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AN OVERVIEW OF THE DEVELOPMENT OF INSULIN DRUG DELIVERY BY POLYMERIC NANOPARTICLES

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ABSTRACT: Anti-diabetic medications, like insulin and glucagon-like peptide1(GLP-1) and its analogues are critical for diabetics to maintain blood glucose control. The difficulty of current insulin-based therapies for Type I & II diabetes mellitus, as well as the risks connected with fluctuations in blood glucose levels (hyperglycemia and hypoglycemia), served as the impetus for the establishment of "smart insulin" technology (glucose-responsive insulin; GRI). Insulin-dependent diabetes can be treated with glucose-responsive nanoparticles, a promising technology. The creation of nanoparticles of diverse sizes, features, and compositions allows for a variety of drug-delivery activities. When combined with a glucose measuring unit, this technology can give exogenous insulin more dependably and painlessly than conventional treatment. Nanoparticles made of polymers that are biocompatible and degradable have been created. These nanoparticles shield insulin from oxidation and make it easier for insulin to enter cells *via* a paracellular or transcellular pathway, whether or not they are linked to the nanoparticles. These techniques can potentially dramatically increase drug administration under controlled conditions, bioavailability, prolonged half-life, and clinical efficacy. The use of recent advancements in polymer chemistry and nanotechnology to a variety of forms and delivery techniques for the efficient and secure administration of insulin for the management of diabetes mellitus will be covered in this review.

INTRODUCTION: A pancreatic hormone known as insulin controls how much glucose exists in our systemic circulation at a time [1-3]. The beta cells in the pancreas produce the majority of the insulin. Additionally, it helps the liver, fatty tissues, and muscles store glucose. Finally, it controls the metabolism of carbs, lipids and proteins in our bodies. Premixed/Combination Insulin, Rapid-Acting Insulin, Short-Acting Insulin, Intermediate-Acting Insulin, and Long-Acting Insulin are the five category of insulin that are majorly used [4].

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The main physiological modulator of glucose homeostasis is insulin production as a result of increased glucose levels. Insulin is responsible for delivering glucose to cells, which they use as a source of energy. Lack of insulin might result in major issues like hyperglycemia because glucose remains in your system. Insulin facilitates glucose uptake, reducing blood sugar levels and providing glucose to cells for energy. When blood sugar levels go too low, the pancreas releases glucagon into the body.

The hormone glucagon causes the liver to produce glucose from stored blood sugar, which causes blood sugar levels to spike significantly [5]. An absolute or relative deficiency of insulin causes these two disorders. Insulin activates glucose absorption in peripheral tissues by attaching to the insulin receptor, a molecular target.

This receptor tyrosine kinase then initiates a complicated collection of intracellular signaling pathways that lead to the cell surface translocation of the glucose transporter GLUT4. The blood glucose level in healthy individuals lies within the range of 80 and 120 mg/dl, and the fasting glucose in the range of 80 and 100 mg/dl, by properly controlling insulin release in response to elevated interstitial glucose levels [6]. Available treatments lack the qualities that make insulin administration ideal, such as the proper secretion of insulin in an adequate concentration-dependent manner over a long period of time. Hence, there is an urgent need to develop new insulin therapies [7].

Novel drug delivery systems (NDDS) and various other delivery methods have already been developed to enhance insulin treatment and administration strategies. Nanotechnology is one such strategy for medical improvement. Nanotechnology uses particles with sizes ranging between 1–100 nm. These particles' size and high surface-to-volume ratio have generated more attention in their potential use as therapeutic targets. Targeted medication administration, controlled release and increased bioavailability are all made possible by the use of nanoparticles (NPs) (TDD).

The development of nanomedicine has now concentrated on the precise, safe and effective administration of medications for various pathological disorders [7]. Since insulin is first supplied to peripheral organs, parenteral injection of the hormone never accurately replicates the pancreatic islets of Langerhans' normal secretion of the hormone. Proteolytic enzymes in the gastrointestinal tract (GIT), which also break down food peptides and proteins, aggressively break down insulin. Insulin has been coupled with absorption boosters such as cyclodextrins, bile salts, or surfactants to boost its intestinal absorption and protect it against biodegradation [8]. The modified approach involved encapsulating insulin in polymeric nanoparticulate structures, which can shield it from proteolytic enzymes and speed up its delivery to its target organs through the GIT (especially the liver, muscle, and fat). Nanoparticles, which were first created for parenteral use as filled polymeric structures, have demonstrated the ability to increase the efficacy of medications while reducing their unfavorable adverse effects [8].

Methods for Oral Insulin Administration: Nanocarriers provide significant potential for effective oral insulin delivery. The surface properties of the polymer or nanoparticles can be changed, and enteric coatings can be added to the nanoparticles, to create nanocarriers that will enhance the gastrointestinal absorption of insulin. These may be combined with absorption boosters or enzyme inhibitors [9].

Polymeric Nanocarrier Approach: Polymeric nanoparticles are used to improve insulin bioavailability from the digestive tract. Polymeric polymers, whether chemically synthesized or natural, can control insulin secretion and the pharmacological properties that follow. Insulin-loaded nanoparticles are made of biodegradable polymers such as poly (lactide-co-glycolide), polyanhydride and polyalkyl cyanoacrylate [10, 11]. They are assimilated from the intestinal epithelium cells and transfer insulin across the intestinal mucosa [12]. Researchers have created nanoparticles with insulin quickly absorbed by the GIT using a biopolymer and a no-biodegradable acrylic polymer [8, 13, 14].

Enteric Coating Approach: Oral insulin is administered by the enteric coating method, which focuses on the pH-dependent feature of the enteric-coated polymers is exploited [15, 16]. Both cellulosic polymers, like HPMCP and polyacrylic polymers, including Eudragit L100-55 and Eudragit S100, have been extensively used for this purpose [17]. It is possible to boost insulin absorption by combining freeze-dried chitosan (CS)/poly-γ-glutamic acid (γ-PGA) nanoparticles into enteric-coated capsules. The enteric-coated capsules swiftly unleash insulin in the proximal portion of the small intestine while protecting the insulin-loaded nanoparticles from the stomach's acidity. Because of this, insulin has a higher relative bioavailability and is absorbed more quickly into the bloodstream [18].

Enzyme Inhibitor Approach: The digestive juices and enzymes in the stomach swiftly disintegrate the protein insulin after oral administration and render it inactive. Along with the nanoparticles, a number of enzyme inhibitors (protease) are administered to

block the function of such enzymes. In the presence of protease inhibitors (such as glycerrizin, capric acid, deoxycholic acid, hydroxypropyl-cyclodextrin and aprotinin), Radwan and Aboul-Enein assert that oral administration of insulin-loaded poly (ethylcyanoacrylate) nanoparticles effectively lowers and maintains blood glucose levels of 200 mg/dL (*i.e.,* the typical blood glucose level after a meal) [19, 20]. Utilizing cationic metal chelating compounds, like diethylenetriaminepentaacetic acid (DTPA), is another strategy for decreasing enzymatic activity. The complexing agent DTPA exhibited a significant protective impact on intestinal proteases when paired to insulin nanoparticles. DTPA alters the structure of the enzymes and impairs their ability to function by combining with cofactors [such as calcium and zinc] of those enzymes [21].

Permeation Enhancers Approach: Co-administration of permeation enhancers (such as paracellular route) that broaden the intercellular connection and/or disturb the membrane phospholipids enhances insulin absorption from the gastrointestinal tract (*e.g.,* transcellular pathway). The formulations contain permeation enhancers such as zonula occludens toxin, fatty acids, surfactants and Ca^{2+} chelatingagents [22]. Through the temporary opening of the tight junctions, fatty acids like sodium caprate and acylcarnitine enhance medication absorption. Surfactants interfere with the lipid bilayer to improve transcellular transport. Chelating drugs combine with calcium ions to create a compound that breaks down tight junctions and facilitates the passage of insulin across cells. Zonula occludens toxins causes comparable transient adjustments to tight junctions to let insulin pass through the mucosal barrier [23].

Polymeric Nanoparticles: Properties and Applications in Insulin Delivery: Nanotechnology and polymer chemistry have been used to create a novel drug delivery component. The size of nanoparticle (NP) formulations for drug delivery must be considered to be somewhere between 100 and 1000 nm if a carrier and an active pharmaceutical component are included in a nanoformulation. Dimensions, molar mass, and surface charge of polymeric nanomedicines affect their capacity to achieve TDD. Size impacts PNPs' capacity to move through barriers and arrive at the desired location. Polymer Nanoparticles must maintain their surface charge and keep moving throughout the body to function as a targeted medication delivery mechanism. Thus, PNPs can be altered to stop the body from quickly opsonizing them [24]. New administration techniques are also being investigated as an alternate to PNPs and traditional insulin injections to improve insulin delivery and boost patient compliance. Stability is essential for insulin to retain biological functions during nano-encapsulation and secretion. Utilizing polymeric chemistry, nanotechnology, and other delivery systems can significantly improve the therapeutic performance of insulin [24]. Naturally occurring polymers like chitosan, alginate, hyaluronic acid, dextran, and gelatin as well as synthetic polymers such copolymers of poly (alkylcyanoacrylate), poly (methacrylate) and acrylic acid are used in the manufacture of insulin nanoparticles. Polyesters are already used both independently and in conjunction with certain other polymers, such as poly (lactic acids), poly (-caprolactone) and poly (lactic-co-glycolic acids) [25].

Natural Polymer: Nonsynthetic or natural polymers are derived from nature and have sparked great interest in advancing "green" research. Microorganisms can totally degrade these polymers since they are biocompatible. They also exhibit minimal toxicity levels, making them attractive for use in insulin drug delivery systems. Non-synthetic polymers can be made of proteins like gelatin and polysaccharides, including chitosan, alginate, hyaluronic acid, and dextran [26].

Chitosan Nanoparticles: Chitosan is a low-cost natural polymer with great biocompatibility, biodegradability, low toxicity, and immunogenicity. A process known as alkaline deacetylation transforms the material present in crab shells known as chitin into Chitosan [27]. The positively charged N-acetyl glucosamine units in the Chitosan structure give this polymer its mucoadhesive properties. C Sis is a widely sought-after polymer for drug delivery research because it exhibits biodegradability, is nontoxic, and is affordable. Chitosan has been utilized to make nanoparticles, and it can also be chemically conjugated on the surface of the particles to improve their stability. Chitosan, on the other hand, is highly soluble in acidic environments and so

ineffective in the stomach, where it would produce an insulin burst [27–29]. According to Bhumkar *et al.*, a study combining nanoparticles and metals for insulin administration dramatically enhanced BGLs. In this study, researchers used chitosan/reduced gold nanoparticles for both oral and nasal insulin administration. Although these delivery methods are practical and painless, they have drawbacks. Orally given insulin crosses the liver to reach systemic circulation, where it loses its therapeutic effectiveness and becomes unstable at the acidic pH of the stomach. Before entering the bloodstream, proteolytic enzymes also break down insulin. The nasal mucous membrane prevents the passage of larger molecules, which is why insulin injections are impeded. Chitosan was used as a carrier in the development of a nanocomplex by Liu *et al* [28]. Polyelectrolyte nanocomplexes based on chitosan-g-polyethylene glycol monomethyl ether (mPEG) copolymers were created to administer insulin. Through in vitro and *in-vivo* investigations, the dosage of the mPEG graft at which the maximum absorption may take place was determined [30–32]. The proceeding step was to compare a naturally occurring mPEG-CS-glyceryl monocaprylate (GMC) copolymer to the chitosan-g-mPEG copolymer in order to determine the impact of the hydrophilic surface modification on the uptake of insulin orally. The study's results indicated that a 10% mPEG graft proportion improved absorption and that, in comparison to GMC-based copolymer, the mPEG-based copolymer exhibited better duodenal permeability and therapeutic efficacy. However, the outcomes also showed that the CS- mPEG 10% with GMC modification enhanced therapeutic effectiveness. The results did, however, also demonstrate that the CS- mPEG 10% with GMC alteration improved therapeutic effectiveness. This research made it easier to understand how the hydrophilic properties of insulin-loaded NPs influence their capacity to cross the intestinal mucous membrane. Elsayed *et al* developed insulin-loaded CS NPs for oral insulin administration. The polyelectrolyte complexation (PEC) method was used to make the CS NPs and their physicochemical characteristics were studied. **Fig. 1** represents the chitosan nanoparticles formation using Tripolyphosphate. **Fig. 1** shows the schematic outline of Chitosan nanoparticle formation.

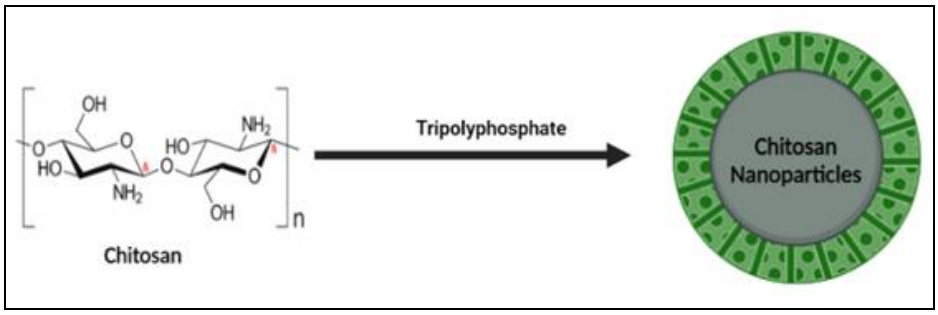

FIG. 1: FORMATION OF CHITOSAN NANOPARTICLES

Alginate Nanoparticles: Alginate is generated from seaweed and is made up of 1,4-linked β-d mannuronopyranosyl andα-l guluronopyranosyl. Alginate is a polyelectrolyte responsive system because of its carboxyl groups, making it polyanionic. Similar to chitosan, alginate has high biodegradability, nontoxicity, mucoadhesion and low immunogenicity qualities, leading to its use in studies on the administration of insulin drugs [30]. Alginate can create gelling complexin low pH environments or when divalent cations are present. A thigh pH, alginate nanoparticles are more soluble, making them better suited to the alkaline environment of the intestine. Attaching enzymes, medicines and proteins to the matrix allows them to incorporate into the nanoparticle. Alginate may encapsulate insulin when combined with CS, according to studies conducted by Mansourpour *et al*. In addition to adding β-cyclodextran, NPs were created to integrate the characteristics of both polymers. This complexation improved the permeability for insulin oral absorption and enabled the effective encapsulation of insulin. Alginate and CS were combined to create a polyelectrolyte nanocomplex used to administer insulin orally. Furthermore, Verma et al. created layer-by-layer Ca3(PO4)2-coated nanoparticles to deliver oral insulin. Due of its pH responsiveness, vitamin B12 was conjugated by the researchers with chitosan and alginate polyelectrolyte polymers. Improved

absorption and blood sugar-lowering effects over a 12-hour period were both seen in *in-vivo* investigations. Alginate and CS were combined to create PEC, which showed great potential for application as nanocarriers and nanoencapsulation systems. To completely comprehend the impact and potential of these alginate-chitosan PEC complexes in insulin administration, in-vivo optimization studies are required, as demonstrated by Zhang *et al* [8, 31].

Hyaluronic Acid (HA) Nanoparticles: N-acetyl-d-glucosamine and glucuronic acid combine to form the glycosaminoglycan known as hyaluronic acid, orhyaluronan. Unbranched, alternate β-(1to3) and β-(1to4) glycosidic linkages hold HA together [33]. HA is negatively charged, in contrast to CS and alginate, and because of its stereochemistry, it is a stable compound. Due to HA's low immunogenicity, biocompatibility, and biodegradability as a natural polymer, its usage in NDDS has attracted attention. Liu *et al.* created calcium carbonate-based nanocarriers for the oral delivery of insulin coated with HA. Compared to insulin injections under the skin, oral administration of insulin to diabetic rats had a more effective blood glucose-lowering effect [8]. Following an investigation by Han *et al*. hyaluronic acid nanoparticles were developed for oral insulin administration. When given orally, the HANPs are guarded against proteolytic and gastric degradation of the insulin by being pH-sensitive. 95% entrapment effectiveness and a dimension of 182.2 nm were attained.

The study also demonstrated in vivo hypoglycemic effects and enhanced insulin transport. Given the positive results of the experiments mentioned above, it is extremely desirable to administer insulin orally, and using HA offers a lot of promise. Therefore, further study must be conducted both *in-vitro* & *in-vivo* before alginate polymers and chitosan may be seen as competitors for insulin administration [34]. The structure of Hyaluronic acid conjugates is shown in **Fig. 2**.

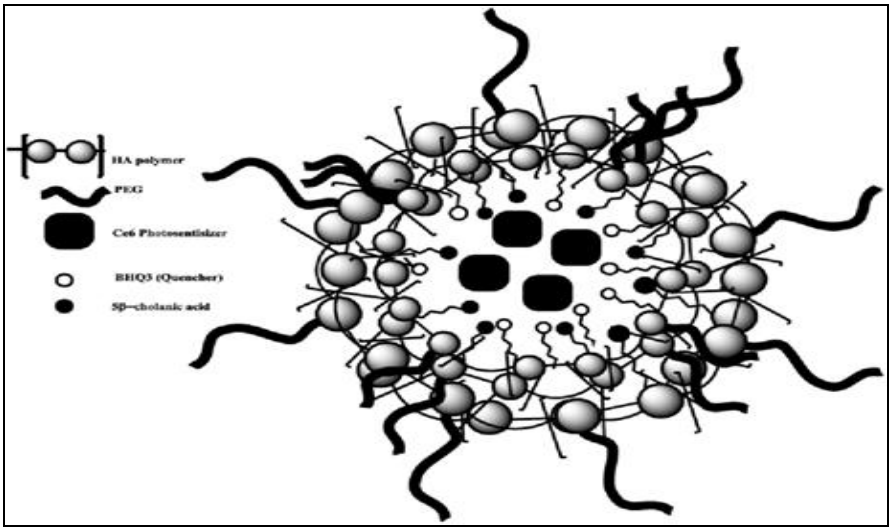

FIG. 2: STRUCTURE OF HYALURONIC ACID NANOPARTICLE

Dextran Nanoparticles: Dextran is a hydrophilic, neutral polysaccharide that is biodegradable, immunogenic, and active. It's used on nanoparticles to help extend insulin's circulation time and boost its bioavailability. A polysaccharide called dextran is formed of D-glucose subunits that connect through glycosidic linkages. Like chitosan, dextran is used in medicine as a component of nanomaterials to deliver insulin. Chalasani *et al.* employed an emulsifying process to create nanoparticles utilizing a variety of dextran having varying molecular weights [35]. A specific target ligand, vitamin B12, was linked to the nanoparticles following surface modification. The system's AE, which varied between 45 and 70%, protected insulin from gastrointestinal proteases to the extent of 65 to 83%. The *in-vitro* release trials also demonstrated a burst followed by a regulated release step of up to 95% in 48 hours. When it comes to the *in-vivo* studies, plasma glucose levels dropped from 70% to 75% after 5 hours of oral treatment (20 IU/kg), reaching baseline levels in 8–

10 hours, and this impact persisted for 54 hours. Their findings revealed that the bioavailability of vitamin B12-conjugated nanoparticles was substantially higher than that of unconjugated nanoparticles and 29.4% higher than that of an insulin injection given subcutaneously [36]. Dextran sulphate was complexed with chitosan in a different investigation. To create nanoparticles with insulin within, use aqueous medium. For up to 24 hours, the process was capable of maintaining insulin release in a gastric simulator and an intestinal simulation model. Additionally, for more than 24 hours, these nanoparticles were able to lower the baseline blood sugar levels in diabetic rats by about 35%. The pharmacological availability of insulin at dosages of 50 and 100 IU/kg was 5.6% and 3.4%, respectively, which, when contrasted to the delivery of oral insulin formulations, indicated a significant improvement (1.6%). The flow chart of dextran nanoparticles is shown in **Fig. 3**.

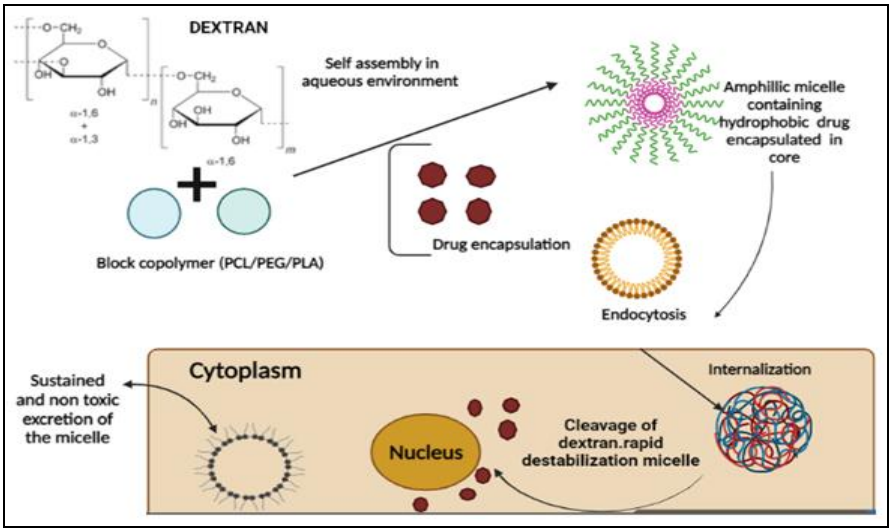

FIG. 3: SCHEMATIC REPRESENTATION OF FORMULATION AND RELEASE OF DEXTRAN NANOPARTICLE

Gelatin's biodegradable and nontoxic qualities make it a popular protein polymer for use in biomedical applications. Gelatin is a polyampholyte with hydrophilic qualities and several functional groups that enable a wide range of chemical manipulations. The degree of crosslinking determines the physical and chemical changes to gelatin. To deliver a regulated release of insulin through swelling for oral delivery, glutaraldehyde crosslinked gelatin nanoparticles (NPs) were created. Insulin release needed to occur at an intestinal pH since the GI tract's acidic pH leads to the breakdown of the hormone. Additionally, scientists wanted to create gelatin to polymer 188 gelatin: insulin NPs with a 1:1 ratio. This research sought to determine whether these nanoparticles may improve respiratory insulin uptake and demonstrate improved therapeutic bioavailability. Insulin uptake through inhalation has received attention because of the pulmonary vascularization and significant alveolar epithelial surface area. As a result, the drug can enter the circulation rapidly [37]. The surfactants must not be disrupted for appropriate breathing to take place since pulmonary delivery of insulin necessitates that it diffuses deeply into the alveoli, potentially inducing an immunological response. To prevent an immune reaction, the synthesized gelatin-poloxamer NPs lowered the amount of insulin that was deposited in the lung; however, this was only noticed one day after delivery. The NPs showed improved bioavailability and a sustained reduction of blood glucose levels. Gelatin, a naturally occurring protein polymer, has proven useful in administering insulin orally and intravenously. Its capability for controlled drug release, resilience to proteolytic and stomach pH disintegration and enhanced absorption across mucosal membranes point to its potential utility in the mucosal delivery of insulin [37, 38].

Synthetic Polymers: Natural polymers may have a range of physicochemical characteristics since they are produced using various preparation methods and resources. However, the composition and physicochemical properties of artificial polymeric

carriers may be tightly regulated, allowing for the modification of their biological behaviors and drug-release characteristics. Synthetic polymers are hydrophobic and naturally stronger in terms of chemical composition and mechanical properties than their non-synthetic counterparts. Because of this mechanical robustness, the polymer degrades at a slower pace, providing the biomaterial a long lifespan [38].

PLGA (Poly-Lactic-co-Glycolic-Acid) Nano-particles: PLGA, an aliphatic polyester co-polymer, is one of the most widely used synthetic polymers for producing oral nanoparticles administering insulin. This is mainly due to its characteristics for continuous release and biodegradability. The Food and Drug Administration (FDA) has permitted triptorelin and leuprolide to be released over a prolonged period using PLGA microparticles. PLGA matrices cannot often capture water-soluble insulin due to their hydrophobic nature. According to earlier research, adding soybean phosphatidylcholine improved the liposolubility of insulin by forming an insulin phospholipid complex, which in turn raised the loading efficiency of insulin in PLGA NPs [8, 33].

PLA (Poly Lactic Acid) Nanoparticles: The hydrolysis of PLA, an aliphatic polyester polymer, into monomeric units within the body makes it deemed biodegradable and biocompatible. In order to administer insulin orally, Xiong*et al* created PLA-b-pluronic-b-PLA (PLA-F127-PLA) vesicles. A biphasic release characteristic of insulin from the PLA-F127- PLA vesicles was seen in the *in-vitro* release research. Because of its amphiphilic characteristics and polyethylene oxide block structure, the pluronic block copolymer displayed excellent penetration characteristics of insulin across the biological membranes and a considerable affinity for the small intestine [7]. The blood sugar level decreased from 18.5 to 5.3 mmol/L during first 4.5 hours to 4.5 mmol/L by the end of the following 5 hours when diabetic mice (50 IU/kg) were administered orally insulin-loaded PLA vesicles. More than 18.5 hours were spent with the blood glucose level remaining constant. These findings demonstrated that insulin-loaded PLA-F127-PLA vesicles may be given orally because of their sustained hypoglycemic effect. In a more recent investigation, PLA-b-pluronic-b-PLA (PLA-P85-PLA) vesicles were made for the same purpose and obtained with a mean diameter of 178 nm. In cytotoxicity tests with human ovarian cancer cell OVCAR-3, the biocompatibility of the generated vesicles was established. Studies on insulin release in both vitro and in vivo showed that it was virtually entirely released 7.5 hours after it was administered. In diabetic mice, the oral administration of insulin-loaded PLA-P85-PLA vesicles (200 IU/kg) decreased blood glucose levels, which peaked 2.5 hours after the treatment at their lowest (15% of the baseline blood glucose level). In 10.5 hours, the blood glucose levels steadily rose to 31.8% of the original blood glucose concentration and stayed there for more than 14 hours [37].

PCL (Poly-ε-Caprolactone) Nanoparticles: The hydrolysis of the ester bonds in PCL makes it a biodegradable polymer. It is interesting to employ hydrolysis in NDDS since it occurs under physiological circumstances. Over time, PCL is broken down, increasing the likelihood of being used to deliver insulin. Solvent displacement, nanoprecipitation, and evaporation are the primary ways to create PCL NPs.

Research conducted at the University of Campinas in Brazil using PCL nanoparticles loaded with insulin revealed that these nanoparticles were biologically compatible and had an efficiency of 90.6 % at encapsulating insulin. Animal experiments demonstrating that the nanoparticle formulations preserved low BGLs indicated a controlled release strategy. French scientists studied polycationic acrylic NPs which have been PCL-blended for application in administering insulin orally. The results indicated that the encapsulation rate was 96%. Because PCL is mucoadhesive, these carriers for oral insulin administration may have contributed to the large prolonged hypoglycemia impact they produced in the control and diabetic animal groups. The ability of the NPs to safeguard the molecule laden with insulin was also demonstrated [39].

An insulin-loaded nanoparticle formulation created by Wu *et al* uses pH-responsive polymers such poly (ethylene glycol)-PCL-poly (N, N-diethylamino-2- ethylmathaerylate). In contrast to the nanoprecipitated insulin-containing NPs, the

mPEG-PCL-PDEAEMA was produced utilizing atom transfer radical polymerization as well as ring expansion polymerization. With BGLs maintained throughout 48 hours, the nanoparticle formulation displayed low-release kinetics and entrapment effectiveness of 81.99%. Even though PCL can provide an NP for the medication delivery of insulin, different polymers and/or metals may improve this system. Researchers may be able to develop the best insulin DDS by utilising PCL in a stimuli-responsive system because of the strong encapsulation and entrapment performance of PCL nanosystems on insulin [40].

PEA (Poly Ester Amide) Nanoparticles: For the administration of oral insulin, He *et al* developed a poly (ester amide) based on L-Lysine/L-Leucine with pendant COOH units. The PEA copolymer with benzyl ester pendants and L-Lysine/L-Leucine-based PEA-COOH were made using the solution polycondensation of three monomers. Insulin was encapsulated in PEA microspheres using the solid-in-oil-in-oil method using N, N-dimethyformamide (DMF)/corn oil as the solvent pairs. Because of this, the amount of leucine in PEA-COOH microspheres could be altered to change their hydrophobicity and the release of insulin was pH-dependent. This increased the medication delivery system's stability and enhanced overall insulin absorption [39]. In their research, arginine-based PEA (Arg-PEA) was also introduced. He *et al* reported by combining Arg-PEA with PEA-COOH/Arg-PEA mix microspheres, the hypoglycemic effects may be further enhanced [41].

PVA (Polyvinyl Alcohol) Nanoparticles: PVA is a polymer with minimal toxicity and thermal stability that is biodegradable and biocompatible. PVA is simple to make and has a high amount of mechanical strength, like most synthetic polymers. Natural polymers and PVA can combine to create innovative DDS with improved characteristics. In order to create hydrogels containing nano-insulin for transdermal delivery, Zu *et al.* crosslinked CS-PVA polymers using glutaraldehyde [41].

The nano-insulin- loaded hydrogels appear to be a viable noninvasive TDD system based on *in-vitro* data that showed strong thermal and physical features with a high penetration. In an aqueous phase media with the surfactant optimised, Rawat *et al.* generated PVA NPs through a solid o/w emulsion. According to the findings, insulin may be stabilized and protected by high-molecular-weight PVA because it possesses favourable chemical and physical characteristics [42]. By keeping insulin bioactivity and displaying hypoglycemia effects, animal studies provided more support for this. In the creation of NPs for oral delivery of insulin, PVA can also be utilized as a stabilizing surfactant [43].

Polyamino Acids Nanoparticles: Amino acids are one of the most important components of biological systems. Their particular traits dictate how they are built and how they work. In contrast to naturally occurring polymers, synthetic polymers with amino acid side chains are simple to manufacture and provide the characteristics needed for various biological applications. For the peroral administration of insulin, chitosan (CS)/poly-(γ-glutamic acid) (γ-PGA) nanoparticles were prepared by heating PGA acid with chitosan in solution. This synthesis was carried out using tripolyphosphate and MgSO4 (TPP). The outcomes showed that the NPs reduced blood sugar levels for 10 hours *in-vivo*, whereas the bioavailability of insulin was about 15.1%. TMC/gPGA nanoparticles, as opposed to CS/gPGA nanoparticles, may be a viable vehicle for the transmucosal administration of insulin across the whole GI tract where the pH levels are near to the pKa of CS [39]. Sonaje *et al.* developed a chitosan-poly (glutamic acid) nanoparticle technology with a gelatin enteric coating for delivering insulin orally. The gelatin is covering guarded against the acidic and proteolytic breakdown of the insulin-loaded NPs. It was concluded that packed insulin successfully moved to the small intestine and produced a long-lasting hypoglycemic activity. To deliver insulin orally, Chinese researchers developed multipurpose chitosan-based carboxyl-, PBA-modified-, and L-valine (LV) NPs. While evidence from animal research indicated considerable oral administration and a successful hypoglycemic outcome *in-vivo, in-vitro* results showed minimal to no harm and effective glucose-responsive characteristics [43].

Acrylic Polymer Nanoparticles: Due to their capacity to decrease protease activity, improve

mucoadhesion, and change cell tight junctions, acrylic polymers have been utilised in the oral administration of insulin to increase intestine absorption [44]. Actually, nanoparticles with various characteristics are created using acrylic acid and its derivatives, which may increase the absorption of insulin when taken orally. In an experiment by Deutel *et al,* PAA-cysteine nanoparticles that were utilised to give insulin orally to non-diabetic rats were made using the mucoadhesive polyacrylic acid (PAA). This combination's enhanced mucoadhesion capacity and strong enzymatic protective qualities allow for improved permeability [45]. A substantial rise in serum insulin concentration and a decrease in blood glucose levels were seen after treatment. Because thiolated polymers have improved mucoadhesive qualities, their insulin area under the curve was 2.3 times larger in thiolated PAA nanoparticles than in unmodified PAA nanoparticles [46, 47]. Another study's goal was to produce a similar carrier to shield loaded insulin from gastrointestinal proteases. According to the *in-vitro* experiments, nanoparticles protected the original quantity of insulin against trypsin, α- chymotrypsin and elastase degradation by 44%, 21% and 45%, respectively, when compared to insulin in solution [48].

Pluronics: The triblock polymers known as pluronics are naturally amphiphilic and immiscible in water. They are additionally called poloxamers. They are made of polypropylene oxide and have polyethylene oxide blocks on either side (PEO-PPO-PEO) [49–51]. Pluronics are biodegradable, thermosensitive gelling agents that come in the form of waxy, white granules with no flavour or odour. Depending on the materials' molecular mass and the physiological state in which they occur, they are categorized into several groups (solid, paste, or liquid). Shu *et al* investigated the effects of poly (lactic acid)-b-pluronic-b-poly (lactic acid) nanoparticles on oral distribution *in-vitro* and *in-vivo* [52]. The results demonstrated that the nanoparticle-based delivery method considerably enhanced oral insulin uptake. During this time, Xie*et al* examined the medical applications of folic acid-pluronic 85-poly (lactide-co-glycolide) on orally administered insulin. To deliver insulin orally, the researchers developed pluronic F127-grafted PLA NPs after in vitro tests revealed the biphasic secretion of insulin [53, 54].

BGLs were seen *in-vivo* within 4.5–5 hours of treatment and they persisted for more than 18.5 hours. Injectable gels may be created using pluronics because of their strong heat sensitivity. Pluronics will solidify under physiological conditions, facilitating the creation of a drug-loaded deposit within the body. The regulated release of insulin will also be possible thanks to the pluronic matrix. Researchers may use pluronics to create a system that enables prolonged, stimuli-responsive insulin administration by using it as a nanoparticulate platform (like a nanogel), for nanoencapsulation, or as a nanocarrier for insulin delivery [51, 55].

Toxicity of Nanoparticles: Numerous studies have demonstrated that nanocarriers given every day to patients are secure, nontoxic, biologically compatible, degradable and that they trigger repeatable biological effects. In contrast, the toxicological effects of nanocarriers on human health have been covered in several literature studies. Recent research reveals that the cytotoxicity of nanoparticles is linked to oxidative stress and the activation of pro-inflammatory genes, although the precise underlying mechanism is yet unclear. The utility of nanocarriers as well as their unforeseen and unfavorable effects on human health must thus be taken into account. To cross biological barriers and cell membranes at the cellular level in tissues and organs, nanocarriers must possess features distinct from those of their bulk conformation. The toxicity of nanocarriers is well known to rely on a number of physiochemical factors, including particle size, shape, surface charge, composition, and subsequent stability of the nanocarriers [56]. In addition, it appears that the administration dosage, route and tissue distribution are significant variables that affect the cytotoxicity of nanocarriers. The need for studies on the cellular toxicity of nanocarriers has increased for the safe creation and usage of nanoparticles [57].

Toxicity of Insulin-Loaded Polymeric Nanoparticles: The insulin and the carrier itself need to be the focus of the toxicity evaluation for oral delivery of insulin-loaded polymer-based nanoparticles. Higher insulin doses must be given

orally compared to subcutaneous administration to get the same results. However, administering large doses in the gut may bring up toxicological issues that most investigators often overlook or underrate. Since the impact of continuous insulin therapy on the intestinal epithelium is yet unknown, Florence reported that, for example, insulin secreted in excessive amounts may result in gastroparesis [9, 58].

The bulk of commonly employed polymers are known to be biocompatible and biodegradable concerning the carrier; nonetheless, biodegraded polymeric compounds can clump within the cells, which can unintentionally alter physiological responses [59]. Hossain and others analyzed this. In addition to cytotoxicity, the immune system could perhaps be compromised. Goldberg and Gomez-Orellana reported that excipients or adjuvants utilized in the production of nanoparticles, such as surfactants and absorption promoters, may also disrupt the intestinal epithelium.

Continuous use of the latter may weaken the integrity of the epithelium, allowing viruses and poisons to enter the body and cause unforeseen negative effects. Gowthamarajan and Kulkarni reported protease inhibitors, which may interfere with protein digestion and cause nutritional issues and mucoadhesive substances, which may alter mucus turnover and disrupt intestinal physiology, are two other potential issues. Since it is presumed that the established carriers are biocompatible, efforts in the field of oral insulin administration have been more focused on increasing the bioavailability of oral insulin than on determining their toxicity. The carriers' long-term toxicity, however, has been disregarded. Nevertheless, several research addressing some toxicity worries have been published [57, 60].

CONCLUSION: Enzymatic degradation, limited intestinal permeability, and decreased oral bioavailability are all significant issues with oral insulin delivery. In order to solve these issues, various methods, including insulin encapsulation in polymer-based nanoparticles have been employed. Utilizing its qualities, such as the capacity to maintain insulin stability, mucoadhesion and to regulate the release and targeting of medications, polymers utilized in the manufacture of nanoparticles may come from either natural or synthetic sources. All these features may be accommodated in one nanocarrier by mixing several polymers. Academic research, as opposed to advancements in the pharmaceutical business, has dominated research on discovering a substitute way to give insulin orally.

Many carriers have been tested and proposed to enhance intestinal uptake of insulin in a way that is much greater than that of an orally administered insulin solution. Although encouraging results have been discovered, they fall far short of the hypoglycemic impact that may be achieved with subcutaneous insulin. In actuality, far more insulin is utilized to create the oral delivery systems than is required to create the subcutaneous formulations. This is an important distinction since the AE of the produced nanocarriers is essential in terms of cost-effectiveness. Large doses of insulin delivered through the intestines may potentially have negative consequences.

Therefore, creating oral insulin nanocarriers that are more efficient and have a comparable biopotency to the subcutaneous route requires further attention in future research advancements. The created nanocarriers need to undergo long-term toxicity testing, and their safety needs to be amply proven. The pharmaceutical businesses are working hard to create an oral insulin delivery system. Still, little attention has been paid to polymeric nanoparticles because so few firms have used this approach and the data available so far is quite tentative. A lot more work still has to be done before an oral insulin delivery system based on nanoparticles can be commercialized. The way is clearly indicated, and using polymeric nanoparticles may provide a solution to the need for an oral insulin delivery method.

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