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# APPLICATION OF POLYMERIC NANOPARTICLE FOR ORAL DELIVERY OF INSULIN

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## ABSTRACT

*Insulin delivery via parenteral route is a painful treatment to the patient. It is an expensive, inconvenient therapy and there is a possibility for developing infection to the patient. Therefore, recently various polymeric nanoparticles have been developed for oral delivery of insulin that has shown success in delivering insulin. These deliveries are designed to overcome the inherent barriers for insulin uptake across the gastrointestinal tract, mucosal membranes and skin. Oral insulin delivery approaches will definitely prove to be a boon to several patients who are currently depending on daily subcutaneous mltiple injections.*

***KEYWORDS: Insulin, Insulin analogs,Liposome, nanoparticles, oral delivery.***

## I. INTRODUCTION

Diabetes is one of the major afflictions of modern western society. To date, blood-sugar levels are controlled by diabetic patients via insulin. Many attempts have been made to improve the gastrointestinal uptake of poorly absorbable drugs such as insulin which is usually administered to diabetic patients through subcutaneous injection.Subcutaneous insulin injection causes itching, pain, allergic reaction, hyper insuliemia and lipodistrophy around the injection area [1].This unpleasant method is required since stomach acid destroys protein-based substances such as Insulin, making oral insulin consumption useless. There are different new systems which are based on inhaling the insulin and on a controlled release of insulin into the bloodstream. The proper delivery of insulin in the blood stream for the treatment of diabetic patients can be achieved by nanotechnology. Production of pharmaceutically active proteins, such as insulin, in large quantities has become feasible. buccal delivery [2], pulmonary delivery [3], nasal delivery [4] transdermal delivery [5]and oral delivery [6] are some different delivery routes considered for delivery of insulin.

Oral administration of therapeutic agents is the preferred means of delivering drugs because of ease of ad ministration, low cost and high patient compliance. However, formulating a drug for oraldelivery is a complicated process. Poor intrinsic protein permeability as a result of large molecular weight, degradation by proteolytic enzymes in the stomach and in the small intestine, and chemical instability are some of the major hurdles for developing effectivedelivery of peptides and proteins. Although there are severalsuccess stories in the development and commercialization oforal dosage forms for small molecules, very few oral deliverysystems have been developed for proteins and peptides.There are different approaches such as microsphere, liposomes, permeation enhancer, enzyme inhibitors [7] and nanoparticles [8] have been used for protecting proteins. These approaches are attractive and able to protect active degradation, improving drug transmucosal transport and provide controlled release properties for encapsulated drugs.

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To convey a sufficient dose of drug to the lesion suitable carriers of drug to the lesion are needed. Most of the new drug delivery systems and the final dosage forms incorporating them require drug substances in a particulate form with specific biopharmaceutical, physiochemical, and size properties. Polymeric nanoparticles present a higher stability, when in contact with biological fluids and their polymeric nature allows obtaining the desired controlled and sustained release. The advantage that nanoparticles hold over other drug delivery systems is their submicron size which makes extravasations possible and occlusion of terminal blood vesselunlikely.

## II. INSULIN

Insulin is the principal hormone that regulates uptake of glucosefrom the blood into most cells during periods of both feeding and fasting. The secretion of insulin is a carefully regulated process which is meant to maintain healthy levels of blood glucose in the bloodstream during periods of both feeding and fasting.Therefore, a deficiency of insulin or the insensitivity of its receptorsplays a central role in all forms of diabetes mellitus. The discovery of insulin is one of the greatest discoveries of modern medical. It is produced and secreted from the β-cells in the islets of Langerhans in the pancreas.Higher insulin levels increase some anabolic processes such as cell growth and duplication, protein synthesis, andfatstorage.

Insulin is the principal signal in converting many of the bidirectional processes of metabolism from acatabolicto an anabolic direction, and vice versa. In particular, a low insulin level is the trigger for entering or leaving ketosis. If the amount of insulin available is insufficient, if cells respond poorly to the effects of insulin or if the insulin itself is defective, then glucose will not be absorbed properly by those body cells that require it nor will it be stored appropriately inthe liver and muscles. The net effect is persistent high levels of blood glucose, poor protein synthesis, and other metabolic derangements, such as acidosis.

### 2.1.INSULIN ANALOGS

Insulin analogs are synthetically produced variations of insulin which have a different in amino acid sequence then that of native human insulin. A diagram of the amino acid sequence of native human insulin is given in all cases, insulin analogs vary from this structure. So the pharmacokinetics of insulin formulation can be altered by bioengineered modifications of the natural amino acid sequence to produce “insulin analogs” Similar to formulator insulin variations, insulin analogs change the timing and duration for the effect of insulin and they are separated accordingly.

- Fast acting analogs – Aspart, Lispro, Glulisine
- Long acting analogs – Glargine and Detemir

### 2.2.ORAL DELIVERY OF INSULIN

The greatest challenge for all approaches to oral insulin delivery is achieving a high bioavailability when compared with subcutaneous delivery.Insulin if administered via the oral route will help eliminate the pain caused by injection, psychological barriers associated with multiple daily injections such as needle anxiety and possible infections [9].Insulin, 51 amino acid protein, can get deteriorated by gastric pH and intestinal enzymes, and even intestinal epithelial cell membranes serve as absorption barrier for intact peptide structure resulting in less than 1 % bioavailabity of total insulin taken orally [10]. In addition, oral insulin is advantageous because it is delivered directly to the liver, its primary site of action, via the portal circulation, a mechanism very similar to endogenous insulin; subcutaneous insulin treatment however does not replicate the normal dynamics of

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endogenous insulin release, resulting in a failure to achieve a lasting glycemic control in patients. In light of the above distinct benefits, pharmaceutical technologists have been trying to design an oral delivery system for insulin.

**2.3.ORAL INSULIN DELIVERY AND ITSCHALLENGES**

The growth of the development of protein and peptide drugs has increased significantly in recent years due to the ability to create them using recombinant techniques. In general these drugs require parenteral delivery, as is currently the case for insulin. Oral delivery is perhaps the most enticing alternative to parenteral delivery due to the general acceptance of orally administered drugs. However, oral delivery arguably represents the most challenging route of insulin delivery and it continues to be the "holy grail" of insulin therapy. Generally, peptides and proteins such as insulin cannot be administered via the oral route due to rapid enzymatic degradation in the stomach, inactivation and digestion by proteolytic enzymes in the intestinal lumen, and poor permeability across intestinal epithelium because of its high molecular weight and lack of lipophilicity. Insulin is one of the most active and robust hypoglycemic agent known for diabetes medication. Oral insulin administration is regarded as a better route of administration since it is delivered directly to the liver , its primary site of action, in such a way that the dosage form replicates the natural route of insulin secretionand absorption via the portal movement. Oral insulin administration can impersonate the physiologicalfate of insulinand thus able to provide better glucose homeostasis. Other significant benefits includes, avoiding use of needles and other injection materials, cost-effectiveness property, deep-rooted acceptability, and fostering patient complianc Thus, to achieve effective oral administration of insulin it is vital to understand the characteristics and functions of these barriers. The main barriers in oral insulin therapy are discussed below:

**2.3.1.ENZYMATIC BARRIER**

Another major barrier to the absorption of hydrophilic macromolecules like insulin is that they cannot diffuse across epithelial cells through lipid-bilayer cell membranes to the blood stream. In other words, insulin has low permeability through the intestinal mucosa. There is no evidence of active transport for insulin. It has been found however that insulin delivery to the mid-jejunum protects insulin from gastric and pancreatic enzymes and release from the dosage form is enhanced by intestinal microflora. The harsh environment of the gastrointestinal tract causes insulin to undergo degradation. This is because digestive processes are designed to breakdown proteins and peptides without any discrimination. Insulin therefore undergoes enzymatic degradation by pepsin and pancreatic proteolytic enzymes such as trypsin and α-chymotrypsin. Overall, insulin is subjected to acid-catalyzed degradation in the stomach, luminal degradation in the intestine and intracellular degradation. The cytosolic enzyme that degrades insulin is insulin-degrading enzyme. Insulin is however not subject to proteolytic breakdown by brush border enzymes. Insulin can be presented for absorption only if the enzyme attack is either reduced or defeated.The rapid luminal enzymatic degradation is observed as a major blockage for low bioavailability of proteins. In GIT gut enzymes possess natural defense mechanism so as to breakdown proteins and peptides into smaller peptide fragments and amino acids to prevent the body from potentially dangerous proteins. Thus, the orally administered insulin undergoes enzymatic degradation in the gastrointestinal tract [11] by pepsin and pancreatic proteases or proteolytic enzymes such as consisting of the serine endopeptidase and exopeptidases.

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### 2.3.2. INTESTINAL EPITHILIAL BARRIER

One of the major obstacle for oral protein delivery is intestinal epithelial barrier since hydrophilic macromolecules such as insulin is not been able to circulate through cell membranes across epithelial cells into the blood torrent. It consist of a single layer of columnar epithelial cells supported by the lamina propria and muscularis mucosa[12]. Across epithelial layer drug penetration occurs either transcellularly (movement through tight junctions between the cells) or paracellularly (movement through intercellular spacebetween the cells). The fenestrate present in porous structure of tight junctions varies in dimension of range 3 to 10 Å [13].The large molecular weight and hydrophilic nature of the peptides or clinical drugs restricts their absorption through transcellular or paracellular pathway, leading to poor bioavailability. The epithelial cells are tightly bound to one another by three types of junctions namely desmosomes , tight junctions, and gap junctions. Tight junctions binds cells with one another strongly providing mechanical strength to cell lining thus these tight junctions inhibits passage between cells[14].

## III. CARRIER SYSTEMS

The oral bioavailability of insulin can be enhanced by the use of novel carrier systems, which deliver insulin to the target site of absorption. One could choose from the galaxy of systems, such as liposomes, micelles, dendrimers, and polymeric nanoparticles **[15]**. The drug of interest is incorporated into or conjugated on to the carrier and administered orally. The carrier then serves one or more of the following functions: to protect the protein from enzymatic degradation, to entrap the protein until it has reached the organ or tissue of choice, enable controlled release kinetics or to improve targeted uptake and/or transport once a target tissue. The delivery of drug molecules through the carrier systems is assumed to avoid their unwanted effects because of controlled biodistribution. Nanoscale drug delivery systems have the ability to improve the pharmacokinetics and increase biodistribution of therapeutic agents to target organs, which will result in improved efficacy **.** Biodegradable polymeric nanoparticles have been extensively used for cancer therapeutics**.** The material properties of each nanoparticles system have been developed to enhance delivery to the tumor. For example, hydrophilic surfaces can be used to provide the nanoparticles with stealth properties for longer circulation times and positively charged surfaces can enhance endocytosis.

### 3.1.LIPOSOMES

These are closed vehicles in which drug molecules are entrapped in a central aqueous space surrounded by membranous lipid bilayers depending on the way of production. Liposomes are the most used nanocarriers for targeted drug delivery in the clinical settings .

### 3.2.DENCRIMERS

Dendrimers are highly branched macromolecules with a controlled three dimensional architecture**.** The branches are structured around a designed central core and, like a tree, expand outward via polymerization

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reactions, which allow for exact shaping of the nanoparticles. The branched structure makes it possible to attach other molecules like drugs and contrast agents to the surface.

### 3.3.MICELLS

Micelles are spherical or globular structure that forms when constituent molecules with a hydrophobic end clump to form the central core of the sphere. The hydrophilic ends of the molecules are then in contact with the liquid environment surrounding the micelle structure and form a mantle. Micelles are useful for the delivery of water insoluble drugs carried in the hydrophobic central core.

### 3.4.POLYMERIC NANOPARTICLES

Polymeric nanoparticles present a higher stability, when in contact with biological fluids and their polymeric nature allows obtaining the desired controlled and sustained release. The advantage that nanoparticles hold over other drug delivery systems is their submicron size which makes extravasations possible and occlusion of terminal blood vessel unlikely . Nanoparticles exhibit attractive physiochemical properties like particle size, high stability, lower toxicity, targeted drug delivery hydrophilic-hydrophobic balance and ability to modify their surface characteristics easily and for this reason they have been recognized as potential drug carriers for bioactive ingredients such as anticancer drugs, vaccines, and oligonucleotides. Although there are many potential improvements to be made in the field of drug delivery and diagnostics, nanotechnology offers advantages that allow a more targeted drug delivery and controllable release of therapeutic compounds**.** The development of effective drug delivery systems that can transport and deliver a drug precisely and safely to its site of action is becoming a highly important research area for pharmaceutical researchers. Due to their extremely small size, nanoscale structures have unique properties for the controlled and targeted release of therapeutic products. Nanotechnology is making a significant impact on drug delivery. Application of nanotechnology in drug delivery systems has opened up new areas of research in sustained release of various drugs.

### 3.5.ADVANTAGES OF POLYMERIC NANOPARTICLES AS DRUG CARRIERS

Polymeric nanoparticles made from natural and synthetic polymers have received the majority of attention due to their stability and ease of surface modification.

(i) Nanoparticles, because of their small size, can extravasate through the endothelium in inflammatory sites, epithelium (e.g., intestinal tract and liver), tumors, or penetrate microcapillaries. The nanosize of these particles allows for efficient uptake by a variety of cell types and selective drug accumulation at target sites and they have been actively developed for application in oral delivery of insulin**.**

(ii) They can be tailor-made to achieve both controlled drug release and disease-specific localization by tuning the polymer characteristics and surface chemistry .

(iii) Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance**.**

(iv) The system can be used for various routes of administration including oral, nasal, parenteral, intra-ocular.

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## IV. CONCLUSION

The oral bioavailability of insulin can be enhanced by the use of novel carrier systems.The drug of interest is incorporated into or conjugated on to the carrier and administered orally. The carrier then serves one or more of the following functions: to protect the protein from enzymatic degradation, to entrap the protein until it has reached the organ or tissue of choice, enable controlled release kinetics or to improve targeted uptake and/or transport once a target tissue is reached. Possible future directions in oral insulin research includealterations to insulin in order to achieve greater stability as wellas combination therapy where insulin substitutes may be co-administered administered with insulin for moreeffective glycemic control but with fewer side effects. Since therehave been many new investigations and discoveries of potential carriers to administer insulin orally, and these formulations are continuously being improved, the future of oral insulin looks promising.The delivery of drug molecules through the nanocarrier systems is assumed to avoid their unwanted effects because of controlled biodistribution. The ultimate goal of drug therapeutics is to increase the survival time and the quality of life of the patient.

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