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Review Article

Novel Carriers and Approaches Insight in Diabetes Mellitus

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Abstract:

Diabetes mellitus is one of the the most common, oldest and non communicable chronic disease in India.Diabetes is a serious, costly and heterogeneous metabolic disorder which ischaracterized by chronically elevated blood glucose levels (BGLs) and an inability to maintain BGL homeostasis. According to Indian council of medical research (ICMR, section 1,2005) diabetes is defined as a metabolic cum vascular syndrome of multiple etiologies factorise by hyperglycemia with disturbance of carbohydrate, protein and fat metabolism resulting from insulin deficiency or resistance to insulin or both.According to American diabetes association (ADA) diabetes is is defined as a group of metabolic diseases characterized by inappropriate hyperglycemia resulting from defects in insulin secretion, insulin action or both.

Introduction

Diabetes is the fourth or fifth leading cause of death in most developed countries with the substantial evidence to be epidemic in many developing and newly industrialized countries, affecting about 25% of the population. The majority of diabetes cases broadly falls in two categories i.e.Type 1 Diabetes and Type 2 diabetes. Type 1 diabetes occurs because the insulin-producing cells of the pancreas (beta cells) are damaged (as shown in fig) Type 2 diabetes is characterized by insulin resistance, or a deficiency in cellular response to insulin in the bloodstream(in fig)Besides these types of diabetes, gestational diabetes has also been reported in pregnant women.Normal blood glucose level is 70 to 100 mg/dL when fasting and upto 140 mg/dL two hours after eating. In diabetes, 100 to 125 mg/dL in prediabetes, more than 140 mg/dL when fasting and more than 200 mg/dL two hours after eating. Treatment of diabetes need constant monitoring of blood glucose level, regulating it through modified dietary sugar intake, physical exercise and insulin therapy (subcutaneous administration) to attain normogly.Therefore the current standard of care for type 1 and advanced type 2 diabetes involves daily subcutaneous insulin injections, and frequent finger pricks to draw blood for the measurement of BGLs.Additionally, periodic measurement of blood glucose may not detect large fluctuations in BGLs which occur between points of measurement. Therefore, systems which improve blood glucose monitoring, or “close the loop” between glucose measurement and insulin delivery, are highly desirable.In order to optimize different routes of insulin therapy, novel drug delivery systems have been suggested, and alternative routes of administration have been investigated. One such method used for the advancement of medicine is nanotechnology. Nanotechnology involves the use of particles within 1–100 nm. It is the size of these particles, as well as their large surface to volume ratio, that has increased interest in their application for molecular therapeutic targeting. The use of nanoparticles (NPs) allows for improved bioavailability, controlled release, and targeted drug delivery (TDD). To date, the advancement of nanomedicine has focused on the safe, effective, and accurate delivery of drugs foran array of pathological conditions. Studies employing biodegradable natural/synthetic polymeric nanoparticles (PNPs) and manipulating the distinctive properties of these nanomaterials for TDD have been undertaken.

Advancements in nanoscience for insulin therapeutics have brought about research for the development of insulin nanocarriers, insulin smart-drug delivery systems (stimuli-responsive), insulin pumps, novel insulin analogs, and insulin nanosensors for the effective treatment of DM. This review will be focusing on the alternative route of administration (oral or pulmonary) or reducing the injection doses are beneficial to reduce the inconvenience and drawbacks associated with this conventional method.

Problems possed by the antidiabetics

Antidiabetics are effortlessly accessible in the internationalmarket Most of the oral hypoglycemics are available either in the form of tablets and capsules.However, these dosage forms offer various untoward effects/limitations like gastric irritation, diarrhea, loss of appetite,lactic acidosis in people with abnormal kidney or liverfunction due to gastrointestinal degradation, insolubility inwater and do not comply with the safety and efficacy of the patients. These adverse effects revealed the limited accessibility of conventional dosage forms at desired site of action, higher systemic toxicity, narrowtherapeutic window, complex dosing schedule for long-termtreatment (Sutradhar & Sumi, 2014). Two major factorsrequired for the drugs to be effective are their optimalconcentration at the desired site of action and persistent effective concentration for a longer period of time. After immediate release, oral hypoglycemics get absorb from thebiological membranes and move toward the site of action.However, to attain the

therapeutic concentration into theblood for whole day, about 2 to 3 doses are required to be administered (Pradhan, 2011; CIMS/MIMS India MedicalDrug Information eBook, 2013). Moreover, insulin and peptide drugs namely GLP-1, GLP1RAs are available primarily as subcutaneous (SC) injections while peptide analogues, i.e. DPP-4 inhibitors (vildagliptin, (Galvus),sitagliptin (Januvia), saxagliptin (Onglyza)) are available inthe global market as tablets. They have been approved by EU and USFDA for the treatment of DM in last decade. LiraglutideLiraglutide, Exenatide and Albiglutide act through GLP-1receptors, which are found in brain, lung, pancreatic islets,stomach, heart, intestine and kidney. Due to the susceptibilityto the proteolytic degradation in gastric environment andshorter plasma half-life, they are less frequently used for oraladministration (Kalra, 2011). Their injections are available in the market but injections of exenatide cause nausea, vomiting and antibody formation when used twice a day, whileliraglutide injections cause mild, transient nausea andvomiting when used once a day (Kalra, 2013). Pain atinjection site and hence injection phobia is another limitation.Enhancing oral bioavailability of these analogues is achallenge. Therefore, thorough investigation is required in the area of drug delivery which could be possible byexamining new and more specific drug delivery carriers.

Need of Novelcarrier based approaches for drug deliveryin Diabetes

The word ‘‘nano” has been originated from Latin and the literally meaning of which is dwarf. Thus, nanotechnologyscience deals objects within the size range of Thus, strategies in successful delivery of therapeutic medications have incorporated the agents in the microenvironmentof the nanocarrier, with the aim to suitably target forimproved efficacy and safety. Synthesis of the nanocarriers are a challenging art of nano-research to get reproduciblenano-products, at the same time, maintenance of the characteristics of the formulated nanocarriers to get reproducibleresults in the in vitro as well as in vivo experiments. Subsequent sections of the article will cover the various nanoparticulate approaches for the improvement of diabetes therapy in hyperglycemia condition.

Roles and possible mechanisms of nanocarriers /novel carriers in oral drug delivery system

Insulin therapy is widely used in treatment of diabetes mellitus. Insulin is used in lowering blood glucose levels for type 1 diabetes and also required at later stages in type 2 diabetes patients. The widely accepted route for delivery of insulin is by parenteral administration but this delivery of insulin usually requires at least three or four daily insulin injections for good glycemic control. So to overcome these consequences, acceptable different routes of insulin delivery have been searched to decrease suffering from discomfort, local pain, irritation, infection, immune reactions and lipoatrophy at the injection site of insulin.

Oral drug delivery is one of the most effective method for delivering the drug directly into the liver through portal circulation and could mimic the physiological fate of endogenously secreted insulin. However polypeptides, like insulin are degraded in the stomach pH and undergo proteolysis by enzymes in the gastrointestinal tract.

Moreover the gastrointestinal mucosa has low permeability for large hydrophilic peptides.In order to overcome the problems associated with parenteral administration of insulin several strategies that are based on nanotechnology has been developed to enhance the intestinal absorption of different protein and peptides. NPs consist of naturally occurring biodegradable polymers are widely investigated in this regard. They have emerged as potential carriers of several therapeutic agents for controlled drug delivery as well as the oral route of insulin. Various natural hydrophilic and hydrophobic polymers used as carrier of oral insulin such as chitosan, alginate, dextran sulphate, etc. are commonly used to prepare NPs.

The bioavailability of orally delivered drugs is influenced by the physico-chemical properties of the drugs (i.e. solubility, pKa, size, etc.). The absorption of drugs and particles in gastrointestinal tract (GIT) occurs through various sites depending upon their size. Particles with 1μm diameter are absorbed via phagocytosis by intestinal macrophages while particles <10 μm in diameter are transported through peyer’s patches (lymphatic islands preesent on GIT).Nanoparticles (<200 nm) are absorbed through endocytosis by enterocytes. Nanotechnology reveals the application of size scale complex systems in various fields due to their unique properties.One of the exten-sively studied areas of nanotechnology is delivering systems for the active ingredient of the medicine. Effective nanomedicine must be stable, biodegradable, non-toxic, non-inflammatory, non-thrombogenic, nonimmunogenic and should escape by reticuloendothelial system. Moreover, nanomedicine should be applicable to different molecules such as small drugs, proteins, vaccines or nucleic acids. It has been proved experimentally that, for therapeutic and imaging applications, nanoparticles may range from 2 to 1000 nm.

Additionally, nanotechnology offers the wide range of advantages to the drug delivery field including oral drug delivery in particular, i.e., increase efficacy, tolerability, specificity and therapeutic index of analogous drugs. Furthermore, for oral delivery of drugs nanotechnology may assist in the delivery of poorly water-soluble drugs, transcytosis of drugs across the tight intestinal barrier, targeting of drugs to the specific part of the gastrointestinal tract and in the intracellular and transcellular delivery of bulky macro molmolecule .

Among various limitations of oral delivery of certain drugs is their poor absormolmolecule the GIT. Such limitations can be overcome by the use of bio adhesive polymers which can facilitate the adhesion of nanocarrier to the mucosal epithelial membrane and can assist in nanoparticle uptake.Other than the oral delivery of drugs using nanocarriers, pulmonary means of delivery is also an efficient route.

The use of biodegradable polymeric nanoparticles have evolved as a better alternative for oral/pulmonary delivery of proteins and

peptide drugs.The stability and functional abilities of the nanoparticles can be modulated by some of the pharmaceutically accepted excipients able to regulate pH responsivity and Pgp effect e.g. cyclodextrin, chitosan, PLGA, TPGS/Vitamin E TPGS, etc. Lowman et al. (1999) formulated pH sensitive nanocarriers to overcome the limitations of oral insulin delivery and observed decrease in blood glucose level for longer time (8 h) in diabetic rats at a dose of 25 IU/kg of loaded insulin. Some of the pH sensitive biodegradable polymers explored so far are PMAA, HPMCP(HP55), dextran sulphate, alginate,PGA etc.

Nanoparticles for insulin delivery

The various types of nanoparticles that are currently studied for their use as drug delivery system are as follows:

- Polymeric biodegradable nanoparticles that include nanospheres and nanocapsules
- Ceramic nanoparticles
- Polymeric micelles
- Dendrimer
- Liposomes.

The applications of various types of nanoparticles and BioMEMS (bio microelectromechanical system) for insulin delivery in the treatment of diabetes are outlined in the following sections.

1.Polymeric nanoparticle :- National Nanotechnology Initiative has defined Nanoparticles as thestructure with the sizes varies from one to one hundred
nanometres in at least one dimension.Nanoparticle has widelybeen used in pharmaceutical, medical and biological field to deliver polypeptides, drugs, nucleic acids, proteins, genes, vaccines and so on. The use of biodegradable polymeric nanoparticles have evolved as a better alternative for oral/pulmonary delivery of proteins and peptide drugs. Most importantly, they can reduce the risk of adverse events and enhance the drug utility.Recently, researchers are more focusing on themodification ion of the nanoparticles in order to advance its use in modern therapy.

Depending on the methods of preparation nanoparticles can be of two types, nanosphere or nanocapsule. These nanostructures have completely different properties and release characteristics for the encapsulated drug.These particles degrade into biologically acceptable compounds by hydrolysis thus delivering the encapsulated medication to the target tissue. The erosion process occurs either in bulk where the matrix degrades uniformly or at the polymer's surface where the release rate is related to the surface area. The polymer is degraded into lactic and glycolic acids, which are eventually reduced to carbon dioxide and water by Krebs cycle. Earlier researches were focused on using naturally occurring polymers like collagen, cellulose, etc as biodegradable systems. The focus has now moved on to chemically synthesize biodegradable polymers with improved characteristics. Examples include polyanhydrides, polyacrylic acids, polyurethanes, polyesters and poly (methyl ethacrylates). Recently polymeric
nanospheres based on methoxy poly (ethylene glycol) and DL-lactide diblock copolymers have been synthesized. The cytotoxicity tests showed that the nanospheres exhibited sustained drug release and no cell damage. Polymeric nanoparticles represent a significant improvement over traditional oral and intravenous methods of administration in terms of efficiency and effectiveness.

Also, polymeric nanoparticles can have engineered specificity, allowing them to deliver a higher concentration of pharmaceutical agent to a desired location. These biodegradable polymers with the help of polymer-insulin matrix surrounded by nanoporous membrane which contains grafted glucose oxidase rises the blood glucose level and triggers a change in the surrounding nanoporous membrane resulting in biodegradation and subsequent insulin delivery. The glucose/glucoseoxidase reaction causes a lowering of the pH in the delivery system's microenvironment, therefore further leading to an increase in the swelling of the polymer system, causing an increased release of insulin.

The polymer systems investigated for such applications include copolymers like N, N-dimethylaminoethyl methacrylate and polyacrylamide. This 'molecular gate' system is composed of an insulin reservoir and a delivery-rate controlling membrane made of poly(methacrylic acid-g-polyethylene glycol) copolymer. The polymer swells in size at normal body pH (pH = 7.4) and closes the gates. It shrinks at low pH (pH = 4) when the blood glucose level increases, thus opening the gates and releasing the insulin from the nanoparticle (Fig)The control of theinsulin delivery depends on size of the gates, the concentration of insulin, and the rate of gates' opening or closing (response rate).

This feature makes polymeric nanoparticles as ideal candidates for diabetes therapy and delivery of insulin.Since these self-contained polymeric delivery systems are still under research while delivery of oral insulin with polymeric nanoparticles has progressed to a greater extent in the recent years.

Oral insulin delivery through polysaccharide conjugated polymeric nanoparticles

Development of improved oral insulin administration is very essential for the treatment of diabetes mellitus in order to overcome the problem of daily subcutaneous injections. Effective oral delivery of insulin by NP-based carrier systems is preferred by the society due to their convenience of administration and good patient compliance compared to
the available parenteral preparations. Insulin when administered orally undergoes degradation in the stomach due to gastric enzymes. Therefore, to enhance the bioavailability of oral insulin nanoparticle delivery, insulin is conjugated with peptide that allows cell penetration and then encapsulated in mucoadhesive nanoparticles. Through these approach the reservation of insulin into the

nanoparticles in intestinal mucus layer can be enhanced whereas the conjugated insulin freed from the nanoparticles would not be deteriorated by the enzymatic degradations

because of the short distance for the drug to reach the absorption site as well as the conjugates have high permeabilitythrough epithelia.

In a study by Sheng et al., insulin was conjugated with a cell-penetrating peptide protamine, followed by encapsulation in the mucoadhesive poly(lactic-co-glycolic acid) (PLGA) NPs coated with N-trimethyl chitosan chloride. Based on theresults obtained, a faster onset with long-lasting hypoglycaemia effect was shown in diabetic rats. A bioavailability ofthis designed oral delivery system of insulin was being17.98 ± 5.61% compared to subcutaneous insulin injection.Interestingly, a significant improvement in this oral delivery system of insulin with improved bioavailability in experimental animals indicating better internalization of the mucoadhesive NPs by the cells as compared to the native insulin.Therefore, the conjugation of insulin with cell-penetrating peptides, and followed by encapsulation in mucoadhesive. NPs could be an useful carrier for the oral delivery of insulin.

In one such other study, calcium phosphate-polyethylene glycol-insulin combination was combined with casein (a milk protein). The casein coating protects the insulin from the gastric enzymes. Due to casein's muco-adhesive property, the formulation remained concentrated in the small intestine for a longer period resulting in slower absorption and longer availability in blood stream.

Over the past few decades, enhancing attention has been paid to the use of polymeric nanoparticles either hydrophilic or hydrophobic as carriers for insulin delivery. Hydrophilic polymers are of particular interest due to their non-toxic, biocompatible, biodegradable and natural polymers. Among them, chitosan is widely used because of its ease of chemical modification and promising biological properties.

Chitosan (CS): CS is well known naturally occuring copolymer of beta [1-4] linked and N-acetyl glucosamine and have been generally found in crustacean (crabs, shrimps and lobsters) shell and in some fungi or yeast. It is a biodegradable, biocompatible, non toxic, non-allergic easily absorbable natural hydrophilic polymer properties that have resulted in a wide array of applications in biomedical and drug delivery research.Moreover it prolongs the intestinal residence time that shows its mucoadhesive property.

It also increases the stability of nanospheres and faciliates effective encapsulation of proteins and drugs that make it as a suitable carrier material.

CS combined with poly(γ-glutamic acid) (γ-PGA) based insulin NPs are used as hydrophilic polymers for oral insulin delivery. In vivo preclinical studies of this formulations at a dose of 30 IU/kg in streptozotocin (STZ) induced diabetic rat models showed increased intestinal absorption of insulin from γ-PGA NPs. It has got long lasting hypoglycemic effect and 15% relative bioavailability comp isared to subcutaneous (sc) injection. The same formulation filled in enteric coated capsules was even better at the same dose, showing 20% oral bioavailability. Also aspart insulin (=monomeric, 3 times faster than regular) is encapsulated in the same CS-γ-PGA; has got 15.7 % oral bioavailability.

Chitosan with sodium alginate is being prepared another insulin loaded nanoparticle product which is used to improve the loading capacity and activity maintenance. It's observed that when insulin-loaded nanospheres (25, 50, 100 IU/kg) administered orally to diabetic rats they reduced glycaemia in a dose dependent manner. Their pharmacological availabilities are found 7.1, 6.8 and 3.4 %, respectively .

Thus, NPs could provide a comprehensive platform toimprove the delivery of both, peptide based and organic hypoglycaemic agentsin the control of high plasma glucose level for a prolonged time during diabetes, minimising the frequency of ingestion. Although various factors are involved in the improvement process, thus close monitoring of such parameters including particle size, polymeric coat, surfacecharge, characteristics of the polymer, etc. could deliver apotential strategy of drug delivery for both management oflong-term and self-regulated diabetes control. Recently,magnetic core has been introduced into the nanoparticulate delivery where the soft ferromagnetic property helps indelivery of the nanocarriers particularly to the site of action to avoid the systemic adverse events of the drugs.Thus, it is obvious that polymeric nanoparticulate deliverysystem can be incorporated in the delivery system of forsuccessful systemic delivery of anti-hyperglycemic agents,although such researches need extension towards clinicalsettings.

Ceramic nanoparticles

Ceramic nanoparticles are made from calcium phosphate, silica, alumina or titanium. These ceramic nanoparticles have certain advantages like easier preparative processes, high biocompatibility, ultra-low size (less than 50 nm) and good dimensional stability. These particles effectively protect the doped drug molecules against denaturation caused by changes in external pH and temperature. Water-insoluble photosensitizing anticancer drugs entrapped within ceramic nanoparticles have been shown as a novel drug-carrier system for photodynamic therapy in cancer treatment.Moreover their surfaces can be easily modified with different functional groups and can be conjugated with a variety of ligands or monoclonal antibodies to target them to desired sites. These nanoparticles can be manufactured with desired size, shape and porosity. Ceramic nanoparticles do not undergo swelling or porosity changes caused by changes in surrounding environment. Self-assembling ceramic nanoparticles have been tested for the parenteral delivery of insulin. Calcium phosphate nanoparticle core was used as theinsulin carrier and these particles were characterized and studied in vivo. The in vivo performanceof this drug delivery system showed better results when compared with the efficacy of standard porcine insulin solution. Recent study has shown that tricalcium phosphate nanoparticles can be used for oral delivery of insulin.

Inhalable polymeric nanoparticle-based drug delivery systems have been tried earlier for the treatment of tuberculosis [36]. Such

approaches can be directed towards insulin delivery through inhalable nanoparticles. Insulin molecules can be encapsulated within the nanoparticles and can be administered into the lungs by inhaling the dry powder formulation of insulin. The nanoparticles should be small enough to avoid clogging up the lungs but large enough to avoid being exhaled. Such a method of administration allows the direct delivery of insulin molecules to the blood stream without undergoing degradation. A few studies have been done to test the potential use of ceramic nanoparticles (calcium phosphate) as drug delivery agents.Porous hydroxyapatite nanoparticles havealso been tested for intestinal delivery of insulin.Porousinical studies in guinea pig lungs with insulin loaded PLGA nanospheres demonstrated a significant reduction in blood glucose level with a prolonged effect over 48 hours when compared to insulin solution. Insulin-loaded poly (butyl cyanoacrylate) nanoparticles, when delivered to the lungs of rats were shown to extend the duration of hypoglycemic effect over 20 hours when compared to pulmonary administration of insulin solution. The major factors limiting the bioavailability of nasally administered insulin include poor permeability across the mucosal membrane, rapid mucociliary clearance mechanism that removes the non-mucoadhesive formulations from the absorption site. To overcome these limitations, mucoadhesive nanoparticles made of chitosan/tripolyphosphate and starchhas been evaluated. These nanoparticles showed good insulin loading capacity, providing the release of 75–80% insulin within 15 minutes after administration.

Liposomes based drug delivery system

Liposomes are small vesicles, consist of one or more phospholipid bilayers that are produced from natural non-toxic phospholipids and cholesterol. These are the innovative technology and promising systems to serve as a transporter for the active molecules to the site of action within the biosystem. The increase usage of liposome in investigational system as well as commercially drug-delivery system is mostly because of their biodegradability, biocompatibility, and low toxicity to entrap both lipophilic and hydrophilic drugs, and also facilitate the site-specific/ targeted delivery of drug. Thus, a lot of studies have been conducted on liposomes to decrease drug toxicity and target specific cells for improved efficacy and safety. Due course of delivery of lipid materials, the liposome fused with the cellular lipid membrane followed by release of liposomal content into the cytoplasm of the cell to produce its pharmacological action.

In a research Zhang et al. investigated the capability of liposome modified with targeted ligand biotin (BLPs) to facilitate transportation of insulin through oral delivery, simultaneously investigated its cytotoxicity. By incorporation of biotin-1,2-distearoyl-sn-glycero-3-phosphatidylethanolamine (DSPE) into the lipid bilayer of liposome, BLPs had been produced. The physiochemical properties of insulin-loaded liposomes have been affected by particle size and entrapment efficiency (EEf). The author has found out that lipid:cholesterol ratio of 3:1 appeared to have potential effect on holding more insulin in liposomes, with desirable membrane fluidity and decreased chances of insulin leakage from internal aqueous compartments. Apart from this, hypoglycemic effect was found to be affected by the biotin-DSPE proportion in liposomes, particle size of liposomes and also doses of the formulation. However, significant hypoglycemic effect was noticed with 153.7 nm liposomes which can further be described due to improved stability of liposomes for smaller diameter.

Micelle and Polymer based drug delivery system

Polymeric micelles are formed by self-assembled amphiphilicco-polymers via aggregation into a core–shell micellar structure when its concentration reached the critical micellar concentration. The outer hydrophilic layer forms the shellto provide protection and functional groups for further micelle modification. Meanwhile, the hydrophobic moietyforms the core of micelles where hydrophobic drugs can beloaded. Nowadays, most of the drug delivery fieldshave been widely applying self-assembled polymeric micellesfrom amphiphilic polymers due to their enhanced pharmacokinetics, bio-distributions as well as preventing protein degradation by enzymes.

As we have discussed earlier, instability of pharmaceuticalformulations is closely associated with the aggregation of insulin. Various modern techniques, viz. circular dichroism,turbidity assay, bis-ANS binding assay, MALDI-TOF MS,thioflavin-T (ThT) binding assay and agarose gel electrophoresis have been adopted by Fang et al. in their study, where theauthors determine the reconversion efficacy to the native configuration on DTT-denatured insulin by the PEG-PEmicelle. The results revealed that PEG-PE micelle have a negative charged-layered hydrophilic nano-cage-like structurewhich is able to prevent aggregation by capturing insulin Aand B chains induced by DDT and interfering hydrophobicinteraction. The reduced insulin A and B chain in the nanocage are also able to recognize each other and 30% of nativeinsulin is formed as measured by hypoglycemic activity analysis in mice. Finally the authors concluded that PEG-PEmicelle is a potential artificial chaperone for in vivo andin vitro protein refolding.

On the other hand, micelles with stimuli responsive functional units on the surface can work as cargo which onlyresponds to specific stimulus signal. Through the smart-cargo-release behavior approach, the efficiency of therapycould be increased whereas the side effects can be reduced.With theconcept of glucose oxidase catalyzed glucose degradation,the insulin and glucose oxidase were co-loaded with thenanomicelles. From the developed formulation, insulin was released rapidly due to the glucose variation in the microenvironment. The tertiary amine groups in PDPA blocks were protonated and caused the expansion of hydrophobic PDPA core which will eventually speed up the release of cargo from the carrier explained the mechanism of rapid cargo release induced by pH. Overall, these micelles may be considered to be applied for the delivery of insulin.

It has been reported by Andrade et al. that amphiphilic polymers such as PluronicF68, PluronicF108, PluronicF127 and Soluplus were extensively applied on the production of lyophilized formulations to deliver insulin viainhalation. The researcher has been

widely studied phenyl boronic acid (PBA)-based polymer in the management of diabetes patients due to its potential applications-responsiveinsulin delivery. Thus to utilise the effectiveness of PBA, a formulation was experimented, although affecting the in vitro release of insulin form micelles; thus, PBA was found not toconfer any glucose-sensitive properties to formulations. Conversely, results have shown that powders for inhalation aremore advantages delivery system compared to liquid formations due to their higher long-term stability, improved patientcompliance since these are only breath-actuated as well as absence of gas propellants. However, powders contain certainproperties including density, size and shape of particles thatwould influence the particles aerosolization and depositioncharacteristics. However, authors determined that the compatibility of powders with aerodynamic diameter <6 mm havegood deposition in the lungs and the in vitro toxicity for respiratory cell lines was not significant. Overall, the formulationsbased on polymeric micelles have shown potential propertiesto develop insulin delivery by inhalation in the future.

Keeping in view, a novel drug delivery system using PBA-based glucose-responsive has been improved by decreasingthe apparent pKa for application in the physiological pH,which lead to the improvement of the rate of responsivenessfor self-regulated drug release, enhancing its responsivenesstowards uncontrolled blood glucose level. Thus, anotherglucose-responsive complex micelles were synthesized byself-assembly of a PBA-containing block copolymer PEG-b-poly(aspartic acid-co-aspartamidophenylboronic acid) (PEG-b-P(Asp-co-AspPBA)) and a PAsp-based glycopolymer poly (aspartic acid-co-aspartglucosamine) P(Asp-co-AGA) by Yanget al. Interestingly, the results in the PBA based complexmicelles displayed response to the glucose level under physiological pH 7.4 with 2 gL-1 glucose which is the condition of hyperglycemia. This indicated that the external glucose concentration was the main contributing factor that decide therelease of insulin from the complex micelles. Further, presence of PEG shell contributed towards advantage of stability against aggregation. Furthermore, the self-assembly of the two polymers with a hydrophilic P(Asp-co-AGA)/P(Asp-co-AspPBA) core enabled faster response to control higher circulating glucose at neutral pH. However, better glucose sensitivity was obtained by decreasing the apparent pKa of the PBA/AGA complex. Most importantly, the poly(aspartic acid)-based polymers together with the glycosyl moieties that utilized in the system has ensured that the PBA-based complexmicelles to have a good biodegradability and biocompatibility.Shortly, this type of complex micelle is hope to be a potential candidate for self-regulated insulin delivery in the management of diabetes patients. Finaly, micelle based nanocarriers are also found to be a developing field of peptide delivery for the protection of molecular structure of the peptides, which could be project towards control of high glucose level in diabetic patients.

These micelle could also found to be an important delivery to control the release of incorporated drug inside the microenvironment based on increased glucose level after food ingestion of food, as well as due to change in plasmaphysiological pH, thus it will mimic the role of b-cells of langerhans of pancreas in the control of hyperglycemia.

Dendrimers

Dendrimers are unimolecular, monodisperse, micellar nanostructures, around 20 nm in size, with a well-defined, regularly branched symmetrical structure and a high density of functional end groups at their periphery. The structure of dendrimers consists of three distinct architectural regions as a focal moiety or a core, layers of branched repeat units emerging from the core, and functional end groups on the outer layer of repeat units. They are known to be robust, covalently fixed, three dimensional structures possessing both a solvent-filled interior core (nanoscale container) as well as a homogenous, mathematically defined, exterior surface functionality. Dendrimers are generally prepared using either a divergent method or a convergent one with an architecture like a tree branching out from a central point.

Dendrimeric vectors are most commonly used as parenteral injections, either directly into the tumor tissue or intravenously for systemic delivery. Dendrimers used in drug delivery studies typically incorporate one or more of the followingpolymers: polyamidoamine (PAMAM), melamine,poly L-glutamic acid(PG), polyethyleneimine (PEI), polypropyleneimine (PPI), and polyethylene glycol (PEG), Chitin. Dendrimers may be used in two major modalities for targeting vectors for diagnostic imaging, drug delivery, gene transfection also detection and therapeutic treatment of cancer and other diseases, namely by (1) passive targeting-nanodimension mediated via EPR (enhanced permeability retention) effect involving primary tumor vascularization or organ-specific targeting and (2) active targeting-receptor-mediated cell-specific targeting involving receptor-specific targeting groups There are several potential applications of dendrimers in the field of imaging, drug delivery, gene transfection and non-viral gene transfer.

Solid lipid nanoparticles (SLNs)

SLNs mainly comprise lipids that are in solid phase at the room temperature and surfactants for emulsification, the mean diameters of which range from 50 nm to 1000 nm for colloid drug delivery applications. SLNs offer unique properties such as small size, large surface area, high drug loading, the interaction of phases at the interfaces, and are attractive for their potential to improve performance of pharmaceuticals, neutraceuticals and other materials. The typical methods of preparing SLNs include spray drying high shear mixing, ultra-sonication, and high pressure homogenization (HPH). Solid lipids utilized in SLN formulations include fatty acids (e.g. palmitic acid, decanoic acid, and behenic acid), triglycerides (e.g. trilaurin, trimyristin, and tripalmitin), steroids (e.g. cholesterol), partial glycerides (e.g. glyceryl monostearate and gylceryl behenate) and waxes (e.g. cetyl palmitate). Several types of surfactants are commonly used as emulsifiers to stabilize lipid dispersion, including soybean lecithin, phosphatidylcholine, poloxamer 188, sodium cholate, and sodium glycocholate.

Advantages of these solid lipid nanoparticles (SLN) are the use of physiological lipids, the avoidance of organic solvents in the preparation process, and a wide potential application spectrum (dermal, oral, intravenous). Additionally, improved bioavailability, protection of sensitive drug molecules from the environment (water, light) and controlled and/or targeted drug release, improved stability of pharmaceuticals, feasibilities of carrying both lipophilic and hydrophilic drugs and most lipids being biodegradable. SLNs possess a better stability and ease of upgradability to production scale as compared to liposomes.

Other nanoparticulate systems for insulin delivery and for the treatment of diabetesassociated symptoms

Other than the ceramic and polymeric nanoparticles, gold nanoparticles have also been tested as insulin carriers. Gold nanoparticles synthesized with chitosan as a reducing agent were tested as a carrier for insulin. The nanoparticles showed long term stability in terms of aggregation and good insulin loading of 53%. Use of chitosan served dual purpose by acting as a reducing agent in the synthesis of gold nanoparticles and also promoted the penetration and uptake of insulin across the oral and nasal mucosa in diabetic rats. The study concluded that oral and nasal administration of insulin loaded chitosan reduced gold nanoparticles improved pharmacodynamic activity of insulin. Dextran nanoparticles-vitamin B12 combination has been tested to overcome the gastro intestinal degradation of vitamin B12-peptide/protein drug conjugates. These nanoparticles were found to protect the entrapped insulin against gut proteases. Dextran nanoparticles- vitamin B12 combination showed a release profile that was suitable for oral delivery systems of insulin.Diabetes causes a lot of systemic complications. The associated conditions are inflammatory diseases of skin and gums, diabetic retinopathy (eyes), diabetic neuropathy (nervous system), heart diseases, kidney diseases, delayed wound healing, etc. Nanoparticulate systems have also been tested for the treatment of these associated conditions. Nanoparticle based ocular drug delivery systems have been already described in the past decade. The recent years have seen the advancement in application of nanoparticles made of polyacrylic acid, polylactide and chitosan for ophthalmic drug delivery. The scientific community is working towards utilizing nanoparticle-based drug delivery systems in the treatment of diabetes-associated complications.

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