Review Article

CHALLENGES IN ALTERNATIVE INSULIN DELIVERY SYSTEM: A REVIEW

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ABSTRACT

The subcutaneous insulin drug therapy, vial and syringe method is burdenful and time consuming. Another question to design an alternative way to deliver insulin by replaces injectable insulin to move comfortable dosage form. Consequently more acceptable at least effective insulin delivery has been developed over past years. This review examines some of many attempts made to developed alternative more convenient route for insulin drug delivery system for the effective treatment of diabetes.

Keywords: Diabetes mellitus, insulin, drug delivery systems, routes of administrations.

INTRODUCTION

Diabetes mellitus is metabolic disorder characterised by hyperglysemia, glycosurea negative nitrogen balanced and sometime ketoneurea. The classic well-known symptoms of diabetes are polyuria, polydipsia, polyphagia and loss of body weight. The epidemiology study indicated that hyperglycemia is the primary cause of diabetes. Chronic hyperglycemia is responsible for long-term sequence of diabetes namely retinopathy, nephropathy, neuropathy, cardiovascular and peripheral vascular disorders.

1. Type I diabetes: It is commonly occurred in childhood and has a relatively acute onset of disorder with an average peak age of onset at 12 years old. The patients require exogenous insulin for survival. Ten percent of those diagnosed with diabetes over the age of 65 are Type 28 diabetic patients.

2. Type II diabetes: It usually occurs later in life and has a more insidious onset of disorder. The patients may or may not require exogenous insulin. The Type II diabetes is a translation of polygenic disorder and to a lesser extent, monogenic disorder. The induction propensity of diabetes via the expression of genetic disorder is stronger in Type II than Type I diabetic patients.

3. Gestational diabetes: The symptoms of diabetes are first recognized during the pregnancy.

4. Other specific types which could have induced from genetic defects of beta cells, genetic defects which bring about type A insulin resistance and/or insulin receptor mutation, drugs, chemicals or diseases which induce pancreatic damage and endocrinopathy[1]

ALTERNATIVE ROUTES OF INSULIN ADMINISTRATION

A) ORAL ADMINISTRATION

The gastrointestinal tract (GIT) is the route of choice for the administration of most drugs and regardless of their molecular structure or weight. The manufacture of an oral dosage form does not have to meet specialized regulatory requirements relating to such issues as sterility, pyrogenicity and particulate contamination. Insulin has an important place in drug therapies for Insulin-dependent diabetes mellitus (type I) and for many patients with non-insulin-dependent diabetes mellitus (type II). However, it is still generally delivered via injections. It would be highly advantageous if insulin could be administered orally,[2] because the oral delivery of insulin can mimic the physiological fate of insulin and may provide better glucose homeostasis. This would also lessen the incidence of peripheral hyperinsulinemia, which is associated with neuropathy, retinoendopathy, and so forth.[3] Various challenges are usually evaluated by determining the fate of insulin in the GIT.[4] The main challenges reported involve overcoming the enzymatic degradation of insulin and the insufficient permeation of insulin through the GIT. Success in the oral delivery of therapeutic insulin would improve the quality of life of many people who must routinely receive injections of this drug. In the last few decades, various attempts have been made to overcome the limitations and drawbacks of conventional oral insulin therapy. The successful oral delivery of insulin involves overcoming the barrier of enzymatic degradation, achieving epithelial permeability and conserving the bioactivity of the drug during formulation processing. Pharmaceutical strategies have been proposed to maximize oral insulin bioavailability in insulin delivery systems, to overcome barriers, and to develop safe and effective therapies.

Absorption Enhancers

The absorption enhancers improve the absorption of drugs by increasing their paracellular and transcellular transport. They involve several different mechanisms of action, including changes in membrane fluidity, decrease in mucus viscosity, the leakage of proteins through membranes, and the opening of tight junctions. Common examples of non-specific permeation enhancers are bile salts, fatty acids, surfactants, salicylates, chelators and

zonula occludens toxin. Bile salts in mixed micellar systems increase the permeation of insulin by accessing a paracellular pathway.[5] A study of N-lauryl-β-D-maltopyranoside also suggested that this enhancer may open the tight junctions of the epithelium, thereby increasing the permeation of insulin via a paracellular pathway.[6] In another interesting study, water-in-oil-in-water multiple emulsions incorporating 2% docosahexaenoic acid or eicosapentaenoic acid had dose-related pharmacological effects on insulin and may potentially become the formulations for the enteral delivery of insulin.[7] Another report demonstrated the hypoglycaemic effects of enteric-coated capsules containing insulin formulated in Witepsol W35 with sodium salicylate, which significantly decreased plasma glucose levels and increased hypoglycaemia relative to the effects of a subcutaneous injection of regular soluble insulin.[8] Morishita *et al.* evaluated the administration of insulin solution to the various colonic and rectal loops of fasted rats in situ, with or without sodium caprate, Na2EDTA, or sodium glycocholate as an absorption enhancer, and with or without protease inhibitors such as aprotinin.[9] Their results suggested that absorption enhancers increase insulin efficacy more effectively in the colon than in the small intestine. An innovative strategy involving the modulation of tight junctions to improve the transport of paracellular drugs and proteins normally not absorbed through the intestine is a very attractive solution.[10]

Enzyme-Inhibitors

Recent studies have evaluated the use of enzyme inhibitors to slow the rate of insulin degradation. The co-administration of enzyme inhibitors provides a viable means to circumvent the enzymatic barrier to the delivery of peptide and protein drug. Insulin is strongly degraded by trypsin, α-chymotrypsin and elastase and to a lesser extent, by brush-border membrane-bound enzymes.[11] In an interesting study, Yamamoto et al. evaluated the effects of five different enzyme inhibitors such as sodium glycocholate, camostatmesilate, bacitracin, soybean trypsin inhibitor and aprotinin on the intestinal metabolism of insulin in rats.[12] Among these enzyme inhibitors, sodium glycocholate, camostat mesilate and bacitracin were effective in improving the physiological availability of insulin in the large intestine. However, none of these enzyme inhibitors was effective in the small intestine, possibly because of the numerous enzymes secreted there. Liu et al. also evaluated the potential utility of various enzyme inhibitors in improving the intestinal absorption of insulin and investigated their efficacy in different intestinal regions.[13]

B) NASAL ADMINISTRATION

This insulin drug delivery system has been widely investigated as an alternative to subcutaneous injection for the treatment of diabetes and is considered to be a promising technique for the following reasons, the nose has a large surface area available for drug absorption because the epithelial surface is covered with numerous microvilli; the subepithelial layer is highly vascularized and the venous blood from the nose passes directly into the systemic circulation, thereby avoiding the loss of drug by first-pass metabolism in the liver; it allows lower doses, more rapid attainment of therapeutic blood levels, quicker onset of pharmacological activity, fewer side effects, high total blood flow per cm^3 and a porous endothelial basement membrane; it is easily accessible; and the drug is delivered directly to the brain along the olfactory nerves.[14] The pharmacokinetic profile of intranasal insulin is similar to that achieved with intravenous injection and in contrast to subcutaneous insulin delivery bears a close resemblance to the 'pulsatile' pattern of endogenous insulin secretion during meal times.[15] A attempt made to implement this approach have indicated that intranasal insulin therapy has considerable potential for the control of postprandial hyperglycemia, especially in the treatment of patients with insulin-dependent diabetes mellitus.[16] Despite the potential of the nasal route, a number of factors limit the intranasal absorption of drugs, especially peptide and protein drugs. Mucociliary clearance, enzymatic activity and the epithelium combined with the mucus layer constitute barriers to the nasal absorption of high-molecular-weight and hydrophilic peptides. Therefore, the use of absorption enhancers and proteolytic enzyme inhibitors and the design of suitable dosage formulations, such as mucoadhesive and dry powder delivery systems have been investigated to enhance the nasal bioavailability of these drugs.[17] The effects of sodium deoxycholate (SDC) in combination with cyclodextrins (CD) as enhancers of the nasal absorption of insulin have been determined by measuring blood glucose levels.[18] Combining SDC with beta-CD lowered the serious nasal ciliotoxicity of SDC and had a marked absorption-promoting effect which was due not to the low concentration of SDC but to the inhibition of leucine aminopeptidase activity. The effects of a soybean-derived sterol mixture and of stearyl glucoside mixture as enhancers of the nasal absorption of insulin in rabbits have been investigated.

A series of new glycosides with extended alkyl side chains (C13–16) linked to maltose or sucrose were synthesized and used effectively to enhance nasal insulin absorption in anesthetized rats. Cross comparisons of alkylmaltoses and alkanoylsucroses showed that the alkyl chain length had a greater effect than the glycoside moiety in determining the potency of potential insulin absorption-enhancing agents. When tetradecylmaltoside was applied to the nasal mucosa 15 min before insulin was applied enhanced insulin absorption was observed. Most of the traditional absorption enhancers, such as surfactants and bile salts, have limited clinical use because of the irreversible damage to the nasal mucosa that accompanies their absorption enhancing effects.[19]

C) OCCULAR ADMINISTRATION

Various research groups have reported early exploratory work on systemic drug absorption via the ocular route. This efficient systemic absorption can be utilized as a non-invasive means of delivering drugs systemically. It also offers the advantages that it is much easier to administer than is an injection the rate of systemic absorption through the ocular route is as fast as via an injection; eye tissues are much less sensitive to the development of immunological reactions than are other tissues; it bypasses first-pass gastrointestinal and liver effects which are responsible for the low oral bioavailability of peptides and other drugs and no tolerance and ocular side effects have been detected after long-term (3 months) daily administration of insulin eye drops.[20] The eye presents unique opportunities and challenges when it comes to the delivery of pharmaceuticals and it is very accessible to the application of topical medications. The potential route for insulin delivery to the anterior segment of the eye has been the conjunctival sac.[21] More recent investigations have shown that the conjunctival route of entry plays an important role in the penetration of drugs into the anterior segment. Furthermore topically applied drugs have been shown to have access to the sclera from the conjunctiva. Therefore, it is conceivable that such drugs could find their way to the posterior segment. It has been shown that even a high molecular-weight peptide like insulin can accumulate in the retina and optic nerve after topical application supporting the contention that topically applied drugs can both reach the posterior segment and be therapeutic. Finally topically applied insulin also accumulates in both the contralateral eye and the central nervous system. After the pioneering work of Christie and Hanzal (1931), numerous investigations of the systemic delivery of insulin via the ocular route were undertaken. Bartlett et al. investigated the feasibility of using insulin eye drops in humans by studying the local toxicity and efficacy of insulin administered without surfactant to the eyes of healthy volunteers.[22] The results of this study suggest that single-dose insulin at concentrations of up to 100 U/mL formulated in saline, has no detectable clinical toxicity on the anterior structures of the human eye. Not surprisingly this therapy was abandoned in humans because of its low bioavailability. A wide variety of absorption enhancers have been evaluated in the delivery of insulin via the ocular route. Yamamoto et al. determined the extent, pathways and effects of absorption enhancers on the systemic absorption of insulin after the instillation of a topical solution to albino rabbit eyes.[23] The absorption enhancers used were polyoxyethylene-9-lauryl ether (POELE), sodiumglycocholate, sodium taurocholate and sodium deoxycholate, all at a concentration of 1%. The nasal mucosa contributed about four times more than the conjunctival mucosa to the systemic absorption of ocularly applied insulin. However, the conjunctival mucosa was more discriminating in its sensitivity to the nature of the bile salts used than was the nasal mucosa. Collectively, these findings indicate that it is feasible to achieve hypoglycemia with ocularly administered insulin. Consequently, eyedrops of 0.25% insulin plus 0.5% POELE or polyoxyethylene-20-stearyl ether (Brij-78) were instilled into rabbit eyes twice a day for 3 months.[24]

No allergic responses or local side effects were detected, indicating that both insulin and the absorption enhancers (POELE and Brij- 78) are safe for instillation into the eyes over long periods. A series of alkylglycosides with various alkyl chain lengths and carbohydrate moieties were tested for their ability to enhance the systemic absorption of insulin after topical ocular delivery in anesthetized rats.[25] Regular porcine insulin was administered as eye drops either alone or in combination with several different absorption enhancers, to healthy euglycemic dogs.[26] No ocular symptoms occurred with the administration of insulin alone or together with 0.5% solutions of Brij-78, fusidic acid, POELE, dodecylmaltoside or tetradecylmaltoside. This study demonstrated that short-acting insulin is systemically absorbed in dogs via the ocular route when applied with certain emulsants. Sucrose cocoate (SL-40) is an emulsifier used in emollients and skin-moisturizing cosmetic formulations that contains a mixture of sucrose esters of coconut fatty acids in an aqueous ethanol solution. Sucrose cocoate was examined to determine its potential usefulness and enhancing effects in nasal and ocular drug delivery.[27]

Significant increases in plasma insulin levels and a decrease in blood glucose levels were observed. To prolong the retention time of the formulation in the precorneal area a positively charged insulin-containing liposome was prepared.[28] This formulation reduced the blood glucose concentrations of rabbits to 65%–70% of the initial levels for up to 5 h. Commercially available Gelfoam®, an absorbable gelatin sponge is used in the fabrication of an ocular insert in the form of a matrix system. Both in vitro flow-through and in vivo methods of device removal were examined to determine the dissolution rate of insulin from a Gelfoam®-based eye device.[29]

D) RECTAL ADMINISTRATION

This route is regarded as a more physiological route for the application of insulin. 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 diet. It is most likely that the presence of degrading enzymes in the gut wall decreases from the proximal end to the distal end of the small intestine and rectum. The most important advantage suggested for the rectal administration of insulin is the possibility of avoiding to some extent, the hepatic first-pass metabolism.[30] Hosny found that insulin suppositories containing 50 U of insulin incorporated with 50 mg of deoxycholic acid, sodiumtaurocholate or both placed in the rectum of Alexon-induced hyperglycemic rabbits caused a large decrease in plasma glucose concentrations, and the relative hypoglycemia was calculated to be 38.0%, 34.9%, and 44.4%, respectively,

compared with that observed for insulin (40 U) injected subcutaneously.

The most pronounced effect was observed with the addition of polycarbophil to a suppository formulation containing a combination of deoxycholic acid and sodium taurocholate which produced 56% relative hypoglycemia compared with that achieved with a subcutaneous injection. These suppository formulations are very promising alternatives to current insulin injections, because they are roughly half as efficacious as subcutaneous injections. Insulin suppositories were formulated using Witepsol W35 as the base to investigate the effects of various bile salts/acids on the plasma glucose concentrations of diabetic beagle dogs.[31] Investigation of the effects of insulin suppositories on the plasma glucose concentrations of diabetic beagle dogs showed that a relative hypoglycaemic effect of about 50%–55% can be achieved using insulin suppositories containing Witepsol W35 as the base, insulin (5 U/kg), and sodium salicylate (50mg) or POELE (1%) as rectal absorption enhancers.[32] Studies have recently shown that the formation of an adhesive interaction between the delivery system and the rectal mucosa can be harnessed as an absorption modifier because it increases the contact time of the coadministered drug and possibly acts as a sustained-release polymer.

A thermoreversible liquid insulin suppository, which undergoes a phase transition to a bioadhesive gel at body temperature, enhances the bioavailability of insulin.[33] The thermoreversible liquid insulin suppository (containing 100 IU/g insulin, 15% poloxamer P407, 20% poloxamer P188, 0.2% polycarbophil, and 10% sodium salicylate) could potentially be developed as a more convenient, safe, and effective rectal delivery system for insulin. Adikwu[34] evaluated snail mucin motifs as rectal absorption enhancers for insulin.

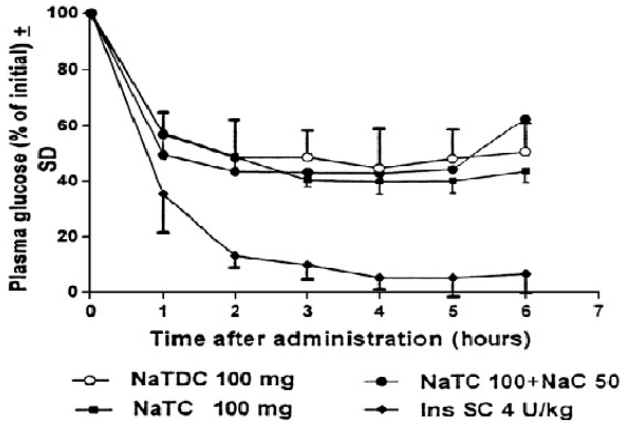

Figure 1: Effect of sodium taurodeoxycholate (NaTDC; 100 mg) or sodium Taurocholate (NaTC; 100 mg) alone or in combination with sodium cholate (NaC; 50 mg) on the mean plasma glucose levels (% of initial values) in Hyperglycaemic beagle dogs after rectal administration of Witepsol W35suppositories containing human insulin (5 U/kg) compared with the effects of subcutaneously injected insulin (Ins s.c., 4 U/kg).[32]

E) TRANSDERMAL ADMINISTRATION

Skin is the largest organ of the human body transdermal drug delivery is an appealing alternative to subcutaneous delivery. It offers good patient compliance and the possibility of controlled release over time while avoiding possible drug degradation resulting from GIT or first-pass liver effects. The skin also provides a painless interface for systemic drug delivery.[35] Despite these advantages, the human skin is an extremely effective barrier that protects against and is impermeable to foreign molecules, especially large hydrophilic molecules. The low permeability of the skin is caused mainly by the stratum corneum, the skin's outermost layer.[36] The development of a sophisticated new approach to overcome the skin permeability obstacle has challenged the pharmaceutical community to develop new delivery methods .Attempt to overcome this barrier to allow the transfer of large drugs have included technique that weaken the barrier with skin absorption enhancers as iontophoresis, ultrasound, or microneedles.[37]

Microneedles: Now a days novel approach that increases transdermal transport involves the use of microneedles that pierce the skin and create micrometer scale openings. Although still extremely small on a clinical level, channels of micrometer dimensions are much larger than macromolecules and therefore should dramatically increase skin permeability to large drug molecules. Microneedles of micrometer dimensions can create transport pathways large enough for small drugs, macromolecules, nanoparticles and fluid flow, but small enough to avoid pain and facilitate highly localized and even intracellular targeting. The microelectronic revolution has provided tools for highly precise, reproducible, and scalable methods to fabricate structures of micrometer dimensions. This lithography-based approach can produce large arrays of microneedles that can be inserted into cells, skin or other tissues. Arrays of micrometer-scale needles could be used to deliver drugs, proteins and particles across skin in a minimally invasive manner. The increased importance of macromolecular therapeutics, combined with the newly acquired power of microfabrication, has recently prompted interest in fabricating and testing[38] microneedles for drug delivery. Practical microfabrication techniques have been developed to yield microneedle arrays of silicon, metal and biodegradable polymers of micrometer dimensions in various geometries.[39]

Skin permeability for diffusion-based transport of large molecules such as proteins. Hollow microneedles have permitted the flow of microliter quantities into the skin in vivo, including the micro injection of insulin to reduce blood glucose levels in diabetic rats. These results suggest that microneedles are a useful approach to transdermal drug delivery. Building on microneedle transdermal studies Martanto *et al.*[40] Designed and fabricated arrays of solid microneedles to be inserted into the skin of diabetic hairless rats for the transdermal delivery of insulin to lower blood glucose levels. Shows that the

microneedles increased the permeability of the skin to insulin, which rapidly and steadily reduced blood glucose levels to an extent similar to that achieved with0.05–0.5 U of insulin injected subcutaneously.

Table 1: Some of the companies involved in various insulin development other than oral routes

Insulin dosage form	Name and address of Manufacturer
Oral	Ariad Pharmaeutical, Cmbridge, Massachusetts, USA AutoImmune, Pasadena, California, USA BioSante Pharmaceuticals, Lincolnshira, Illinois, USA Cortecs, Flintshire, UK. Elan, Dublin, Ireland. Emisphere Technology, Inc., Tarrytown, New York, USA Nobex Corporation, Raleigh, North Carolina, USA Transgene Biotek Ltd., India. Unigene Laboratories, Inc., Fairfield, New Jersey, USA
Pulmonary	AeroGen Inc., Mountain View, California, USA Alkermes,Cambridge, Massachusetts, USA Aventis, Bridgewater, NJ, Pfizer, NY Dura Pharmaceuticals, Menlo Park, California, USA Epic Therapeutics Inc., Norwood, Massachusetts, USA ImaRx Therapeutics, Tucson, Arizona, USA Inhale Therapeutics, San carlos, CA Nektar Therapeutics Inc., San Carlos, CA NovoNordisk, Bagsvaerd, Denmark
Transdermal	Altea Development Corporation, Altanta, Georgia, USA Cygnus Pharmaceuticals, Redwood city, California, USA Helix Biopharma Corporation, Aurora, Ontario, CA IDEA, Munich, Germany ImaRx Therapeutics, Tucson, Arizona, USA Noven Pharmaceuticals, Miami, FL Sontra Medical Corporation, Cambridge, Massachusetts, USA Vector Medical Technologies Inc., Miami, FL
Intranasal	Bentley Pharmaceutical Inc., North Hampshire, USA ML Laboratories, Warrington, UK Odem Ltd., Cambridge, Massachsetts, USA Pari GmbH, Midlothian, Virginia, USA West Pharmaceutical Services, Lionville, Pennysylvenia, USA
Ocular	BioSante Pharmaceuticals Lincolnshira, Illinois, USA.

CONCLUSION

Over the last several decades with a view to ease pain and stress of multiplidely injections to the millions of diabetic patients worldwide. Needle phobia and stress led to the investigation and exploitation of all promising routes, ranging from oral to rectal, by a wide variety of devices and delivery systems. Several pharmaceutical companies are also involved actively in developing a non-injectable insulin delivery system. Some of the companies are mentioned in Table 1. Among the various routes of insulin administration, each has it shown set of favorable and unfavorable properties. Most of the approaches described above represent long-term possibilities for insulin delivery, but difficulties in securing adequate blood insulin concentrations are yet to overcome. The quest for a permanent cure of diabetes still continues and the advent of time will show some promising light on the new horizon on the insulin therapy.

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