Available online on 15.06.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Review Article

Current Challenges in Non-Invasive Insulin Drug Delivery System: A Review

Komal V. Harak*[1], P.B. Patil[1], R.B. Saudhagar[2]

[1] Department of Pharmaceutics, R. G. Sapkal College of pharmacy, Anjaneri, Nashik- 422213, Maharashtra, India

[2] Department of Quality Assurance Techniques , R. G. Sapkal college of pharmacy, Anjaneri, Nashik- 422213, Maharashtra, India.

ABSTRACT

The Frederick Banting and Charles Best extracted insulin from bovine pancreas in 1922, who received the Nobel prize for their contribution in the medical field with Johan McLeod, The gastrointestinal tract (GIT) is the route of choice for the administration of most drugs, regardless of their molecular structure or weight and administration of insulin exogenously via subcutaneous route which mimic the pancreatic insulin secretion, for In todays era, insulin delivery by noninvasive route is an area of current interest in diabetes mellitus treatment by parenteral route for type-I and type-II diabetes mellitus , while noninvasive therapy through oral delivery is greatly desired, there are challenges that include the low bioavailability due to the rapid enzymatic degradation in the stomach. This review article patent that provides the novel approaches for noninvasive insulin drug delivery system to the bloodstream through the go tract.

Keywords: Diabetes mellitus, insulin, non-invasive insulin drug delivery, modern insulin drug delivery, absorption enhancer, insulin pump.

Article Info: Received 02 May 2019; Review Completed 03 June 2019; Accepted 09 June 2019; Available online 15 June 2019

Cite this article as:

Harak KV, Patil PB, Saudhagar RB, Current Challenges in Non-Invasive Insulin Drug Delivery System: A Review, Journal of Drug Delivery and Therapeutics. 2019; 9(3-s):982-988 **http://dx.doi.org/10.22270/jddt.v9i3-s.3065**

***Address for Correspondence:**

P.B. Patil, Department of pharmaceutics, R.G. Sapkal college of pharmacy, Anjaneri, Nashik- 422213, Maharashtra, India.

INTRODUCTION

Diabetes mellitus is a chronic condition associated with abnormal high blood sugar (glucose) levels. Normally diabetes is of two types. Type I DM/Insulin Dependent Diabetes Mellitus (IDDM) is due to body's inability to produce insulin due to the autoimmune destruction of the beta cells in the pancreas[8]. Type 2 diabetes mellitus, in which peripheral cells become resistant to the insulin secreted by the patients body. Selective individuals with type 2 diabetes mellitus or those at a later stage of type 2 diabetes mellitus require exogenous insulin supply. the hormonal changes during pregnancy causes glucose intolerance in some women. This is caused due to the resistance of peripheral cells to insulin. This condition is called as gestational diabetes mellitus and this condition usually reverses after delivery. In a few cases this condition persists for lifetime. Insulin therapy, which is the exogenous supply of insulin is highly effective in regulating blood glucose level in diabetes patients[7]. Type I diabetes is a noninsulin dependent diabetes mellitus (NIDDM) and results in an insulin resistance- a condition in which body cells fail to use insulin properly, sometimes combined with reduced amount of insulin secretion. When insulin was discovered , it was first delivered by parenteral route. Insulin is delivered to diabetic patients exclusively via the subcutaneous route. The usual duration of action is relatively short; i.e., 48 hrs and therefore daily 2 to 4 injections are required for proper control of severe diabetic condition. The parenteral route is satisfactory in terms of efficacy. However, it may result to some severe adverse conditions like, a peripheral hyperinsulinemia, a smooth muscle cell proliferation, and a diabetic micro and macro angiopathy 3. In addition, the burden of daily injections, physiological stress, pain, inconvenience, cost, and the localized deposition of insulin leads to a local hypertrophy and fat deposition at the injection sites 4. Therefore, now a day there has been more focus on noninvasive route of insulin delivery. In 1996 AD, the FDA approved the first recombinant DNA human insulin analogue, lispro (Humalog). In 2001 AD, FDA approved Cygnus' firstgeneration model of the GlucoWatch Biographer for use by adults - the first frequent, automatic and noninvasive glucose monitor. Research approaches for noninvasive insulin delivery are given in table 1[3].

Table 1: It shows research approaches for noninvasive insulin delivery

Devices	Method of delivery
Oral route	Uptake of insulin occurring, within the GI tract or buccal mucosa.
Pulmonary	Uptake of insulin occurring in the highly vascularized alveoli of the lung
Intranasal	Use of nasal membranes as absorptive surface for insulin
Iontophoresis	Transdermal delivery of insulin by direct electrical current
Ultrasound	Process by which sound waves increases by several fold the permeability of human skin to macromolecules.

Insulin is a hormone secreted from the β cells of the islets of langerhans of pancreas. Insulin is a protein consisting of two polypeptide chains, one of 21 amino acid residues and the other of 30, joined by two disulfide bridges[2]. Insulin therapy is effective at lowering blood glucose in patients with diabetes. Insulin is a key player in the control of hyperglycaemia for type 1 diabetes patients and in selective patients with type 2 diabetes mellitus of insulin was considered as the most successful step in the history of diabetes treatment. It was isolated in 1921 and clinically used in 1922[12]. The major achievements in this area include the synthesis of human insulin analogues by recombinant DNA technology [11]. Insulin which is very close to human insulin is porcine insulin. Currently available forms of insulin delivery include insulin syringes, insulin infusion pumps, jet injectors and pens [11]. Subcutaneous route is the most commonly used route of administration of insulin. The main drawback of these methods is of invasive nature and generally in type I diabetes; a patient should take insulin two to three times daily and also may be taken in the form of multiple injections. Due to this there is a chance of develop hypoglycaemia and cases of hypoglycaemia are observing very often. In order to decrease the suffering of patient, new ways of administration are developed such as supersonic injectors, infusion pumps, sharp needles, and pens [13]. But they are also of invasive type and in turn develop a problem of patient compliance, medication adherence and patient inconvenience in administering insulin. So, there is a need of developing alternative methods of administration and this leads to the development of non-invasive methods of insulin administration in order to increase the patient compliance, medication adherence etc. Generally the route of administration is said to be succeeded when its ability to increase effectiveness and lowering the blood glucose levels and finally reducing the diabetic complications [13].This review discuss about the recent developments in the non-invasive routes of administration of insulin for diabetes mellitus[8].

2. NON-INVASIVE DRUG DELIVERY SYSTEM:

2.1. Oral 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; Sarmentoet 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)[2].since insulin is large molecular peptide, it is the gastrointestinal tract (GI). Proteolytic enzymes like pepsin, trypsin, chymotrypsin and carboxypeptidae, which are located in the stomach and small intestinal lumen. These proteolytic enzymes are responsible for about 20% degradat ion of ingested proteins. The remaining of the degradation occurs at the brush-border membrane (by various peptidases) or within the enterocytes of the intestinal tract[3].

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)[2]. To overcome these problems regarding the ora linsulin delivery three approaches could be possible. By changing the following:

(i) physicochemical properties of the insulin, for example, lipophilicity;

(ii) crosslinkingwithmacromolecules;

(iii) Use of carrier systems[5].

2.2. 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[2]. The liposomes are generally unstable and thus need to be lyophilized for long-term storage. Insulin can be protected from enzymatic attack inside the GIT by preparing insulin in the form of liposomes. SDG, Inc. (an Ohio Corporation) [29] describes a method of preparing orally bioavailable insulin formulations of variously sized liposome constructs, such as liposome fragments, lipid particles comprising insulin, gelatin and targeting agents such as biotin. Fan [30] describes a process of lyophilization of insulin liposome powder[4].

2.3. Nanoparticles:

Nanoparticles 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[2]. Among these chitosan has a good permeation property. In a diabetic rat model nanoparticle with chitosan significantly reduces the blood glucose level. Emulsions or double emulsion technique, solvent evaporation, or spray drying are the presently available methods of preparation of these devices. Some factors should be optimized during preparation of these devices like release rates and encapsulation efficiency to improve their therapeutic efficacy. Insulin delivery from oral delivery devices is a better approach to overcome the frequent administration of subcutaneous injections of insulin. Polymeric devices have been widely used for oral insulin delivery through hydrogels, nanoparticles, or microparticles[8]. Prustyetal prepared the nanoparticles incorporated with insulin by the complex coacervation method. They have been studied antidiabetic activity of orally administered insulinin rats.These nanoparticles have been evaluated for entrapment efficiency, particle size, and in vitro release studies, in vivo pharmacological studies, pharmacokinetic evaluation, and biochemical parameters. Insulin present in serum has also been determined by the use of human insulin ELISA kit. Biochemical parameters like creatinine and protein levels in the serum were estimated by spectrophotometry. Particle size of nanoparticles loaded with insulin was observed as 551.67nm ± 45.5 and it was determined by scanning electronmicroscopy (SEM). Loading efficiency of nanoparticles containing insulin was found highest for 50IU/mL insulin loaded nanoparticles and lowest for 51IU/mL insulin loaded nanoparticles. Korsmeyer's equation was used in in-vitro studies for determination of drug release pattern.There lease of kinetics was found to be 0.18. In vivo antidiabetic studies showed the significant reduction of serum glucose level[5]. Najafzadeh et al. evaluated efficacy of formulation of insulin having polar and nonpolar ingredients which has been administered by oral route. They concluded that novel excipients used in formulation prevent the degradation of insulin from gastric enzymes. This formulation significantly reduces the concentration of glucose in blood plasma in healthy and diabetic rats[8].

2.4. Microspheres:

Microspheres are solid spherical particles with a size range f rom 1 to 600 mm and are prepared by double emulsion solv ent evaporation technique. The microspheres are prepared u sing natural biodegradable polymers (gelatin or albumin) or synthetic polymers (polylactic or polyglycolic acid). In emuls ion, the dispersed phase consists of droplets of polymerdrug solution and they are linked by entrapment, ionic or covalent bonding. Microspheres can be prepared either by incorporat ing the drug in a microcapsule[2].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-cosebacic) anhydride microspheres loaded with insulin(Stacia Furtado et al,.2007) showed to be effective as oral insulin delivery[3].

2.5. Niosomes:

A niosome is a non-active surfactant containing liposome. They is very similar to liposomes in structure except they contain surfactant which will enhance the stability f 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 thepapeutic effect of peptides by reducing the clearance time from systemic circulation, increased bioavailability[2]. Recombinant human insulin can be delivered by using niosomal formulations[7].

2.6. 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 threedimensional network of polymer chains and water is used as a dispersion medium to fill the spaces between these macro molecules[2].Hydrogels have been of considerable interest for developing self-regulated drug delivery system in which a reversible gel-sol transformation controls the delivery of solutes as a function of glucose in its surroundings. Hydrogels can be made to undergo sol-gel transition by various stimuli such as pH and temperature. In the hydrated state, they have a mechanical behavior and water content similar to soft tissue and as a result they exhibit excellent biocompatibility Parket al developed glucose-sensitive hydrogels by mixing glucose-containing polymers and Poly Ethylene Glycolated(PEG) concanavalin A(Con A). Glucose was incorporated into the polymer backbone by copolymerization of allyl glucose with co-monomers, such as 3-sulfopropylacrylate, potassium salt (SPAK), N-vinyl pyrrolidone (VP) and acrylamide (AM). The authors examined different types of insulin delivery systems; diffusion-controlled reservoir, diffusion-controlled matrix and erosion-controlled matrix systems. They observed that, onset of insulin release in the in vitro studies showed a time lag of 30 min from the addition of glucose and the insulin release took 2 h to stop on completed removal of glucose[6]. Hydrogels significantly enhance oral absorption of insulin with notable hypoglycaemic effect[7].

3. MORDERN INSULIN DRUG DELIVERY SYSTEM

3.1. Inhaled delivery of insulin:

Generally lungs are having a larger surface area (approximate of about 100 square metres) and acts as an ideal target for insulin delivery [3]. The first attempt to deliver insulin by inhalation was made more than half century ago [4]. Clinical experience has shown that inhaled insulin has the potential to be an effective treatment in patients with diabetes, with particular utility in the treatment of postprandial hyperglycaemia [5,6]. In this mode of administration the drug has a relatively faster onset of action than subcutaneous route. Inhaled insulin has longer glucose lowering activity [7]. Generally insulin inhalers work as asthma inhalers. These products are generally available in two forms as dry powder formulations and solutions [4]. Each of these formulations is prepared basing on regular human insulin [8]. Exubera was the first inhaled insulin preparation available. It was delivered with an aerosol devise called exubera inhaler. Nebulizers, metered dose inhalers and aqueous mist inhalers are being investigated. Inhalation is an excellent mode for delivering pre-meal time insulin. It can be used for delivering fast acting insulin only. It is less effective in smokers and those with pulmonary diseases. The incidence of hypoglycaemia is also increased with this route[2,3,6].

3.2. Buccal delivery of insulin:

These are the drug delivery systems in which drug are 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 p H 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 mucoadhesives. 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 nanoparticles through buccal route in diabetic rats and rabbits (Venugopalan et al,. 2001)[4]. One of the disadvantage associate the buccal route is low bioavailability which can be enhance by the used various permeation absorption enhancers like polysorbate 80, sorbitol and phosphatidylcholine. A buccal insulin delivery is under clini cal development by Generex and Lilly under the names of Or alyn in Europe and Oralgen in the USA. Administration is si milar to an angina spray; with an aerosol (RapidMist®) deliv ering a fine spray directly onto the buccal mucosa[4].OrallynT M is human regular insulin in a proprietary liquid formulatio n utilizing surfactants, absorption enhancers, and other GRA S ingredients in very low quantities. It is delivered to the buc cal mucosa using a spray device similar to that used in asthm a. RapidMist™ device is designed to the liquid formulation in to the oral cavity as a fastmoving and a fineparticle aqueous spray.

The mixed micelles containing the insulin molecules transve rse the superficial layers of oropharyngeal mucosa and with the aid of absorption enhancers, insulin is rapidly absorbed i nto the blood. Bernstein, G. has suggested the insulin delivery by the buccal route in diabetes mellitus in large number of patient, particularly in type 2 dibetes mellitus [3]. In the buccal mucosa the blood supply in reticulated veins is very high, so absorption will be also high and this route prevents hepatic first pass metabolism. Delivery by inhaler containing high pressure droplets of insulin to the back of the throat is beneficial. Due to low permeability of buccal mucosa more puffs are required for optimum drug delivery [8,5].

3.3. Mouth spray:

Mouth sprays deliver insulin through an aerosol spray and hence, they differ from inhalers. In mouth sprays, the insulin is absorbed through the inside of cheeks and in the back of mouth instead of lungs. Two forms of mouth spray (Rapid Mist/Oralin) are being developed by Generex Biotechnology. One of the forms is fast-acting whereas, another one covers the basal rate of insulin (the basal rate is the amount of insulin required throughout the day to keep blood sugars stable). (ARIDA AI et al., 2008) [9]. The patient does not inhale with the buccal spray device as the formulation is delivered as fine spray onto the buccal mucosa as shown in the. Rapid absorption into the bloodstream is allowed with high-speed spray. Inhaled insulin formulation shows the risks to lung tissue, this can be avoided as the drug gets deposited onto the buccal mucosa[10].

3.4. Pills:

The concept of delivering insulin by mouth ("peroral" delivery) for absorption across the intestinal wall into the portal vein has long been regarded as a difficult challenge, but of substantial clinical and commercial potential. Presently, the biggest challenge with insulin pills is posed by the human digestive system. Either the gastrointestinal tract breaks the insulin down or the insulin passes out intact because it is unable to pass through the gastrointestinal membrane[9]. Controlling postprandial glycaemia requires several daily injections of insulin. Treatment using insulin through subcutaneous or other parenteral route results in peripheral hyperinsulinaemia, this may also include coronary artery disease, hypertension, dyslipidemia and weight gain along with the risk of hypoglycaemia[10].

3.5. Transdermal delivery of insulin:

Transdermal delivery of insulin is an alternative to the subcu taneous injection of insulin in diabetic patients. Apart from b eing a conventional painless procedure, it can potentially ma intain a long lasting effect by producing steady blood insulin levels over a long period of time. During recent years, variou s experimental methodologies have been developed for facili tating transdermal delivery of insulin A chemical enhancers based on biphasic lipid system or flexible lecithin vesicles containing insulin showed good hypoglycemic effect in experimental animals[5,6]. An additional approach to facilitate the transdermal delivery of insulin included altering skin characteristics by physical tools such as iontophoresis, sonophoresis, electroporation and photomechanical treatment [2,6]. Insulin has a tendency to form dimers and hexamers in pharmacological compositions, which are considered to be too large for transdermal delivery[3]. The entrapment efficiencies of conventional and flexible vesicles were 35% and 81%, respectively. When flexible vesicles were non-occlusively applied to the abdominal skin of mice at a dose of 0.90 IU/cm2, an in vivo hypoglycemic study showed a percentage decrease in blood glucose of 21.42%± 10.19% at 1 h, which reached 61.48%±8.97%at 5 h and was still greater than 50% at 18 h. An advanced study evaluated the pharmacokinetic and pharmacodynamic effects of transdermally delivered insulin using novel CaCO3 nanoparticles in normal mice and those with diabetes [1].

Iontophoresis, it is a technique that enhance the transdermal delivery of compounds through the skin via the application of a small electric current. one of the most advanced technologies that have been developed in the 20th century to overcome low skin permeability to insulin is iontophoresis. Iontophoresis is a technique used to enhance the transdermal delivery of compounds through the skin by the application of a small electric current. Using the processes of electro migration and electro-osmosis, iontophoresis increases the permeation of charged and neutral compounds. It offers the option of a programmed drug delivery technique that physically facilitates the transport of permeates across the skin[1].

Ultrasound/Sonophoresis, uses ultrasound and it has been shown to increase skin permeability to various low and high molecular weight drugs, including insulin. However, its therapeutic value is still being evaluated**.** Ultrasound has an ever-increasing role in the delivery of therapeutic agents, including genetic material, proteins, and chemotherapeutic agents. There is a tremendous corpus of literature on the use of ultrasound to enhance the permeability of the skin for transdermal drug delivery. Therapeutic levels of ultrasound (1–3 MHz, 1–3 W/cm2) have been used for years to drive small hydrophobic molecules, like steroids, into or through the skin. Absorption enhancers have sometimes been used to increase skin permeability further. However, no significant transport of protein was achieved until 10 years ago[1].

Microneedles, offers a cost-effective, minimally invasive, and controllable approach to transdermal insulin delivery. It involves the creation of micronized channels in the skin, and therefore disturbs the stratum corneum barrier. Upon creation of the microchannels, interstitial fluid fills up the channels, resulting in hydrophilic pathways. Microneedles deliver the drug into the epidermis without causing any damage or disruption of nerve endings [10]. Microneedles have been regarded as a healthy technology approach to be used either alone or with other enhancing techniques such as Electroporation and Iontophoresis, as well as with different drug carriers (lipid vesicles, micro- and nanoparticles) [8]. As Microneedles inserted into the skin of human subjects are reported to be painless, microneedles are considered as a promising technology to deliver drugs into the skin [9,8].

Microdermabrasion, is a method to increase skin permeability for transdermal drug delivery by damaging or removing skin's outer layer, stratumcorneum. Microdermabrasion can increase skin permeability to deliver insulin [8,1].

Characteristics of transdermal insulin drug delivery system are given below:

i. It gives passive delivery of insulin.

ii. Patch, cream, and spray forms can be used.

Iii. It requires a day to diffuse through skin and to have systemic effect.

The advantages of transdermal delivery of insulin includes :

1. Convenience

2. Good patient compliance

3. Prolonged therapy and

4. Avoids liver's first-pass metabolism and degradation in the gastrointestinal tract.

The main drawback of the transdermal drug delivery is that insulin molecules are large enough to penetrate the skin at therapeutically useful rates. This requires the usage of Microneedles as said above as one of enhancing techniques available [8].

Drawback of transdermal drug delivery is that insulin molecules are large enough to penetrate the skin at therapeutically useful rates. So nowadays microneedles are being fabricated with different sizes, shapes, and so forth to increase transdermal delivery. Various in vivo and in vitro studies have shown better results with solid microneedles. Needle arrays increase the transport by diffusion and iontophoresis and as drug carriers [5].

3.6. Gene therapy:

Gene therapy is the use of DNA as a pharmaceutical agent to treat disease. Fig. 8 illustrates gene therapy using an adenovirus vector. A new gene is inserted into a cell using an adenovirus. If the treatment is successful, the new gene will make functional protein to treat a disease [55]. To regulate insulin a gene called SHIP2 has been identified which provides a potential gene therapy target for the treatment of type 2 diabetes [56]. The first FDA-approved gene therapy experiment in the United States occurred in 1990, when Ashanti De Silva was treated for ADA-SCID[10].

3.8. Absorption enhancer:

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 para-cellular 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 glycholate (Morishita et al.,1993).Mixed micellar systems of bile salts increase the absorption of insulin by increasing its para-cellular 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 etal., 1994, Carino, et al,. 1994).Substances like aprotinin (Morishita et al,.1990),bacitracin,soyabean 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) [2].

4. INSULIN DEVICES

Insulin infusion devices may be classified as two types such as open-loop and closed-loop systems.open-loop micropump insulin delivery device consist of a small, lightweight, portable insulin micropump and plastic tubing which connects the pump to a needle inserted under the skin. Insulin release patterns in them can be preprogrammed and initiated by timer or by the diabetic patient himself. This device demands a very careful monitoring of blood glucose level. Also the patients using these devices were reported to show high incidence of ketoacidosis. Implantable versions of open loop insulin infusion devices were also introduced. Chemically controlled closed loop insulin delivery devices work by alternative in the absence of an effective pancreatic activity. They are biocompatible and non-toxic. The biohybrid artificial pancreas is another type of insulin diffusion device, which is under research. These contain B-cells enclosed within a semi permeable membrane, which is biocompatible. The semi permeable membrane is permeable to glucose and insulin. Special has to be given to exclude immune cells in order to prevent rejection by the body[11].

5. INSULIN PUMPS:

Insulin pumps were developed to avoid repetitive subcutaneous injections. The pump itself is essentially. The insulin pump is an open-loop system that has two concurrent modes of insulin delivery:

(1) Continuously through basal infusion and

(2) Intermittently through bolus insulin delivery. Insulin replacement can be provided in a near physiologic fashion, integrating both lower basal insulin secretion and higher postprandial requirements.

Insulin pumps have provided additional flexibility of modifying basal insulin replacement in response to circadian rhythms[10]. Moreover, it can be preprogrammed to decrease during exercise and increase during times of inactivity[11]. Studies conducted with improved versions of insulin such as insulin lispro, show that when used in external insulin pumps, it provides better glycemic control than buffered regular human insulin with a similar adverse event profile possibly due to rapid absorbtion[13]. The major advantages over multiple injections are a reduction of nightly instability and hypoglycemia and time flexibility. Patients poorly controlled under injections and/ or with recurrent

hypoglycemias thus represent the best candidates for therapy with pumps[3,5].

A basic problem with insulin pumps is the potential alteration of the administered insulin by motion, contact with pump surfaces and changes in temperature. Insulin forms aggregated macromolecules that have reduced insulin activity and tend to precipitate in the catheter, causing obstruction. Insulin must be buffered and treated with additives to increase viscosity, thereby improving its physical stability. The other drawback is of encapsulation by the dense fibrous tissue of the implant[7]. Early versions of insulin pumps were plagued by problems with fluid leakage into the system, short battery life, insulin blockage of the pump or catheter and tissue blockage of the peritoneal catheters and adhesions. Information on plasma glucose level is prerequisite for effective metabolic control by external insulin pumps as well as conventional subcutaneous injection. Therefore, there is a continuing need for self-regulated delivery systems, having the capability of adapting the rate of insulin release in response to changes in glucose concentration, in order to keep the blood glucose levels within the normal range. The attempt is to restore the feedback between blood glucose and insulin delivery[6].

Advantages of pump therapy

i. More physiologic

ii. Less variable insulin absorption.

iii. Better match between insulin and food

iv. Greater lifestyle flexibility

v. Easier to travel - improved portability[6].

CONCLUSION:

The natural history of diabetes mellitus requires steady, precise and predictable insulin delivery, to preserve euglycemia. Too much or too little insulin and at an improper time can quickly cause an emergency Recent alternatives developed in insulin therapy have potential for reducing some of the negative aspects of current methods. Oral insulin in particular could prove to be promising alternative method, especially with nanotechnology allowing for several types of encapsulations to bypass the gastric acidic environment. Oral delivery offers the benefits of ease of administration by increasing the acceptance of patient, improved absorption rates, and mimicry of the normal route of insulin through the liver. Apart from few drawbacks, inhaled insulin is also a good achievement in the field of noninvasive delivery of insulin due to its good absorptive nature, fast onset of action, longer blood glucose lowering activity and also has a potential to treat postprandial hyperglycemia effectively when compared to traditionally administer subcutaneous route.

From this review we have concluded that there is a need of developing noninvasive therapy of insulin for diabetes mellitus, as it has greater advantages than existing invasive therapy of insulin.

REFERENCES:

1. A. Cilek, N. Celebi, F. Tırnaksız, A. Tay, Lecithin-based microemulsions of rhinsulin with aprotinin for oral administration: investigation of hypoglycemic effects in non-diabetic and STZ-induced diabetic rats, Int. J. Pharm:2005;298: 176–185
2. Mehanna AS, "Insulin and oral antidiabetic agents," American Journal of Pharmaceutical Education, 2005; 65(5):89.
3. Alba Therapeutics Corp. EP1993356 (2008).
4. Daugherty AL, Mrsny R, Transcellular uptake mechanisms of intestinal epithelial barrier: part one, Pharm. Sci. Technol. Today 1999; 4:144–151. 41.
5. "Diabetes Fact sheet N°312". WHO. October 2013. Retrieved 25 March 2014.
6. Duckworh WC, Saudek CD, Giobbie-Hurder A, Henderson WG, Henry RR, Kelley DE, et al. The Veterans Affairs Implantable Insulin Pump Study: effect on cardiovascular risk factors. Diabetes Care 1998;21:1596-602.
7. Emisphere Technologies, Inc. US7429564 (2008).
8. "The top 10 causes of death Fact sheet N°310". World Health Organization. Oct 2013.
9. Chaturvedi K, Ganguly K, Nadagouda MN, Aminabhavi TM, "Polymeric hydrogels for oral insulin delivery," Journal of Controlled Release, vol. 165, pp. 129–138, 2013.
10. Valerie Ravaine, Christophe Ancla, Bogdan Catargi- Chemically controlled closed-loop insulin delivery, J. Contrl. relea, 2008;132:2-11.
11. Maniatis AK, Klingensmith GJ, Slover RH, Mowry CJ, Chase HP. Continuous subcutaneous insulin infusion therapy for children and adolescents: An option for routine diabetes care. Pediatrics 2001;107:351-6.
12. Duckworth WC, Saudek CD, Giobbie-Hurder A, Henderson WG, Henry RR, Kelley DE, et al. The Veterans Affairs Implantable Insulin Pump Study: effect on cardiovascular risk factors. Diabetes Care 1998;21:1596-602.
13. F.Veuillez,Y.N.Kalia,Y.Jacques,J.Deshusses,andP.Buri,"Factorsandstrategiesforimprovingbuccalabsorptionofpeptides," European Journal of Pharmaceutics and Biopharmaceutics, vol. 51,no.2,pp.93–109,2001.
14. Sudhakar Y, Kuotsu K, Bandyopadhyay AK, "Buccal bioadhesive drug delivery—a promising option for orally less efficientdrugs,"JournalofControlledRelease,vol.114,no.1,pp. 15–40,2006.
15. Novo Nordisk. US20140056953 (2014).
16. Emisphere Technologies, Inc. US7429564 (2008).
17. Emisphere Technologies, Inc. US20100151009 (2010).
18. GP Medical, Inc. US8361439 (2013).
19. Song L, Zhi LZ, Pickup JC. Nanolayer encapsulation of insulin–chitosan complexes improves efficiency of oral insulin delivery. Int. J. Nanomed. 9, 2127–2136 (2014).
20. Nano and Advanced Material Institute. US20130034589 (2013).
21. Oshadi Drug Administration Ltd. US20100278922 (2010).
22. Ward CW, Lawrence MC. Ligand-induced activation of the insulin receptor: a multi-step process involving structural changes in both the ligand and the receptor. Bioessays 31, 422–434 (2009).
23. Blair JA, Sustained release of insulin from sodium hyaluronate based dry powder formulations after pulmonary delivery to beagle dogs, J. Control. Release: 2003; 91:385–394.
24. Kim, A., Yun, M.-O., Oh, Y.-K., Ahn, W.-S., Kim, C.-K. Pharmacodynamics of insulin in polyethylene glycol-coated liposomes. Int. J. Pharm.:1999; 180:75–81.
25. Kim, B., Peppas, N.A., Synthesis and characterization of pHsensitive glycopolymers for oral drug delivery systems. J. Biomater. Sci. Polym. : 2002a; 13: 1271–1281.
26. Kiran Sonaje, Yi-Jia Chen, Hsin-Lung Chen, Shiaw-Pyng Wey, Jyuhn-Huarng Juang, Ho-Ngoc Nguyen, Chia-Wei Hsu , Kun-Ju Lin , Hsing-Wen Sung. Enteric-coated capsules filled with freeze-dried chitosan/poly (g-glutamic acid) nanoparticles for oral insulin delivery. Biomaterials:2010;31: 3384–3394
27. Kisel, M.A., Kulik, L.N., Tsybovsky, I.S., Vlasov, A.P., Vorb'yov, M.S., Kholodova, E.A., Zabarovskaya, Z.V. Liposomes with phosphatidylethanol as a carrier for oral delivery of insulin: studies in the rat. Int. J. Pharm. :2001; 216:105–114
28. Kleir, J., Peppas, N.A. Complex-forming hydrogels sensitive to physiological conditions. Proc. Adv. Biomed. Polym. : 1989; 1:107–109.
29. Lambkin, I., Pinilla, C. Targeting approaches to oral drug delivery. Exp. Op. Bio. Ther. : 2002; 2 (1):67–73. Lee, V.H.L., Kashi, S.D., Grass, G.M., Rubas, W. Oral route of protein and peptide drug delivery. In: Lee, V.H.L. (Ed.), Peptide and Protein Drug Delivery. Marcel Dekker, New York: 2000; pp. 691–740.
30. Lowman, A.M., Cowans, B.A., Peppas, N.A. Investigation of interpolymer complexation in swollen polyelectolyte networks using solidstateNMR spectroscopy. J. Polym. Sci. B: Polym. Phys.:2000; 38: 2823– 2831.

31. Lowman, A.M., Morishita, M., Kajita, M., Nagai, T., Peppas, N.A. Oral delivery of insulin using pH-responsive complexation gels. J. Pharm. Sci.:1999; 88: 933–937.
32. Gordberg M, I. Gomez-Orellana, Challenge for the oral delivery of macromolecules, Nat. Rev., Drug Discov. :2003;2: 289–295
33. Higaki M, Higaki M, Kameyama M, M. Udagawa, Y. Ueno, Y. Yamaguchi, R. Igarashi, T. Ishihara, Y.Mizushima, Transdermal delivery of CaCO3-nanoparticles containing insulin, Diabetes Technol. Ther. : 2006; 8: 369–374.
34. Katsuma M, Watanabe S, H. Kawai, S. Takemura, K. Sako, Effect of absorption promoters on insulin absorption through colontargeted delivery, Int. J. Pharm. :2005; 307 : 156–162 M.
35. Morishita, I. Morishita, K. Takayama, Y. Machida, T. Nagai, Site dependent effect of aprotinin, sodium caprate, Na2EDTA and sodium glycocholate on intestinal absorption of insulin.Biol. Pharm. Bull. :1993;16: 68–72
36. Goto T, Morishita M, Nishimura K, M. Nakanishi, A. Kato, J. Ehara, K. Takayama, Novel mucosal insulin delivery systems based on fusogenic liposomes, Pharm. Res. 23 (2006) 384–39
37. D.K. Pettit, W.R. Gombotz, The development of site-specific drug-delivery systems for protein and peptide biopharmaceuticals, Trends Biotechnol. 16 (1998) 343–349.
38. Daugherty AL, R. Mrsny, Transcellular uptake mechanisms of intestinal epithelial barrier: part one, Pharm. Sci. Technol. Today 4 (1999) 144–151. 41. R.J. Mrsny, The colon as a site for drug delivery, J. Control. Release 22 (1992) 15–34.