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Non invasive insulins: advanced insulin therapy over this decade

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ABSTRACT

Frederick Banting and Charles Best extracted insulin from bovine pancreas in 1922, who received the Nobel Prize for their contribution in Medical field with John McLeod. Conventional insulin treatment involves replacement therapy, which involves the administration of insulin exogenously via subcutaneous route to mimic the pancreatic insulin secretion. Many people with types 1 and 2 diabetes over the world have used subcutaneous injections daily in order to control blood glucose level and/or to eradicate ketoacidosis which is really life threatening. Although, these injections avoid many complications, they became a source of inconvenience and lack of comfort. currently many other techniques have been investigated which resulted in delivering insulin other than subcutaneous route. These formulations are designed in such a way that they will overcome the inherent barriers of insulin uptake across the skin, gastro intestinal tract and mucous membrane. Various routes other than sub cutaneous which are under investigation for insulin therapy include oral, pulmonary, transdermal; nasal, buccal, ocular, rectal etc. Many approaches have been pursued in order to deliver insulin orally which include the use of absorption enhancers, inhibitors of proteases, inclusion of mucoadhesive components, buffers, micro and nano particles, liposomes, niosomes, microspheres, hydrogels, smart polymers etc. Over last few decades research is going on several non invasive routes for the delivery of insulin and many of them have stepped into pre clinical and clinical trials. Even products like Exubera ® and Oral-lyn™ were marketed after passing phase 3 clinical trials. Non invasive insulin delivery will definitely prove to be a boon to several patients who are currently depending on daily subcutaneous multiple injections.

Keywords: Subcutaneous, ketoacidosis, absorption enhancers, liposomes, microspheres, niosomes, hydrogels.

INTRODUCTION

Frederick Banting and Charles Best extracted insulin from bovine pancreas in 1922, who received the Nobel Prize for their contribution in Medical field with John McLeod, Banting et al., 1922). Conventional insulin treatment involves replacement therapy, which involves the administration of insulin exogenously via subcutaneous route to mimic the pancreatic insulin secretion. Many people with types 1 and 2 diabetes over the world have used subcutaneous injections daily in order to control blood glucose level and/or to eradicate ketoacidosis (Hanas et al., 1990) which is really life threatening. Currently people are reliant on multiple dose of subcutaneous injections of insulin as a standard treatment of diabetes. Although, these injections avoid many complications, they became a source of inconvenience and lack of comfort and cause lipohypertrophy (Hanas et al., 1990) and atherosclerosis (Nordestgard et al., 1997). which occurs due to irregular absorption of insulin. Inadequate control of blood glucose level and poor patient compliance are associated drawbacks with this treatment (Carino et al., 1999, Zambanini et

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al.,1999). It may also lead to diabetic micro- and macroangiopathy (Gwinup et al., 1990). Other problems associated with subcutaneous insulin therapy include pain at injection site, infection due to improper administration (self administration), hypertrophy at the injection site due to insulin deposition and lastly cost effective and risky [Kennedy et al.,1991]. Currently many other techniques have been investigated which resulted in delivering insulin other than subcutaneous route. These formulations are designed in such a way that they will overcome the inherent barriers of insulin uptake across the skin, gastro intestinal tract and mucous membrane (Lee et al., 2000).

Various routes other than subcutaneous which are under investigation for insulin therapy include oral, pulmonary, transdermal; nasal, buccal, ocular, rectal etc. (Owens et al., 2002, Cefalu et al., 2004, Gordberg et al.,2003, Kublik and Vidgren, 1998; Surendrakumar et al., 2003 (Onuli et al.,2000, Brand et al., 1997; Kanikkannan et al., 1999; Boucaud et al., 2002,)

ORAL ROUTE FOR INSULIN

It is very challenging for the formulators to deliver a peptide like insulin via oral route (Saffran et al., 1997; Jung et al.,2000; Soppimath et al., 2001; Lambkin and Pinilla, 2002; Shen,2003; Hamman et al., 2005; Cui et al., 2006; Mahkam et al., 2006; Qian et al., 2006; des Rieux et al., 2006; Liu et al., 2006; Sarmento et al., 2007; Simon et al., 2007), especially if it is particular to deliver the peptide physiologically to liver through hepatic portal circulation, which will mimic the endogenously secreted insulin by beta cells of pancreas (Owens et al., 2003).

Fragility in structure, hydrophilic character of the molecule (Saffran et al., 1997; Jung et al., 2000; Soppimath et al., 2001; Lambkin and Pinilla, 2002; Shen, 2003; Hamman et al., 2005; Cui et al., 2006) and obviously the high molecular weight of this large peptide, makes the drug difficult to absorb through the gastro intestinal tract. and moreover being rapidly eliminated from the blood, it will effect the therapeutic efficacy of the drug. (Cleland et al., 2001; Drews, 2003).

It is also affected by chemical and enzymatic degradation when it enters into the gastro intestinal tract. Highly acidic conditions will also accelerate the breaking of di sulfide bonds between the chains of insulin molecule which will lead to the chemical degradation of the molecule. (Gowthamarjan et al.,2003.)

Insulin is also inactivated due to the enzymes like pepsin trypsin and chymotrypsin that are secreted in various parts of gastro intestinal tract and hence will decrease the bioavailability of the drug. (Schilling and Mitra, 1991; Saffran et al., 1997; Jung et al., 2000; Soppimath et al., 2001; Lambkin and Pinilla, 2002; Shen, 2003; Calceti et al., 2004; Hamman et al., 2005; Cui et al., 2006; Mahkam et al., 2006).

Despite of these limitations, oral delivery promises to be a good option for administering various peptides (which include vaccines, hormones and many biomodulators) by making some modifications in the formulation (Sastri et al., 2000).

Many approaches have been pursued in order to deliver insulin orally which include the use of absorption

enhancers, inhibitors of proteases, inclusion of mucoadhesive components (Ponchel and Irache, 1998; Arango et al., 2000), buffers, micro and nano particles (Fan et al., 2006), liposomes (Soppimath et al., 2001), smart polymers etc.. (Gordon-Still, 2002; Marschütz et al., 2000; Damagè et al., 1997; Lowman et al., 1999; Haupt and Rubinstein, 2002).

An ideal oral drug delivery system for insulin should be able to increase the residence time of drug in gastrointestinal tract by preventing its enzymatic degradation in stomach and git (Saffran et al., 1990) and thus increasing the absorption of the drug. It should be also able to increase the permeability (Iwanaga et al., 1999). of this hydrophilic molecule through the highly lipophilic mucosal membrane.

Peptide drug can be delivered orally by using techniques like:

Absorption enhancers and enzyme inhibitors

Certain compounds like bile salts, chelating agents, long chain fatty acids and amphiphilic surfactants can be used as absorption enhancers (Eaimtrakarn et al.,2002, Aungst, 1994; Coudhari et al., 1994; Senel et al., 1997). These substances increase the paracellular transport either by increasing the fluidity of the membrane or by decreasing the viscosity of thick mucosal lining of the git and hence increase the absorption (Mahato et al.,2003). It was found that the bioavailability of insulin was enhanced to many times when it was formulated along with absorption enhancers like sodium glycolate (Morishita et al.,1993). Mixed micellar systems of bile salts increase the absorption of insulin by increasing its paracellular permeability (Lane et al.,2005).

As insulin gets rapidly degraded in git by intestinal enzymes like trypsin, chymotrypsin and elastase, inclusion of compounds which act as inhibitors to these enzymes may provide a viable enzymatic barrier for insulin delivery via oral route (Yamamoto et al.,1994, Carino, et al., 1994). Substances like aprotinin (Morishita et al.,1990), bacitracin, soybean trypsin inhibitor, chick and duck ovomucoids (Agarwal et al.,2000) have shown to offer protection against these enzymes and thus increasing the bioavailability of orally administered insulin (Yamamoto et al,1990).

Liposomes

Liposomes are defined as multilamellar, concentric bilayered vesicles in which aqueous volume is entirely enclosed by a membranous lipid bilayer composed of natural and synthetic phospholipids. Liposomes can be used to target the drug to liver spleen and bone marrow.

Liposomes can be used for oral delivery of peptides (Spangler et al., 1990, Katayama et al.,2003, Takeuchi et al., 1996; Kim et al., 1999; Iwanaga et al., 1999; Kisel et al., 2001; Wu et al., 2004), if they are prevented from degradation in git by bile salts. Resistance to bile salts can be achieved by coating the surface of liposomes with PEG or mucin. Hence, surface coated liposomes of insulin will have greater stability in gastro intestinal tract and can be a choice of oral drug delivery of insulin (Ashada, et

al.,1995).Even lectin modified liposomes can also increase the stability of insulin in GI tract(Na Zhang et al,2005).Chitosan coated liposomes showed muco adhesive character which will increase the residence time in the GI tract and hence increase absorption(Takeuchi et al.,1996).

Enteric coated capsules

Enteric coating prevents the drug being released before reaching the intestine i.e. in the stomach and upper gut.It prevents the drug being released in the acidic environment (stomach).So it is a useful means for the delivery of peptide drugs like insulin which rapidly degrade in the stomach (Hosny et al., 2002).

It was found that enteric coated capsules filled with freeze dried chitosan nanoparticles can be used for the oral delivery of insulin(Kiran Sonaje et al.,2010).As the capsules were pH sensitive, insulin was prevented from being degraded in the stomach by gastric proteolytic enzymes.Later on in the intestine drug dissolves rapidly and hence oral absorption of insulin increased.Even Eudragit S100 enteric-coated capsules containing sodium salicylate as an absorption enhancer increased in bioavailability of oral insulin in dogs(Ehab A Hosny et al 2002).

Microparticles or microspheres

These are small spherical particles having their diameter in range of 1 to 1000 microns having different densities.They are made up of natural and synthetic substances like polymeric, waxy, or other natural polysaccharides like starches,and even waxes, gums, proteins and fats are used as drug carrier matrices for drug delivery(Krauland et al., 2006). Polymers like gelatin and albumin are also used as carrier matrices in the preparation of these microspheres.The microspheres are porous and have high efficiency for the absorption of wide variety of lipophilic and hydrophilic substances. These microspheres aid in the protection of proteins by preventing them to interact with any substance till the complete degradation of the polymer, and hence reducing the contact with solutions which will degrade the proteins. The micro particles can be prepared by coacervation process regulating temperature conditions.Insulin can be imbibed into these microparticles by diffusion loading.

Micro particles of mucin and sodium alginate which are loaded with insulin(Philip F. Builders et al.,2008) and poly(fumaric-co-sebacic)anhydride microspheres loaded with insulin(Stacia Furtado et al.,2007) showed to be effective as oral insulin delivery.

Niosomes

A niosome is a non active surfactant containing liposome.They are very similar to liposomes in structure except they contain surfactant which will enhance the stability of the drug delivery system. They contain non-ionic surfactant belonging to the class of the alkyl or dialkyl polyglycerol ether and cholesterol with subsequent hydration in aqueous media. They can improve the therapeutic effect of peptides by reducing the clearance time from systemic circulation, increased bioavailability

and targeted and controlled drug delivery to the site of action (Yoshida et al.,1992).

Peptides such as insulin can be formulated in the form of niosomes as they will prevent the degradation of insulin by encapsulation of drug along with the surfactant in its hydrophilic matrix. Formulation of oral insulin in the form of polyoxyethylene alkyl ether niosomes showed that peptides like insulin can be delivered as niosomes which will show sustained release of drug in the intestine(Abbas Pardakhty et al.,).

Nanoparticles

Nano particles are defined as the submicron particles having their diameter about 100 nanometer and less.They are used as carriers for the oral delivery of peptides like insulin [Damge et al., 1998] as they are highly stable, feasible for the incorporation of many hydrophilic and hydrophobic substances, and can release the drug in controlled rate from the polymeric matrix and hence increase the bioavailability of the drug in the desired site of action. They are synthesized using several biodegradable and biocompatible polymers. These polymers may be natural like albumin and gelatin or synthetic like polyacrylic acid polymers and polylactides.Drug is released from the polymeric matrix either by diffusion or the degradation of the matrix.Insulin loaded nanoparticles are taken by the peyer's patches of the intestine.It was found that insulin loaded poly(isobutylcyanoacrylate) nanoparticles were effective in oral delivery of insulin and showed significant hypoglycemic effect.(Mounir S. Mesiha et al.,2004) .Entrapment of insulin into alginate/chitosan nanoparticles increased the contact time in the gastrointestinal tract due to the bio adhesive nature of the chitosan and alginic acid.(Sarmento et al,2007.). Promising results were obtained when Cyclodextrin-insulin complex encapsulated polymethacrylic acid nanoparticles were used in the oral delivery of insulin (Sajeesh et al., 2006.).Poly acrylic acid based polymers have a capability of preventing the proteins being degraded in the gastro intestinal tract by binding to the divalent cations and also by enhancing the permeation of peptides.Complexation with cyclodextrins increases the absorption of insulin by stabilizing the molecule against aggregation and degradation.Even Nanocubicles (Chung et al.,2002),Nanospheres_(Damge et al., 1997; Carino et al., 2000; Foss et al., 2004), were investigated for oral insulin delivery.

Hydrogels

Hydrogels (Kahyap.,et al 2005), are the colloidal drug delivery systems in which drug is dispersed in aqueous medium.These are multicomponent systems which contain a three-dimensional network of polymer chains and water is used as a dispersion medium to fill the spaces between these macro molecules.As they have the capability to hold water they are hydrophilic in nature.As they have the ability to absorb aqueous solutions without losing shape and mechanical strength, are commonly met in many natural constituents of a human body, like muscles they can be used for the delivery of peptides.In addition to that,they have good biocompatibility with bodyfluids and blood.

Hydrogels are capable to prevent insulin being released in the stomach (acidic pH). As the pH increases towards the small intestine drug releases from the hydrogel due to the interaction with solvent content (Bell and Peppas, 1996; Lowman and Peppas, 1999; Peppas et al., 1999, 2000; Kim and Peppas, 2002a,b; Robinson and Peppas, 2002; Blanchette et al., 2003).

Hydrogels can be prepared by using poly (methacrylic acid-g-ethylene glycol) dissolved in water. Drug release profile from the gel will depend upon the amount of water added as it will influence the mesh size and the swelling behavior of the gel. As the solvent content is increased, the mesh size is increased and as a result swelling increases (Amit kumar et al., 2006).

Microemulsions and reverse micelles

Micro emulsions are defined as monodispersed, transparent, isotropic thermodynamically stable mixtures containing water oil and surfactant along with the combination of co surfactant. It consists of an aqueous and oily phases. The surfactant or co surfactants are added to incorporate stability characteristics to the molecule. The surfactant molecules orient themselves in such a way that hydrophilic part is directed towards the centre and hydrophobic projecting outside towards the solvent. The droplet size of this micro emulsion ranges from (10 – 200 nm). Lesser particle size will enhance the absorption and permeation of the drug. The co-surfactant is added to incorporate flexible o/w interface which results in thermodynamically stable optimized system.

Micro emulsions (Ritschel, 1991; Spernath and Aserin, 2006, A. Cilek et al., 2005). and reverse micelles can be used as oral peptide drug delivery systems because of their unique solubilizing tendency of poorly soluble drugs by maintaining them as a molecular dispersion in the gastro intestinal tract. They can act as penetration enhancers and increase the motility of the drug across the gastro intestinal membrane.

Micro emulsions loaded with insulin were formulated using didocecyl dimethyl ammonium bromide as surfactant and propylene glycol as co-surfactant to form a low shear reverse micelle showed increase in insulin bioavailability as these micro emulsions will increase the bioavailability of insulin by enhancing the penetration of drug in gastric mucosa, increasing its retention time in git and preventing the drug against the degradation by gastric enzymes (Sharma et al., 2010).

Colon targeted drug delivery

Recently, colon specific drug delivery is gaining importance in the oral delivery of proteins and peptides because it offers advantages like long residence time in colon, less number of digestive enzymes relative to other places in the gastrointestinal tract, negligible brush border activity and less number of pancreatic enzymes compared to the small intestine (Mrsny et al., 1992, Haupt et al., 2002, Katsuma et al., 2005).

The only problem associated with this drug delivery system is low bio availability as it has lower surface area available for drug absorption and lesser water content at this site.

The colon targeted drug delivery can be used for the delivery of insulin by incorporating absorption enhancers like EDTA which will increase the bioavailability of the drug.

It was found that there was prolonged hypoglycaemic effect in dogs when insulin in combination with sodium glycocholate and poly ethylene oxide (gelling agent) when administered orally for colon target drug delivery. Sodium glycocholate will prevent the aggregation of insulin in aqueous medium. It was found that many other compounds like citric acid (solubilizing agent), meglumine (for adjusting pH), sodium lauryl sulphate and Camostat mesilate (inhibits proteases) when co administered with insulin for colon targeted drug delivery increased the bio availability of insulin and showed satisfactory hypoglycaemic effect (Katsuma et al., 1995). Azo polymer coated insulin pellets also showed prolonged hypoglycaemic effects (Tozaki et al., 2001).

Although producing promising results, due to the lack of validated procedures and toxicity these delivery systems remain as controversies in the development of this formulation.

Resealed erythrocytes

Investigations were made on erythrocytes as potential carriers for the oral delivery of proteins like insulin and macromolecules because of their biodegradable nature, biocompatibility and inert nature in biological fluids. They release the encapsulated material in sustained zero order release and have longer half lives in blood circulation. Encapsulation will prevent the loaded drug from degradation by the gastric enzymes. The diffusion rate of these molecules depend upon the lipophilicity of the molecule (Lewis et al., 1984).

Such Resealed erythrocytes can be synthesized by collecting the blood from desired organism, centrifugation to separate erythrocytes. The separated erythrocytes are loaded with drug by placing them in hypotonic drug solution. Then they are resealed in isotonic environment.

This therapy has gained remarkable interest in drug delivery as these carriers will release the drug in steady state within the therapeutic window which reduces the other side effects of the drug. Resealed erythrocytes were developed as carriers for peptides like oligonucleotides, antineoplastic peptides, interleukin 3, AZT and erythropoietin.

Although having many advantages these systems need optimization of various parameters. Moreover Storing these erythrocytes, contamination when exposed to environment and lack of validated process of preparation remain as challenges for their development. Many investigators are working on these resealed erythrocytes as carriers for peptide drug delivery which may step into pre clinical and clinical trails which state that resealed erythrocytes are promising drug delivery systems for peptides and macromolecules (Summers et al., 1983).

INHALATION INSULIN

Pulmonary route has faster absorption compared to other routes due to the larger surface area (about 150 square meters) and

very thin epithelium of alveoli which make this route promising for the delivery of proteins and peptides like insulin. Moreover the first pass metabolism is avoided and the activity of other metabolic enzymes was also found to be less. Insulin aerosol was formulated as an alternative for the patients who take daily multiple subcutaneous injections to enhance the patient compliance and quality of life with diabetes mellitus. As it is non invasive route of administration, it is considered to be a novel approach alternative to the subcutaneous insulin injections (Agu et al, 2001).

It was found that when insulin was formulated as dry powder inhalation in the form of microcrystals showed sustained hypoglycaemic effect in rats (Chen et al.,2002).

Insulin when formulated along with hyaluronic acid as dry powder inhalation showed more reduction in glucose levels due to the mucoadhesive nature of HA(Surendrakumar et al., 2003).Even phospholipids and cyclo dextrin derivatives also enhanced the pulmonary absorption of insulin(Mitra et al 2001, Hussain et al.,).

Poly (lactide-co-glycolide) (PLGA) and polylactide particles were also used in the insulin delivery by pulmonary route and showed sufficient BAV (Huang et al., 2006).

Polybutylcyanoacrylate nanoparticles loaded with insulin showed significant decrease in blood glucose levels when administered intra tracheally in rats (Zhang et al., 2001).

This route remains challenging for formulators as several factors need to be optimized during the development of the dosage form moreover regulation of dose for asthmatics and smokers becomes a problem.Mild gastric irritation and persistent cough were observed in patients. However this route can be considered as efficient and safe for clinical use.

TRANSDERMAL INSULIN

Transdermal drug delivery systems are the dosage forms in which drug is delivered across the skin into the systemic circulation.Transdermal drug delivery offers several advantages like larger surface area of skin, bypassing first pass metabolism, controlled and site specific drug delivery, avoids enzymatic degradation in the gastrointestinal tract, avoids pH pitfalls which cause drug degradation and good patient compliance as it is non invasive route of administration.Transdermal drug delivery systems can be used for the delivery of peptides and proteins because of these advantages(Prausnitz et al., 2004). The rate of transfer of drug across the skin can be increased by incorporating permeation enhancers, and techniques like micro needles, iontophoresis and sonophoresis.It was found that there was significant decrease in blood glucose levels when insulin loaded calcium carbonate nanoparticles were administered transdermally in mice(Higaki et al., 2006).

Iontophoresis increases the permeation of charged or neutral compounds by applying small amount of electric current.It facilitates the absorption of these ionic moieties through skin by electro migration. Gels are used as vehicles for the delivery of drugs in this technique because of their miscibility with drugs and their compatibility with skin contours. Iontophoresis releases the drug in continuous pulsatile manner. It was found that there is potential

increase in systemic insulin when bovine insulin was administered by iontophoresis in streptozotocin induced diabetic rats (Kanikkannan et al., 1999).

Sonophoresis is a technique which utilizes ultrasound about 3 MHz for the permeation of small lipophilic molecules. Sonophoresis has been used to enhance the delivery of insulin and other therapeutic peptides (Mitragotri et al., 2004). Recently it was found that insulin transversal drug delivery using ultrasound has profound hypoglycemic effect in rabbits(Lee et al.,2004)Even though producing satisfactory results,transdermal insulin delivery remains as a challenge due to formulation difficulties, stability problems, skin irritation, irregular release profiles and high cost of the product.

NASAL INSULIN

Nasal route of administration is defined as the route of administration in which the drug is absorbed through the nasal mucosa into systemic circulation. This route of administration has been studied for the delivery of proteins and peptides alternative to subcutaneous route because of larger surface area of nasal epithelium due to microvilli, inhibits first pass metabolism, not effected by gastric enzymes, highly vascularized and lesser side effects.

It was found that insulin when administered along with sodium deoxycholate and cyclodextrins intranasally decreased the systemic glucose levels to a significant extent(Zhang et al.,2001). In another investigation insulin was formulated as lipid emulsion but did not show significant absorption through nasal mucosa (Mitra et al.,2000).

Although larger surface area allows rapid absorption factors like thick mucous layer, enzymatic activity and mucociliary clearance limit the formulation of larger hydrophilic drugs like insulin via this route.

BUCCAL INSULIN

These are the drug delivery systems in which drug is administered over the buccal mucosa lining the inner cheek and upper gingivae.This route promises to be potential route for the delivery of large hydrophilic molecules like proteins and peptides like insulin because this route will prevent first pass metabolism, prevent the drug being degraded by gastric pH and enzymes, rapid absorption by jugular veins, and finally good patient compliance(Sudhakar et al.,2006).Several water soluble polymers are added to impart adhesive nature to the mucous membrane which will increase the site specific drug absorption. Increased bioavailability was observed when insulin was administered along with absorption enhancers and muco adhesives.

It was found that buccal administration of insulin when formulated along with fatty acids like oleic acid, eicosapentaenoic acid and docosahexaenoic acid showed sustained hypoglycaemic effect in rats.(Morishita et al., 2001).A significant hypoglycaemic effect was observed when insulin was administered in the form of muco adhesive polymeric nano particles through buccal route in diabetic rats and rabbits(Venugopalan et al., 2001),

Insulin buccal spray was formulated in combination with absorption enhancers like soyabean lecithin and propane diol showed significant decrease in blood glucose levels (Xu et al., 2002).

Although having many advantages this routes remains still as challenge for the formulators as there are limited safety reports for this route of administration.

RECTAL INSULIN

Rectum, the terminal portion of the gastrointestinal tract can be used as a potential route for the administration proteins and peptides because of having advantages like less number of degrading peptidases, independent on gastric emptying time and intestinal motility, inhibits hepatic first pass metabolism, independent on gastric p H, drugs that are absorbed in the lower part of the rectum directly reach into inferior venacava.

Investigations made by Hosny showed that insulin suppositories formulated along with deoxycholic acid and sodium taurocholate produced significant decreased levels of blood glucose in alloxan induced diabetic rabbits (Hosny et al.,1998). It was found that insulin suppositories formulated with witepsol produced hypoglycaemic effects in hyperglycaemic beagle dogs (Hosny et al, 2001).

Even though having significant benefits this route is under the subject of investigation as it is difficult to regulate the drug release and moreover lack of patient compliance are the questions for the formulators in developing this dosage forms.

OCCULAR INSULIN

These are the drug delivery systems in which drug is administered in anterior part of eye i.e. conjunctival sac.This route can be used as an alternate route for subcutaneous insulin injections.This route offers several advantages like, non invasive route, more absorption compared to subcutaneous route, bypasses hepatic first pass metabolism,non immunogenic and moreover no adverse effects and tolerance after prolonged usage(Lee et al., 2002).

It was found by Bartlett et al that insulin eyedrops were feasible in decreasing blood glucose levels without using surfactants when administered in humans to study the local toxicity and efficacy.The only drawback of this route of administration is low bioavailability due to less residence time in the conjunctival sac.To prolong the research time several approach were tried.One of these was the development of insulin loaded positively charged liposomes.This resulted in significant decrease in blood glucose levels in rabbits(Srinivasan et al.,1998).

Ocular devices like Gelfoam® containing sodium insulin and zinc insulin have been developed without surfactant and absorption enhancer which produce toxic effect to eye.Lee and Yalkowsky investigated the role of acid in the enhancer-free absorption of insulin from Gelfoam® ocular devices (Lee et al.,1999)

Above mentioned investigations state that insulin can be delivered through ocular route but still this route remains as less

feasible route and requires more research work in toxicological, stability and regulatory areas.

CONCLUSION

Over last few decades research is going on several non invasive routes for the delivery of insulin and many of them have stepped into pre clinical and clinical trials. Even products like Exubera ® and Oral-lyn™ were marketed after passing phase 3 clinical trials. Non invasive insulin delivery will definitely prove to be a boon to several patients who are currently depending on daily subcutaneous multiple injections.

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