery by the oral route using liposomes and reported that a substantial blood glucose reduction was observed in diabetic animals, but these results could not be reproduced.[21]

In this context, bioadhesion technologies offer some new perspectives. The original idea of oral bioadhesive drug delivery systems was to prolong and/or intensify contact between controlled-release dosage forms and the stomach or intestinal mucosa.

In recent years, a number of innovative oral insulin delivery technologies have been developed, including entrapment within small vesicles and passage through the space between adjacent intestinal cells (paracellular transport). The studies in rabbits and rats demonstrate that concomitant administration of *Zonula occulandes* toxin with insulin effectively enhances the intestinal absorption.[22] Furthermore, experiments in diabetic rats demonstrate that orally administered insulin retains its activity up to 15 times more than the effective parenteral insulin dose. Another new promising approach that may be used to improve the insulin absorption is to load the insulin into the poly(alkyl cyanoacrylate) microsphere and directly administer it into the duodenum, jejunum, ileum, and colon so that they can help in protecting insulin from degradation by proteolytic enzymes.[23]

Nobex Corporation (Raleigh, North Carolina, USA) (formerly Protein Delivery) developed an oral insulin product called M2 for treatment of type I and II diabetes. Results from phase I and II clinical stu-

dies showed that oral insulin had no significant side effects, and it lowered the blood glucose level more rapidly than any other form of insulin delivery.[24,28] Emisphere Technology, Inc. (Tarrytown, New York, USA), developed a new technology to deliver insulin and other large macromolecular drugs via oral route and announced that it has started successful clinical studies in the Netherlands, the United Kingdom, and Israel for oral insulin capsule formulation.[25] An online article published by Jerusalem's Hadassah University Hospital, showed the results of an oral insulin capsule delivered by using emisphere technology that could pass through the intestine and reach the liver and blood within 20–30 min in 12 healthy human volunteers.[26] Another U.S. company, Auto-Immune (Pasadena, California, USA) has developed oral insulin agent, AI-401, EliLilly is conducting clinical trials for this product.[27,28]

In Europe, the U.K. biotechnology company, Cortecs (Flintshire, UK), is also developing an oral form of insulin called Macrulin. This product is in phase II trials in patients with diabetes and has shown promising results.[28] Another oral form of insulin is being developed by the Irish company, Elan (Dublin, Ireland). This particular product is in phase I trials.[28] Endorex (Lake Buff, Illinois, USA) has a preclinical oral insulin product for further exploration.[28]

Most recently, Ariad Pharmaceutical (Cambridge, Massachusetts, USA) developed a novel technology called RAPID™ (Regulated Accumulation of Proteins for Immediate Delivery) that will allow rapid, pulsatile delivery of insulin using gene therapy regulated by an orally administered drug.[29] Intelligent Micro-Engineered Drug Delivery (IMEDD), under the stewardship of Professor Ferrari, developed the concept of using micro-fabricated particles (Oral MEDDS) for oral delivery of insulin.[30] In Israel, at BenGurion University, the Unit of Applied Biotechnology and the Institutes of Applied Research developed a new system that can deliver biologically active insulin through the intestinal brush border and have been able to reduce the blood sugar levels in unconscious rats.[31]

Unigene Laboratories, Inc. (Fairfield, New Jersey, USA) successfully completed preclinical studies for its insulin capsule.[32]

Ocular Administration

In 1931, Christie and Hanzel[33] introduced ocular administration of insulin in the rabbits. However, it had to be abandoned in humans because of its low bioavailabilty. Since then, development of ophthalmic drug delivery systems has always been challenged by the presence of local irritation, loss in drainage, blinking, and tearing. The potential route for insulin delivery to the anterior segment of the eye has been the conjunctival cul-de-sac. Because of drawbacks associated with this route, new techniques have been investigated for delivery of drugs to the eye by means of polymeric delivery systems. Permeation enhancers (i.e., BL-9, Brij-78, and alkylpolysaccharides) were introduced and found safe for use on a long-term basis (b.i.d. for 3 months); as a result, systemic absorption of insulin has been significantly improved in rats.[34–37] For many practical reasons, the ocular route has an advantage over the other routes. Bioerodible polymers and polymeric gelation have been at the forefront of such systems. They are very important because they eliminate the need for removing the implant after complete drug release. One of the main concerns with the ocular route is the need to create patient awareness that this route is safe and feasible for systemic administration of insulin. An ocular insert with a gelfoam absorbable gelation sponge USP as a carrier with Brij-78 as absorption enhancer was used. This insulin-loaded device produced significant blood glucose reduction.[38] Later, Lee et al.[39] developed a gelfoam-based surfactant without any absorption enhancer and were able to get a blood glucose reduction. Some success has been reported by the University of Arizona research team with regards to lowering blood glucose levels in rabbits when insulin solution is given through the eye over an 8-hr period by using gelfoam treatment.[40] Dr. Koevary, at New England College of Optometry (NECOO), has shown in a rat model that topical insulin eye drops, when instilled to the surface of the retina, resulted in increased insulin levels in the retina.[41] BioSante Pharmaceuticals (Lincolnshire, Illinois, USA) presented their results from their new technology, calcium phosphate nanoparticulate (CAP delivery system in delivering drugs into the eyes; the company is working on Bio-Air™, using CAP to improve the delivery of insulin into the eyes).[42]

Pulmonary Administration

Attention was also given to the potential of a pulmonary route as an alternative noninvasive means for systemic delivery of peptide/protein-based therapeutic agents because the lung provides a huge but extremely thin absorptive mucosal

membrane (0.1–0.2 μm) with a large surface area (100 m^2) and good blood supply. The pulmonary delivery of peptides and proteins that included insulin has provided encouraging results and thus has generated great interest from the biotechnology industry. Several years ago, interest in the possibility of administering insulin via the pulmonary route surfaced; since that time, several methods have evolved that may eventually lead the idea of interpulmonary administration of insulin to fruition.

In a recent clinical study on patients with diabetes, an insulin-containing aerosol generated by a raindrop nebulizer secured about 80% deposition of inhaled insulin in the lungs.[43] In another study, nebulized poly(lactic-co-glycolic acid) (PLGA) nanospheres were administered in guinea pigs. This caused significant blood glucose reduction and prolongation of hypoglycemia.[44]

Inhale Therapeutics (San Carlos, CA) and Aradigam Corporation (Hayward, CA) developed inhalation systems that use different technology to deliver insulin via the pulmonary route.[45] Epic Therapeutics, Inc. (Norwood, Massachusetts, USA), succeeded in producing insulin microspheres in a optimal size range (1–2 μm) for its delivery to the lungs. They applied the Epic ProMaxx™ formulation system to administer insulin with non-CFC propellants, such as Hydrofluroalkane (HFA).[46]

A new drug delivery system, Technosphere (Cambridge, Massachusetts, USA), was developed to facilitate the absorption of Technosphere/insulin via pulmonary administration. This Technosphere/insulin system is an ordered lattus array of Technosphere and recombinant human insulin (Fig. 1).[45]

More recently, Alkermes (Cambridge, Massachusetts, USA) developed a more attractive, porous, dry particle aerosol technology known as AIR™, which was used to deliver both fast-acting and slow-acting pulmonary insulin formulations. The small aerodynamic size (1–3 μm) particles were used in this technology to provide systemic absorption and to attain high bioavailability of insulin formulations.[45]

Dura Pharmaceuticals (Menlo Park, California, USA) is currently developing a method to deliver inhaled insulin using the motorized Spiros® blister-disk drug delivery system in collaboration with a giant pharmaceutical company. These inhalers (insulin is one of these) operate by specifically targeting improvement in the drug's disposition.[47] AeroGen, Inc. (Mountain View, California, USA), reported, in an annual European meeting that one of their products, Aerodose insulin inhaler, was found effective and efficient in 15 type II patients with diabetes. The study was conducted at the Profil Institute for Medicine Research (Neuss, Germany).[48]

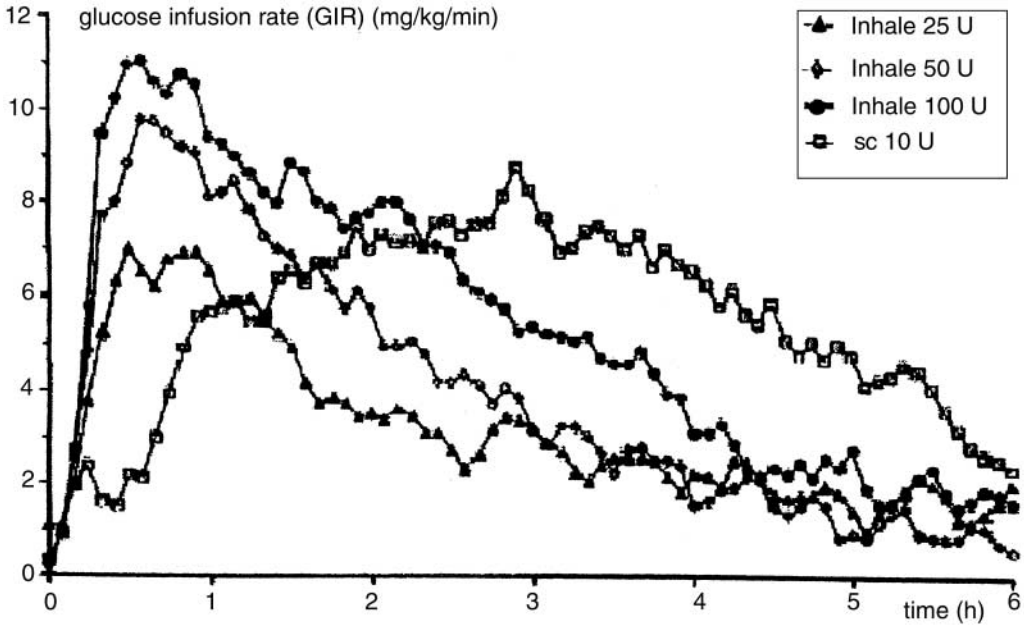

Figure 1. Maximal metabolic effect (GIR) profile following the increasing dose of inhaled technosphere/insulin formulation. (▲) Inhaled insulin (25 units); (○) inhaled insulin (50 units); and (●) inhaled insulin (100 units) compared with (□) subcutaneous recombinant human insulin (10 units). Each point represents the mean of 12 healthy volunteers. (Reproduced with permission from the Pharmaceutical Discovery Corporation, Ref.[45].)

ImaRx Therapeutics (Tucson, Arizona, USA) used PulmoRx™ technology to deliver proteins like insulin via inhalation. In PulmoRx technology, the company developed microbubble-based carriers, which can deliver insulin via inhalation and decrease blood glucose significantly in diabetic rats more than conventional aerosols.[49]

Transmucosal Administration

Transmucosal delivery through absorptive mucosa represents one of the alternatives. The high vascularity and easy accessibility of mucous membranes have made this tissue a potential and reliable route of drug delivery. This route has the advantage of being noninvasive and bypassing presystemic metabolism (hepatic first-pass effect). The absorptive mucosa that may allow systemic access of peptides and proteins includes the buccal, nasal, rectal, and vaginal membranes.

Generex Biotechnology (Toronto, Ontario, Canada), a Canadian Company, conducted phase II clinical trials with Oralin by using RapidMist™, device in which insulin is sprayed into the buccal cavity of a patient at various sites in North America and Europe.[28] Generex clinical trials of ORALGEN (Oralin in Canada) showed significant insulin absorption rates; according to the company web site, it could be on the market in Canada by the end of 2002 and in Europe and the United States at a later stage.[50]

DelRx, a New Jersey-based company, is collaborating with the University of Texas at Austin to develop a unique, novel composition containing insulin. If they succeed, it will be the first delivery ever of insulin from the inside cavity of the cheek.[51]

Internasal Administration

The concept of nasally administered insulin first appeared in 1935.[52] Nasal delivery of peptide and protein drugs has been studied extensively and has been the most successful among all available mucosal routes because of the permeability of the membrane to drug particles (e.g., nasal sprays for buserelin, desmopressin, oxytocin, and calcitonin are already available commercially).[53]

Many preclinical and clinical studies with inhaled proteins, peptides, and DNA have been completed, and demonstrate that efficacy can be achieved within the lungs and systemically. Despite the promising results, the development of inhaled biotherapeutics is beset with unique problems that require an integrated and rational approach to development. Aqueous protein formulations are often not stable to aerosolization, whereas stability of powder formulations can be difficult to evaluate in the solid state. Inhaler efficiency and reproducibility are unacceptable with existing devices and, although improvements in technology have brightened the outlook, new devices are not yet available and remain untried on most biotherapeutics. Once delivered to the lungs, these molecules are also subjected to a variety of efficient clearance mechanisms that can significantly reduce the probability of them being effective.

Despite these problems, the number of potential drugs being tested via inhalation continues to increase, suggesting some promise of future success. This discusses the issues and highlights a variety of biotherapeutics that have been administered as inhalation aerosols. Bentley Pharmaceuticals, Inc. (North Hampton, New Hampshire, USA), recently announced preclinical evaluation studies for its internasal insulin formulations; results are very encouraging and, according to the company, insulin formulation is more effective and efficient than any other alternative insulin delivery form currently under investigation.[54] Like many other pharmaceutical companies mentioned in this article, Vectura Ltd. (Cambridge, UK), and ML Laboratories (Warrington, UK) are collaborating to develop an inhaled insulin dry powder inhaler.[55] West Pharmaceutical Services (Lionville, Pennsylvania, USA) is developing nasal technology by using chitosan as an absorption enhancer with insulin to improve insulin bioavailability in human volunteers.[56] Odem Ltd. (Cambridge, Massachusetts, USA) and Pari GmbH (German company Midlothian, Virginia, USA) are cooperating to develop an aerosol technology. Touch-Spray, which can deliver insulin to the lungs and nose.[57]

Rectal Administration

Rectal insulin delivery offers several advantages over some of the other enteral routes. First, the rectal route is independent of intestinal motility, gastric-emptying time, and the presence of diet. Most likely, that the presence of the degrading enzymes in the gut wall decreases from the proximal end to the distal end of the small intestine and rectum. The best suggested advantages of rectal administration of insulin are the possibility of avoiding, to some extent, the

hepatic first-pass metabolism. To our surprise, insulin is probably the most often investigated polypeptide with regard to rectal administration. Animal studies in the early 1920s generally showed no sign of blood glucose reduction after rectal administration of insulin, followed by early 1970s experiments using adjuvants that reported an increase in insulin bioavailability.[6,7,58] Sodium salicylate was found to be most effective of all the absorption enhancers used with insulin in a suppository.[59]

Vaginal/Uterine Administration

Like rectal administration, insulin delivery through vaginal mucosa can also prevent presystemic degradation. Investigational attempts have been made with lysophosphatidylcholine-containing insulin, as an aqueous solution and as a lyophilized powder with bioadhesive starch microspheres, has been administered intravaginally to sheep.[60] Similar attempts were also made in placing insulin through intrauterine delivery in rats; thus, insulin was found to be absorbed in a biologically active form in the uterus of rats.[61]

Buccal Administration

Drugs delivered via the mouth cavity are absorbed through thin mucosa into the reticulated vein and enter into the systemic circulation directly, thus bypassing the liver.

Several absorption promoters/enhancers were used in insulin buccal formulations, and a significant reduction in blood glucose level was achieved in all preparations with alkylglycosides,[62] sodium glycolate,[63] sodium lauryl sulfate, sodium laurate, and a lauric acid/propylene glycol vehicle.[64] In August 2000, Valentis, Inc. (Burlingame, California, USA), and Flemington Pharmaceutical Corporation (Flemington, New Jersey, USA). announced development of a PEGylated insulin lingual spray.[65]

Transdermal Administration

Considerable effort has been made to deliver proteins as large as insulin via the skin. It seems to be an attractive option because of the lack of degrading enzymes. However, the poor permeability and larger molecular sizes of peptide and protein drugs limit absorption capacity via the transdermal route to some extent.

Iontophoresis (or ion transfer) is a mechanism that allows migration of ions or charged substances when an electrical current is passed through an electrolyte medium containing ionized species. In 1995, Dr. Henley has developed a technology (Ionosonic) that combines the iontophoresis and ultrasound together, therefore permitting the delivery of insulin through the skin. He envisioned a wearable band that would be used to deliver the insulin.[66] Insulin is successfully absorbed through the hairless skin of small laboratory animals by iontophoresis.[67] It has been reported that insulin can also be delivered across the skin at therapeutic concentrations with the application of ultrasonic energy (phonophoresis).[68] However, more studies, including clinical work, are needed to assess their potential impact on novel insulin delivery technique. Although the progress in transdermal delivery of insulin and other peptides seems encouraging, it is still doubtful if this delivery route could provide a general approach to noninvasive delivery of these proteins and peptides.

Cygnus Pharmaceuticals (Redwood City, California, USA) has developed an electroporation technology, which allows the delivery of insulin when high voltages are applied for short periods. It can produce slowly reversible enlargement of skin pores at one level, thus driving cells apart electronically and allowing insulin's easier intracellular passage through the skin.[69] A relatively new technology is developed by Encapsulation Systems (Broomwall, Pennsylvania, USA) in working with Penn State University by using ultrasound (sonophoresis) to transport insulin via a wearable, portable, and programmable drug sonic applicator device through a patch on the arm or abdomen. The company completed successful animal studies and began human clinical trials in 2002.[70]

Sen and coworkers[71] developed a novel method using electric pulses and lipid formulations to achieve a transient increase in skin permeability, thus enabling delivery of insulin. This method is already tested in mouse model. Altea Development Corporation (Altanta, Georgia, USA) is focused on bringing to the drug delivery market an innovative "needleless injection" MicroPor™ technology. This technology enables delivery of an insulin preparation directly through the skin without using a needle; it also provides controlled delivery of insulin.[72]

Helix BioPharma Corporation (Aurora, Ontario, Canada), in Canada, has reported that they have achieved effective response in reducing blood sugar levels for more than 2 days in animal studies by the application (using their technology—the BIPHASIX

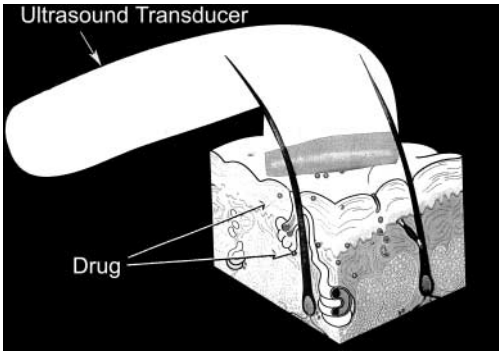

Figure 2. An ultrasound transducer is used to induce or deliver drug molecules (insulin) through the various layers of skin. (Reproduced with permission from ImaRx Therapeutics, Inc., Ref.[77].)

microencapsulation system) of a single patch.[28] In another study, hypoglycemic effect was induced in rats after dermal application of the insulin-containing patch.[73]

In Germany, IDEA (Munich, Germany) introduced a noninvasive new technique to apply insulin epicutaneously by using transfersomes (phosphatidylcholine-based carriers). The Transfersulin (transfersomes-associated insulin), as they are called, easily penetrate the intact skin barrier and lower the blood glucose level by 30% of that induced by SC insulin injection. The company is conducting phase I trials.[74]

Back in the United States, Vector Medical Technologies, Inc. (Miami, FL), announced a successful completion of clinical trials of their transdermal basal insulin product in type I diabetes.[75] Noven Pharmaceuticals (Miami, FL) is also exploring the possibility of developing an insulin transdermal patch.[76] ImaRx Therapeutics (Tucson, Arizona, USA) also developed a ultrasound-mediated drug delivery (SonoRelease™ technology) (Fig. 2). According to the company, their novel technology has the potential to enhance transdermal insulin delivery.[77] Sontra Medical developed its own Technology (SonoPrep Transdermal Delivery System), and the company showed the feasibility of using ultrasound-mediated skin permeation and insulin delivery on six nondiabetic pigs.[78]

CONCLUSIONS AND FUTURE DEVELOPMENTS

A novel route to deliver insulin still eludes the researchers. From all the work that has been reviewed, it appears that the initial plasma/serum glucose level is more or less accepted as a measure of the pharmacodynamic parameter of a novel insulin drug delivery system. Each of the planned strategies discussed in this article has merit and is promising to the development of a successful delivery system. It is highly unlikely that a single strategy using absorption enhancers/promoters or enzyme inhibitors could do much in producing a new oral insulin delivery system; such a system would only deal with one or two barriers to improve oral bioavailability. Combined strategies, however, look more promising to counteract various barriers. More research with respect to animals and human subjects is in fact needed to overcome the existing absorptional and enzymatic barriers. Currently, most promising among all formulations appears to be implanted pancreatic islet cells, nasal insulin, and iontophoretic transdermal insulin. Furthermore, any success with an effective nasal delivery system for insulin remains a demanding, yet exciting, challenge; undoubtedly, a commercial nasal insulin preparation would be an assest in the treatment of diabetes mellitus. There have been several exciting developments in the implantation of islets cells over the past year. A recent published report on successful implantation of encapsulated pancreatic islets in a patient with diabetes has opened a new era in the effectiveness of an alternative insulin delivery.[79] In the summer of 2000, a breakthrough success was reported by Shapiro and colleagues[80] in Edmonton, Canada, in which seven insulin-dependent diabetes mellitus patients were made 100% independent of insulin for more than 1 year. The researchers succeeded in performing living islet cells transplantation in patients with an increase in immunosuppressive drugs other than glucocorticoids. Later, in June 2001, Duke University[81] reported in an international conference that it had success in keeping diabetic baboons insulin-free for nearly 9 months by injecting encapsulated insulin-producing pancreas cells from the pig; the same researchers showed optimism in beginning the human clinical trial for insulin-dependent patients. A research team at the University of Illinois at Chicago developed a device that encapsulated insulin-producing cells in a microfabricated silicon membrane and delivered insulin in the systemic system (Fig. 3).[82] However, more work is needed to improve the biocompatability of the encapsulating polymer and overall acceptance by the human body. Diabetes Research Institute (DRI) is also involved in studying various chemical substances for their use in encapsulation devices and conducting research to make sure the best available material is used for encapsulating

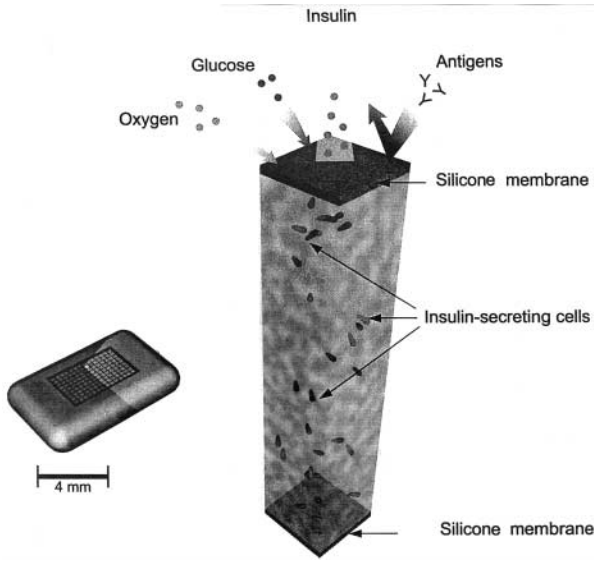

Figure 3. Insulin-secreting cells (living cells) are encapsulated in a silicone membrane, which allows the release of insulin and prevents entry of antibodies inside the biocapsule. (Reproduced with permission from the National Science Foundation. Image credit: Kirk Woellert/National Science Foundation, Ref.[82].)

islet cells; this could lead to successful islet encapsulation.[83] In a recent article,[47] the authors showed that DNA technology lead to the ability to synthesize insulin analogs. As of today, more than 300 insulin analogs have been produced in laboratories by using DNA technology. A most recent technological advancement in this direction is use of the self-regulating delivery system, which involves the development of artificial β-cells that consist of glucose-sensitive hydrogel membrane that is responsible for the feedback-controlled delivery of insulin.[84] We should be able to develop a safe and effective insulin delivery system, regardless of its route that could replace, wholly or in part, the invasive insulin delivery.

Insulin Delivery Patents

Aradigam Corporation[85] patented at least 57 of their products at the U.S. Patent Office covering the delivery of insulin by inhalation. Aradigam reported in February 2000 that patents were added to cover the delivery of insulin and insulin analogs by inhalation. Most of Aradigam patents explained the method and formulation for delivery of insulin; and some of them told us how we could deliver inhaled insulin to patients. An early Aradigam Patent U.S. 5672581 disclosed a method to deliver aerosolized insulin to the patients; and programmed, portable, hand-held devices were used in the delivery procedure. It also disclosed that, in one type of device, insulin was contained within a low boiling propellant that was held within a canister under pressure, whereas in the other type of device, insulin was held within a container in solution form, and this formulation was moved through a porous membrane to create an aerosolized preparation that was eventually inhaled by patients.[86] Aradigam Patent U.S. 5970973 informed us that a aerosolized insulin formulation was delivered to the lungs. The rate at which the insulin was absorbed through the lungs into the systemic circulation was increased by the incorporation of monomeric insulin and/or an inhale–exhale breathing maneuver. Monomeric insulin can be easily absorbed into the blood.[87] U.S. Patent 5941240 was related to an aerosolized insulin delivery controlled within a narrow range by controlling the total volume of air inhaled by a patient.[88] Aradigam (Hayward, California, USA) Patent U.S. 6167880 controlled the inhaled insulin dosage by controlling total inhaled volume that could be measured within a delivering device that had the means to measure inhaled volume and halting inhalation at a predetermined point.[89] Like many others, this Patent U.S. 6085753 gave the details of using the inhale–exhale breathing maneuver to enhance the absorption of insulin into the blood.[90] Patent U.S. 5915378 disclosed the creation of an aerosolized insulin formulation and how the device containing insulin formulation should be handled.[91]

Helix BioPharma Corporation (Aurora, Ontario, Canada) has been granted European and U.S. patents for developing an insulin patch using the BIPHASIX delivery system to deliver a steady basal level of insulin for patients with diabetes; the patent covers the process of preparing and manufacturing BIPHASIX microsphere and also the means by which insulin was encapsulated within the BIPHASIX.[92] Islet Sheet Medical LLC (San Francisco, California, USA) has been granted approval of the U.S. patent for the retrievable bio-artificial pancreas.[93]

Dura Pharmaceuticals, Inc. (Atlanta, Georgia, USA), announced that they had been issued a U.S. patent for the dry powder method of inhaled insulin delivery using the motorized Spiros blisterdisk drug delivery system.[94] Altea MicroPro™ technology for the delivery of macromolecular drugs was covered by

several U.S. patents.[72] iMEDD acquired patents for their oral MEDDS drug delivery technology.[30] Dr. Sen and coworkers[71] held patents for their discovery. Epic Therapeutic, Inc. (Norwood, Massachusetts, USA), obtained a broad patent for ProMaxx™ microspheres covering the water-based production of microspheres for use in sustained release delivery of proteins, peptides, and other pharmaceuticals. The company currently owns seven pending and issued U.S. patents.[46] Generex Biotechnology (Toronto, Ontario, Canada) is protected by 25 approved and pending patents. The company's most important patent disclosed its technology, RAPIDMIST, which was used to deliver insulin formulation into the oral cavity as a fine spray by a hand-held aerosol applicator.[95] Waratah Pharmaceuticals Inc. (Woburro, Massachusetts, USA), acquired a U.S. patent for its Islet Neogenesis Therapy (or I.N.T.), which is a short course of injections of two well-defined human growth factors to stimulate regeneration of insulin-producing cells.[96] Islet Technology (St. Paul, Minnesota, USA) is developing an insulin-producing islet cell encapsulation product and has 15 patents so far.[97] AutoImmune has been granted four patents for their oral and nasal technologies in the United States.[98]

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