Research and Reviews: Drug Delivery

Modern Drug Delivery Systems for Oral Insulin Delivery in Diabetes Mellitus

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Review Article

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ABSTRACT

Medicine research is based on the dogma that to cure a disease its cause must be thoroughly understood. The treatment of any disease lies on the correct diagnosis of its cause. Diabetes is one such disease that has been thoroughly understood and despite having a clear picture of its nearest cure i.e make insulin available orally, nothing promising yet has been achieved. Diabetes sets a perfect example of the importance and challenges in discovery of medicine for the ultimate cure. Type 2 diabetes mellitus (DM) is a chronic metabolic disorder in which prevalence has been increasing steadily all over the world. As a result of this trend, it is fast becoming an epidemic in some countries of the world with the number of people affected expected to double in the next decade due to increase in ageing population, thereby adding to the already existing burden for healthcare providers, especially in poorly developed countries. This review is based on a various approaches which could be used to deliver insulin orally to the patients. The forms may include nanoparticles, microspheres, intestinal patches, hydrogels ,tablets and capsule.

INTRODUCTION

Diabetes Mellitus (DM) is an endocrine disease in which the production of hormone named insulin does not release sufficient by the pancreas which is responsible for the maintenance of blood glucose level [1,2]. DM is basically a disease related to carbohydrate metabolism disorder leading to deficiency in insulin secretion; it may also lead to its resistance or may cause both. In other words it is very important for the rescue to understand that diabetes is an endocrinological disorder that encompasses the malfunctioning of pancreas gland. Its symptoms include polyuria, polydipsia, polyphagia and loss of body weight. There are four main types of diabetes namely:-Type 1 diabetes:- It commonly occurs in childhood at an average age of 12 years in which secretion of insulin is stopped in the body and patients need external insulin for survival. Type 1 diabetes causes damage to beta cells. Glucose doesn't move into your cells because insulin isn't there to do the job. Instead, it builds up in your blood, and your cells starve. This causes high blood sugar, which can lead to-

Dehydration: When there's extra sugar in your blood, you pee more. That's your body's way of getting rid of it. A large amount of water goes out with that urine, causing your body to dry out.

Weight loss: The glucose that goes out when you pee takes calories with it. That's why many people with high blood sugar lose weight.

Diabetic ketoacidosis (DKA): If your body can't get enough glucose for fuel, it breaks down fat cells instead. This creates chemicals called ketones. Your liver releases the sugar it stores to help out. But your body can't use it without insulin, so it builds up in your blood, along with the acidic ketones. This mix of extra glucose, dehydration, and acid buildup is known as ketoacidosis and can be life-threatening if not treated right away.

Damage to your body: Over time, high glucose levels in your blood can harm the nerves and small blood vessels in your eyes, kidneys, and heart. They can also make you more likely to get hardened arteries, or atherosclerosis, which can lead to heart attacks and strokes.

Type 2 diabetes: It occurs at later stages of life and the patient may or may not need external insulin for his survival, but It can be managed by oral hypoglycemic agent. It is a translation of polygenic disorder to a monogenic disorder. People with type 2 diabetes make insulin, but their cells don't use. At first, your pancreas makes more insulin to try to get glucose into your cells. But eventually, it can't keep up, and the glucose builds up in your blood instead. Usually, a combination of things causes type 2 diabetes. They might include: (i) Genes:- Scientists have found different bits of DNA that affect how your body makes insulin. (ii) Extra weight :- Being overweight or obese can cause insulin resistance, especially if you carry your extra pounds around your middle. (iii) Metabolic syndrome :- People with insulin resistance often have a group of conditions including high blood sugar, extra fat around the waist, high blood pressure, and high cholesterol and triglycerides. (iv) Too much glucose from your liver :- When your blood sugar is low, your liver makes and sends out glucose. After you eat, your blood sugar goes up, and your liver will usually slow down and store its glucose for later. But some people's livers don't. They keep cranking out sugar. (v) Bad communication between cells:- Sometimes, cells send the wrong signals or don't pick up messages correctly. When these problems affect how your cells make and use insulin or glucose, a chain reaction can lead to diabetes. (vi) Broken beta cells:- If the cells that make insulin send out the wrong amount of insulin at the wrong time, your blood sugar gets thrown off. High blood sugar can damage these cells, too.

Gestational diabetes: Its symptoms are firstly recognized during pregnancy. Gestational diabetes is associated with multiple adverse pregnancy outcomes.Women with gestational diabetes are at subsequent high risk of type 2 diabetes, especially three to six years after delivery. Exposure to hyperglycaemia in the womb predisposes children to a high risk of becoming overweight or obese, associated with the development of type 2 diabetes. Gestational diabetes mellitus (GDM) is a severe and neglected threat to maternal and child health. Many women with GDM experience pregnancy-related complications including high blood pressure, large birth weight babies and obstructed labour [3].

Approximately half of women with a history of GDM go on to develop type 2 diabetes within five to ten years after delivery. The prevalence of high blood glucose (hyperglycaemia) in pregnancy increases rapidly with age and is highest in women over the age of 45. Other specific types which could have induced from genetic defects which bring about type A insulin resistance and/or insulin receptor are mutation, drugs, chemicals, or diseases which induce pancreatic damage, endocrinopathy and others.

Referring to Type 1 and other types of diabetes where the patient relies on insulin, the mode of insulin therapy is by subcutaneous injections (s.c). But s.c. insulin administration may also have some side effects like hypoglycemia, allergy, resistance, edema and lipodystrophy with minimal patient compliance. Due to fear some patients also avoid injections and many subcutaneously administered injections of insulin reaches wrong targets i.e. muscles and kidneys.

Other than injections, other routes like pulmonary, nasal or buccal also deliver insulin into the systemic circulation but only a small percentage of it reaches to the liver which is primary site of action.

Another important aspect is to obtain insulin for its formulation. Primarily the hormone being obtained from bovine cadavers was the source of insulin having immunological disagreements with the patient's body due to the presence of some protein impurities in it. Further a major breakthrough was obtained when pure insulin was obtained by recombinant DNA technology, also cost effective.

In the present scenario oral insulin has advantages over the other forms of insulin as it follows the normal physiological pathway i.e *via* hepatic portal circulation when firstly it reaches the liver followed by the peripheral tissues. Normally, the level of glucose in the bloodstream is controlled by liver therefore it means that insulin released from the pancreas firstly act on liver. Therefore if level of insulin is decreased in liver it leads to reduced amount of insulin that reaches the systemic circulation and the risk of hypoglycemia is also minimized. Now the question arises what happens when insulin is not available in the body? As we know that in the absence of insulin the glucose, which is first source of energy, is not available to the cells to generate the energy. As a result lots of glucose remains unused resulting in the disorder called diabetes. These body cells craving for the energy source shift to fat as the new source of energy generation is required. These fat globules are now on a journey from their reserves called adipose tissues to their metabolism factory called liver [4].

As we know that insulin being a protein gets degraded in the Gastrointetsinal tract (GIT), and hence is not available to the systemic circulation unhampered, thus diminishing its efficacy. Structurally insulin is a two chain polypeptide (A and B chains) with the bridge of disulphide linkages between the two. It is a polypeptide of molecular weight 5800 Da and regulates the metabolism of glucose. It acts as the enhancer of glucose uptake by the body cells results in glycogenesis forming glycogen, fatty acids and proteins. It reveals that glucose can be stored as glycogen and fatty acids through the agency of insulin.

Medicine research is based on the dogma that to cure a disease its cause must be thoroughly understood. The treatment of any disease lies on the correct diagnosis of its cause. Diabetes is one such disease that has been thoroughly understood and despite having a clear picture of its nearest cure i.e make insulin available orally, nothing promising yet has been achieved. Diabetes sets a perfect example of the importance and challenges in discovery of medicine for the ultimate cure. It is a well known fact that insulin could not be delivered orally without any protection to it and let us enlist compendiously why it is so? The reasons are:-

1. The imbalance in the Hydrophilic Lipophilic balance (HLB) value of insulin results in its shifting towards being more hydrophilic thus finding difficulty to get absorbed.

2. Being large polypeptide insulin finds physical barrier to cruise through the tight epithelial linings of intestine.

3. Being a protein of high affinity for the stomach HCl and GI enzymes insulin is liable to breakdown.

All these factors contribute to the unavailability of insulin due to degeneration in GI and impose one of the toughest challenges for the oral delivery of insulin.

MODERN SCHEMES OF INSULIN DELIVERY

Nanoparticles

Out of the various ways to overcome the problem of absorption through intestinal mucosa the use of Nanocarriers (nanoparticles) is one important tool making the absorption possible and preventing enzymatic hydrolysis of macromolecular insulin. On top of it the use of excipients like mucoadhesives and absorption enhancers may further augment the efficiency of the nanoparticles. The modern biological study is concentrated on Nanomedicine with the simple concept that smaller is the particle size of the system higher is the energy/surface area and better is the efficacy.

Nanoparticles are polymeric spheres of nanosize (nm). Such nanoparticles are prepared using both non biodegradable and biodegradable polymers. Many studies have really encouraged the oral use of nanoparticles showing very near efficacy to the same formulation administered subcutaneously. However the problems of drug depot formation in the case of non biodegradable polymers like isobutyl 2 – cyanoacrylate loaded with insulin can be overcome using biodegradable polymers for the formulations of nanoparticles. The clinical importance of nanoparticles lies in their affinity to the cell membrane of M cells of Peyer's Patches which is the lymphatic tissue in GI called GALT (Gut associated lymphoid tissues). The M-cells endocytose insulin resulting in its absorption [5].

Nanoparticle is a collective name of two diverse formulation *via*. nanocapsules and nanospheres. On one hand nanocapsules contain a polymeric film enclosing a liquid core and on the other hand nanospheres constitute the entire polymeric surface.

The formulation principle of nanoparticles can be broadly categorized into two classes based on the polymer used:-

1. Polymerization is to be done for the formulation.
2. An already synthesized polymer or macromolecule is used for film forming.

The choice between the two depends upon the requirements of the formulations. The polymerization reaction can be best and fastest obtained through an emulsion procedure which is further classified into two types based on the use of an organic phase or the more common use of an aqueous continuous phase. The use of synthetic polymers for the use of nanoparticles is done using the dispersion of preformed polymers using the techniques like nanoprecipitation, emulsification/solvent evaporation, emulsification/solvent diffusion, salting out, desolvation, complexation, emulsification/polymer gelation etc.

Polymers are very important component for the preparation of nanoparticles. The choice of polymers depends on many requirements like route of drug administration, Active Pharmaceutical Ingredient (API) and desired kinetics . A number of organic and inorganic polymers are used for the development of nanoparticles example: polyalkylcyanoacrylates, polymethacrylic acid/acrylates, chitosan, alginates ,calcium phosphate etc. The use of polyalylcyanoacrylates supports more retention of the nanocapsules in the intestine or liver. The use of poly(lactic-co-glycolic acid) (PLGA) is attributed to the development of linear and star branched PLGA nanoparticles . Such nanoparticles are studied to exhibit reduced burst effect and provide sustained release. Otherwise PLGA has many disadvantages as the polymer like its degradation products (Lactic acid and glycolic acid) reduce the pH of the immediate environment resulting in the denaturation of encapsulated insulin (protein). Also if hydrophilic macromolecules like insulin are entrapped in PLGA it becomes difficult for the macromolecule to diffuse through the polymer. Another disadvantage is that insulin gets adsorbed onto the surface of PLGA nanoparticles along with its burst release resulting into the poor bioavailability of orally administered nanoparticles. Polymethacrylic acid based nanoparticles are important due to their mucoadhesive and proteolytic enzyme inhibition properties and enhanced drug absorption. A combination of polymethacrylic acid with chitosan and polyethylene glycol (PEG) results in the nanoparticles exhibiting good encapsulation efficiency as well as pH dependant release profile [5].

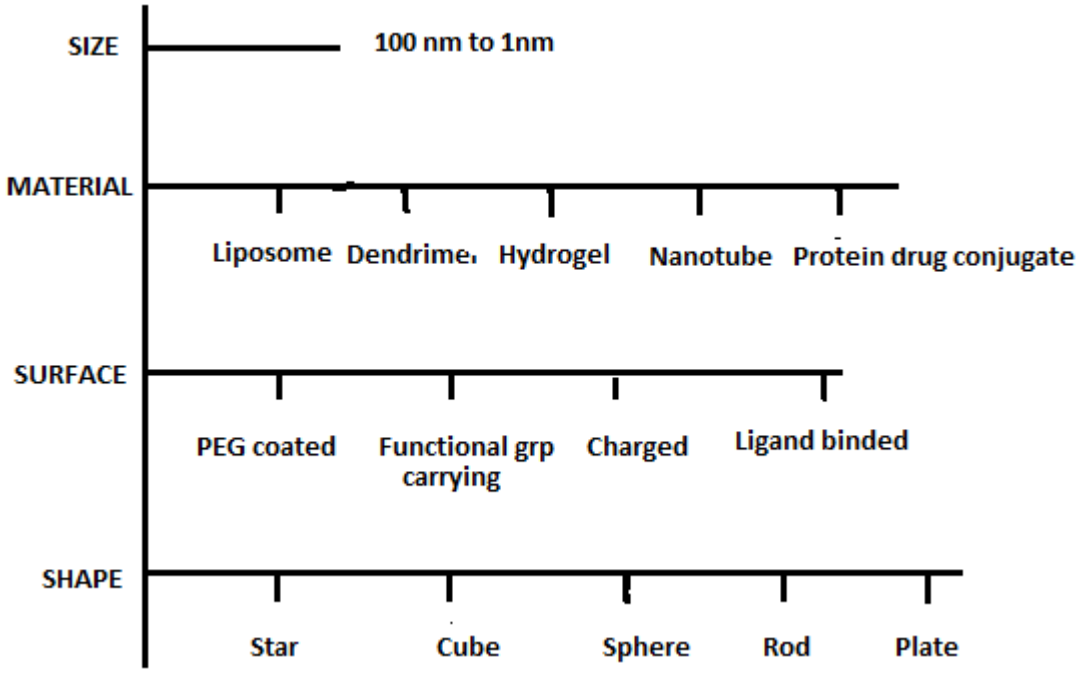
Also it such nanoparticles inhibit trypsin activity resulting in prevention of enzyme degradation of insulin.

Natural polymers are of choice for development of Nanoparticles. Chitosan is a prime example of natural biocompatible, bioresorbable, biodegradable and mucoadhesive polymer. Chitosan in original and modified form is used as a polymer or copolymer for preparation of nanoparticles. The special advantage of chitosan over other polymers as insulin carrier is that its nanoparticles lie in the improved extracellular interaction with Caco-2 cells to cellular internalization through clathrine mediated endocytosis. A novel derivative of chitosan, Laurylsuccinyl chitosan (LSC) has shown remarkable results to cure diabetes. Insulin can be administered as nanocarriers which may be nanoparticles, liposomes and micelle. Nanoparticles can also be classified into Polymeric nanoparticles and Solid lipid nanoparticles:-

Polymeric nanoparticles are made up of biodegradable polymers and can be further classified into two types, nanosphers and nanocapsules [6].

Solid lipid nanoparticles are formulated using physiological lipids dispersed in aqueous surfactant solution. Insulin loaded solid lipid nanoparticles coated with chitosan have been prepared showing mucoadhesive and enhanced intestinal absorption properties (Figure 1).

Figure 1. Types of Nanoparticles.



Insulin loaded nanoparticles can be prepared in different forms as discussed below:-

(i) pH sensitive nanoparticles where the size of nanoparticles dramatically increase with the rise of surrounding pH above the pKa of the polymeric network. Thus resulting in charge generation and repulsion between the polymeric chains.

(ii) pH sensitive nanoparticles where mucoadhesive gel confers the entry of acidic dissolution medium into the matrix of the nanoparticles thus preventing the acidic degradation of insulin.

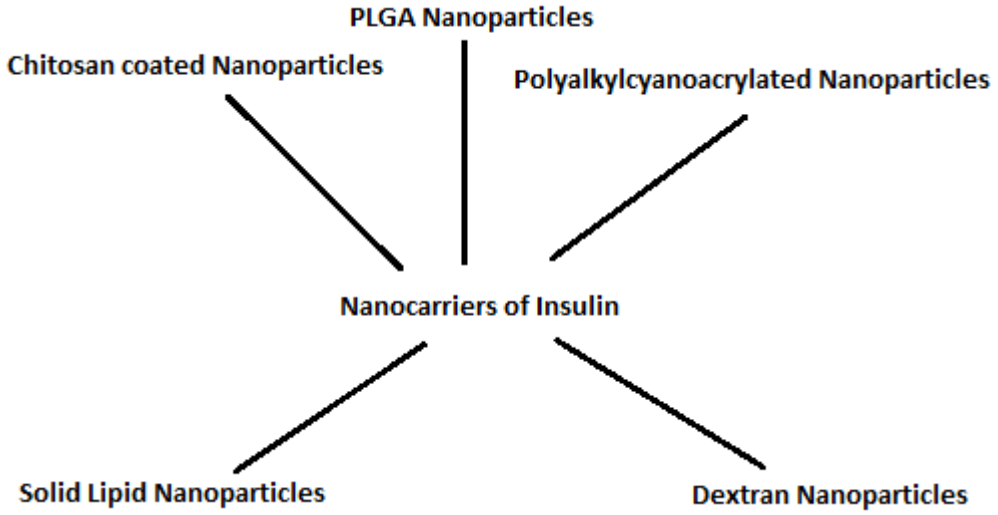
(iii) Hydrophobic nanoparticles are formed using hydrophobic polymers thus enhancing the absorption through the M cellsof Peyer's Patches.

(iv) Bioadhesive nanoparticles exhibit high level of adhesiveness with intestinal mucosa thus resulting in the prolonged retention time of insulin in the intestinal tract finally increasing its bioavailability (Figure 2).

(v) Insulin complex nanoparticles formed in the form of water insoluble complex of insulin embedded in the nanoparticles.

Such nanoparticles provide sustained release of insulin through gradual deaggregation of nanoparticles and introduction of barrier exudates coat that delays penetration of dissolution medium into the core of nanoparticles.

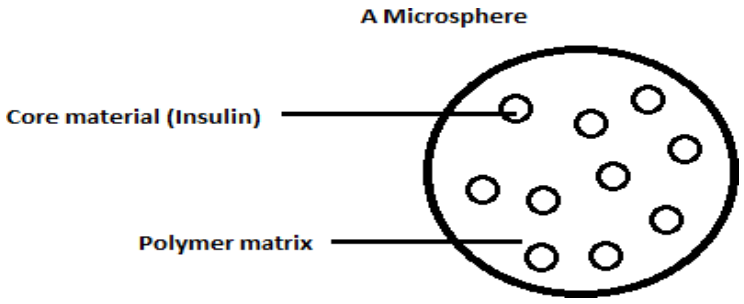
Figure 2. Types of Nanocarriers for Insulin.



Microspheres/ Microparticles

These are the particles with size ranging from 1-1000 micrometres. These are spherical particles made up of polymeric material (Figure 3). There advantage as drug carrier for proteins like insulin is that it prevents protein degradation and help in the intestinal absorption of insulin [7].

Figure 3. A Microsphere.



Various techniques using microparticles as drug delivery system for insulin have been adopted like :Wheatgerm agglutinin conjugated microparticles:- The principle of such microparticles is the affinity of non immunological lectin with sugar. As sugar being a part of mammalian cell membrane (Glycoprotein and glycolipids) hence any molecule having the affinity for sugar will bind and remain adhere to the intestinal mucosa. Lectin of wheat origin shows this affinity hence microparticles made of alginate with lectin wheatgerm agglutinin adhere to the intestinal mucosa and enhancing the insulin absorption.

(i) **pH sensitive microparticles**: As nanoparticles the microparticles made of poly(methacrylic acid) and PEG show pH responsive insulin delivery to the body.

(ii) **Charged coupled micro-magnet microparticles**: The principle lies in the response of charges to the external magnetic fields.the negatively charged insulin loaded microparticles when coupled positively charged micromagnets form a complex due to the interaction between the opposite charges. This complex can be driven to the desired location by applying an external magnetic field. The external field makes the charged complex available to the intestine thus enhancing the insulin absorption [8].

(iii) **Insulin complex microparticles**: Non-ionic surfactants are added to the primary emulsion of insulin. This affects the interaction

between insulin and PLGA and gives rise to biphasic release of insulin. The initial burst makes insulin available to the body.

The amount of insulin released by this burst depends on the amount of insulin present on the surface of the microparticles. This burst is followed by zero order release of insulin from the polymer matrix. The slow release of insulin protects it *via* journey through GI tract and makes it available to the intestine in the later stages of its journey.

Hydrogels

Microflora activated hydrogel beads: Hydrogel beads loaded with insulin form another dosage form for oral administration have been prepared. Pectins have been used to form the polymer matrix as insulin carrier. The pharmacokinetic study reveals that the first release of insulin due to solubilization of pectin gel in alkaline medium is a bolus release and the subsequent release is due to the digestion of pectin marix by the intestinal bacteria. It is found that insulin released by hydrogels sustains long ion the plasma than by subcutaneous route.

Molecular weight modulated hydrogel beads: The polymer made of two monomers one temperature sensitive and other pH sensitive along with acrylic acid is the base of such hydrogel beads. This polymer being enteric in nature helps to survive in acidic media. Also the high molecular weight polymeric beads swell slowly and take approximately eight hours to release insulin hence giving prolong activity.

Glucose responsive hydrogel matrix: It is an intelligent responsive system made of pH sensitive amino group containing polymer matrix holding immobilized enzyme glucose oxidase. The presence of glucose in the plasma leads to swelling of the matrix and interaction between the enzyme and the glucose. Due to the released protons interaction the NH_2 groups of the matrix get positively charged, repel each other, increase the distance between the polymeric membranes following the release of insulin through these gaps.

Super porous hydrogels: It is a newly designed oral delivery of insulin having a rapidly swelling property being superporous in structure and imbibing large amount of water. These hydrogels enforce mechanical pressure to open the tight intestinal junctions thus giving a wide route for insulin to get absorbed through these gaps [9].

Capsule

The property of insolubility of coating polymers like Eudragit S 1000 is used to promote the insulin absorption from intestinal mucosa. Such polymer coating can be incorporated on the surface of capsule shell to provide the protection of the contained drug from acid and gastric enzyme attack.

Tablet

The use of enzyme inhibitor such as sodium glycocholate can be made to formulate insulin loaded tablets to prevent enzymatic degradation of insulin. Permeation enhancers like glutathione can also be used to augment the protein (Insulin absorption). Such tablets are classified under the class of polymer- inhibitor conjugate tablets. Another category of insulin loaded tablet is pH sensitive and micro flora activated tablets. Such tablets contain three coatings – enteric coating, non-ionising polymer coating and acid soluble polymer coating (moving from outside to the core of the tablet) with core containing the insulin. Such tablets are categorized as CODES standing for colon specific drug delivery system. The role of intestinal bacteria lies in the interaction of polysaccharide like lactulose loaded in the tablet core, converting the lactulose into organic acids resulting in the lowering of surrounding pH thus dissolving the inner most acid soluble layer and releasing the insulin in colon [10-12].

Intestinal patches

These disc like patches having a very small radius upto 1 mm are filled in the enteric coated capsules. In the intestine with release of these patches the surface layer of the polymer like pectin, Carbopol 934, sodium CMC etc are transformed into intestinal adhesive mass due to the change in the surrounding pH followed by release of insulin to get absorbed through intestinal mucosa.

Due to relatively large size of patch in comparison to very small size formulations like nanospheres, microspheres etc the probability of getting the formulation phagocytosised by macrophages is minimal also the large size provides a large surface area for the release of insulin.

Receptor mediated drug delivery system

It is known that the duodenum of large intestine due o its very tight cell junctions provides least permeability to drugs of all kinds. Hence active transport of insulin through receptor mediated mechanisms can be a route of choice. Due to the presence of insulin receptors of the surface of enterocytes the absorption of insulin through these receptors can be possible. Transferrin receptors present on the surface of GI epithelium allow the probability of insulin bondage with receptors resulting in its absorption. This study is used to administer oral formulations containing a conjugate of insulin and Transferrin where Transferrin provides the safety against gastric enzyme digestion and allows the passage of insulin to intestines [13-16].

Liposomes

These are vesicular structure formed from phospholipids like lecithin and cholesterol. Biotinylated liposomes enhance the delivery of insulin because such liposomes have better physical stability and better absorption. Due to their size and hydrophobic and hydrophilic character(besides biocompatibility), liposomes are promising systems for drug delivery. Liposome properties differ considerably with lipid composition, surface charge, size, and the method of preparation. Furthermore, the choice of bilayer components determines the 'rigidity' or 'fluidity' and the charge of the bilayer. For instance, unsaturated phosphatidylcholine species from natural sources (egg or soybean phosphatidylcholine) give much more permeable and less stable bilayers, whereas the saturated phospholipids with long acyl chains (for example, dipalmitoylphos phatidylcholine) form a rigid, rather impermeable bilayer structure [17-20].

SALIENT FEATURES

- Diabetes Mellitus is one of the biggest problems with multiple causes in today's world.
- Currently insulin therapy by subcutaneous administration is the available treatment.
- Insulin therapy is surrounded with many drawbacks but still it has no alternative.
- Many researches to administer insulin orally have been done.
- Being a protein insulin is susceptible to GI degradation.
- Polymer protection may increase the life of insulin.
- Adhesion with intestinal walls may increase the absorption of insulin.
- Nanoparticles , microspheres like novel drug delivery system loaded with insulin is tried to be formulated.
- An attempt to prepare biocompatible and non-toxic novel formulation of insulin shall be done.
- Novel drug delivery system could provide an alternative oral insulin therapy to bypass the invasive subcutaneous root of insulin.

CONCLUSION

Diabetes is one of the major disorders and health problem of the present scenario. Many factors including stress, food habits etc. contribute to the occurrence of the disease. It is now considered to be a life style disorder and the percentage of diabetes patients is increasing all through the globe including India. Insulin being the major source of management of insulin dependent diabetes becomes an important hormone to deal with. The commonly used subcutaneous route of insulin delivery brings non-compliance to the patient and makes him feel disturbed, also difficult for child patients in some

cases.

Though non parenteral routes of insulin delivery are worked upon yet no major breakthrough can be stated to bring patient compliance. Hence a continuous study to search for a formulation to administer insulin by oral route is required. The use of modern schemes like nanoparticless, microspheres, hydrogels etc for oral insulin administration is considered most promising and successful route. Thus the study has been done to compile all the major work done for oral insulin delivery.

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