A REVIEW: POLYELECTROLYTE POLYSACCHARIDES NANOPARTICLES ON DIABETIC MELLITUS

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ABSTRACT

Diabetes mellitus is a group of metabolic disorder in which a person has high blood sugar because either the body does not produce enough insulin or because cells do not respond to the insulin. Targeted drug delivery for the treatment of Diabetes using nanotechnology is one of the recent advances in nanomedicine. Polymeric nanoparticles, either natural or synthetic have been used as matrices for oral antidiabetic drug delivery. Natural polysaccharides, due to their outstanding merits, have received more and more attention in the field of drug delivery systems. In particular, polysaccharides seem to be the most promising materials in the preparation of nanometeric carriers. The natural polyelectrolyte polysaccharides polymers mainly used for oral anti diabetic drug delivery, positive polyelectrolyte polysaccrides is widely explored owing to its ease of chemical modification and favorable biological properties. In addition, many advantages such as safety, biodegradability, widespread availability and low cost justify the continuing development of promising hypoglycemic drug delivery system. This manuscript palpably discusses the polyelectrolyte polysccrides polymeric nanoparticles drug delivery systems in the treatment of diabetes.

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INTRODUCTION:

Diabetics has become a worldwide pandemic effected approximately 160 million individuals in the world in 2000 and are expected to rise to 370 million individuals in 2030 which is about 50% increase over 30 years in the number of individuals suffering from diabetes [1]. The disease results from the body's inability to regulate blood glucose levels with insulin, the hormone responsible for cell uptake and storing of glucose (**Fig 1**). It occurs in two main forms. The first is classified as type 1 Insulin dependent mellitus (IDDM) or Juvenile-onset diabetes. In this type of diabetes there is an absolute lack of insulin and it begins in late childhood (8–12 years) but it can occur at any age. Diabetes in this category is managed on diet and insulin is slightly different, whereby β cells in the pancreas do not produce insulin due to autoimmune reactions against insulin. The second type is classified as Type 2, non-insulin dependent diabetes mellitus (NIDDM) or maturity onset diabetes. One of the major pathophysiological features of type 2 diabetes is insulin resistance in peripheral tissues; that is, lack of insulin effects despite hyperinsulinaemia. Majority of patients in this class are obese. Common symptoms of diabetes include increased risk for various disorders including hypertension, dyslipidemia, coronary heart disease, and metabolic disorders among many others. Control of blood sugar level through modified dietary sugar intake, physical exercise, insulin therapy and oral medications have been advised for control of Type 2 diabetes mellitus [2].

Nanomedicine research over the past few decades have been aimed at the applications of nanoparticles for diabetes mellitus treatment through effective Drug delivery.
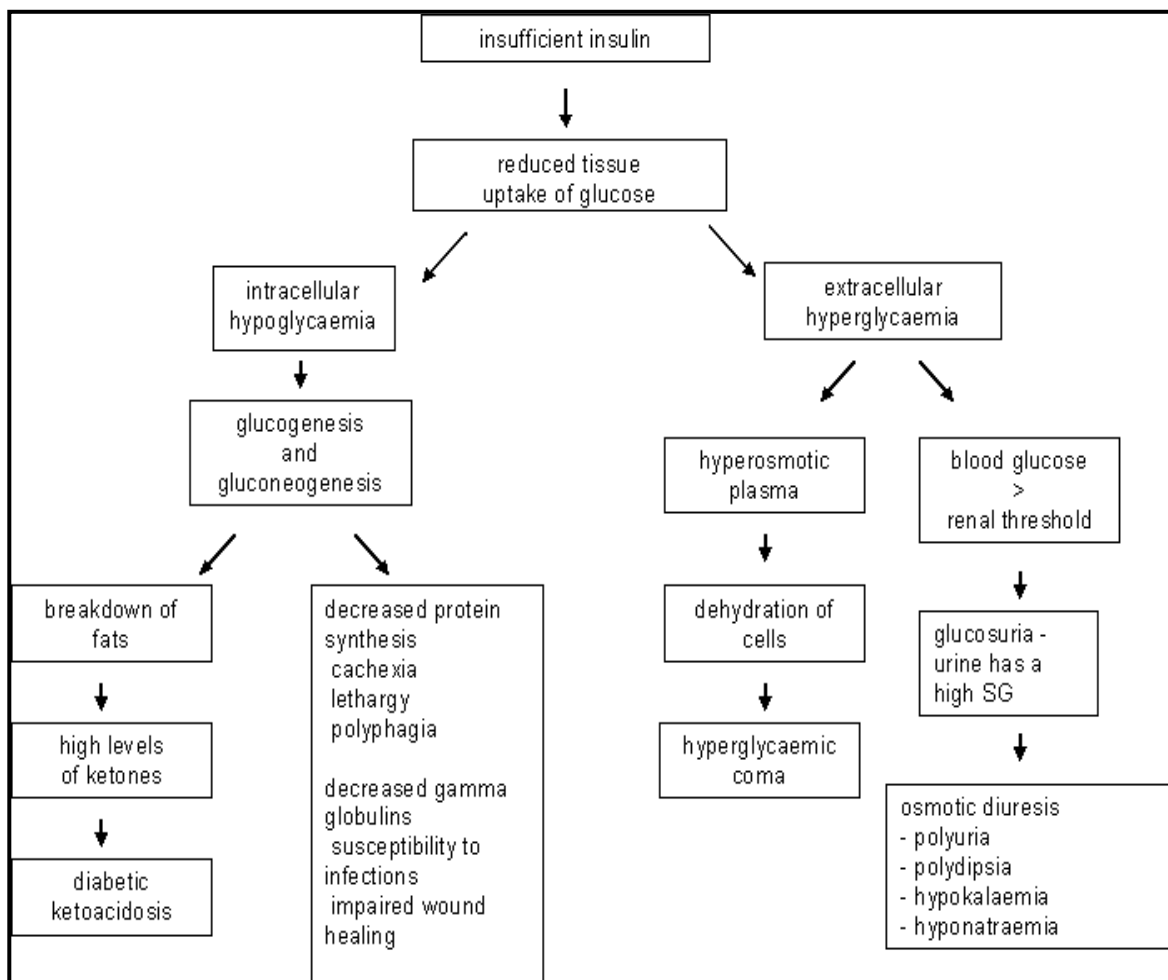

Fig-1: Pathophysiology of diabetic mellitus

NANOTECHNOLOGY

The field of nanotechnology has been undergoing tremendous development in the recent decade. Nanotechnology plays the key roles in the development of various scientific disciplines such as electronics, material science, space research and robotics. Nanotechnology is expected to make major advances in mainstream biomedical applications, including the areas of gene therapy, imaging and novel drug discovery and drug delivery in the treatment of diseases like diabetes, cancer, etc [3].

Nanoparticles in drug delivery:

Nanoparticle drug delivery systems have outstanding advantages (1) they can pass through the smallest capillary vessels because of their ultra-tiny volume and avoid rapid clearance by phagocytes so that their duration in blood stream is greatly prolonged (2) they can penetrate cells and tissue gap to arrive at target organs such as liver, spleen, lung, spinal cord and lymph (3) they could show controlled release properties due to the biodegradability, pH, ion and/or temperature sensibility of materials (4) they can improve the utility of drugs and reduce toxic side effects etc. As drug delivery system, nanoparticles can entrap drugs or biomolecules into their interior structures and/or absorb drugs or biomolecules onto their exterior surfaces.

Presently, nanoparticles have been widely used to deliver drugs, polypeptides, proteins, vaccines, nucleic acids, and genetic materials (**Fig-2**). Over the years, nanoparticle drug delivery systems have shown huge potential in biological, medical and pharmaceutical applications. Currently, the researches on nanoparticle drug delivery system focus on: (1) the selectness and combination of carrier materials to obtain suitable drug release speed (2) the surface alteration of nanoparticles to improve their targeting ability (3) the optimization of the preparation of nanoparticles to increase their drug delivery capability, their application in clinics and the possibility of industrial production (4) the investigation of *in vivo* dynamic process to disclose the interaction of nanoparticles with blood and targeting tissues and organs, etc[4].
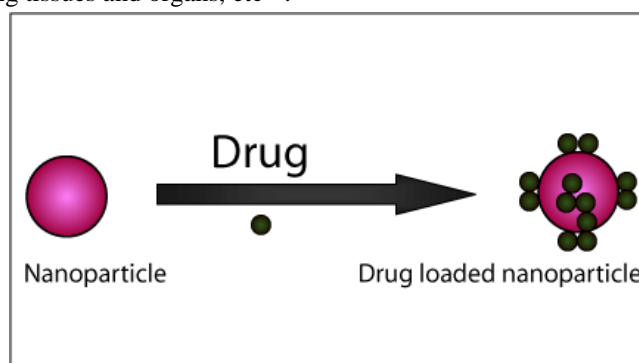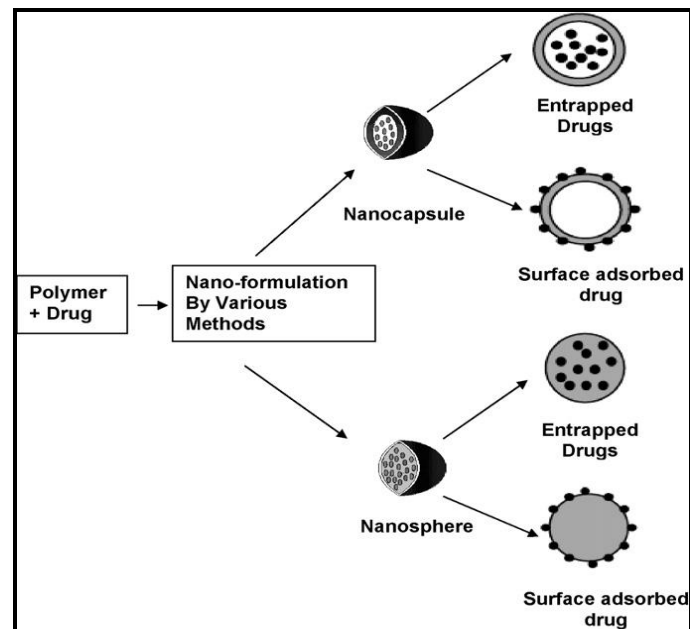

Fig-2: Nanoparticles on drug delivery

Polymeric nanoparticles on drug delivery:

Polymeric nanoparticles made from natural and synthetic polymers have received the majority of attention due to their stability and ease of surface modification (**Fig-3**). Polymeric materials used for preparing nanoparticles for drug delivery must be biocompatible and biodegradable best. The polysaccharides are the most popular polymeric materials to prepare nanoparticles for drug delivery. **Fig-3:** Biodegradable nanoparticles are classified as nanocapsule, and nanosphere. The drug molecules are either entrapped inside or adsorbed on the surface.

In recent years, a large number of studies have been conducted on polysaccharides and their derivatives for their potential application as nanoparticle drug delivery in the treatment of diabetics. The number of polysaccharides that have been investigated for the preparation of nanoparticles suitable as delivery systems is extremely large. As a result, attention has been focused on the latest studies and exploitations related to such systems, including some of the most used polysaccharides, a concise description of their structural features and their influence in drug delivery on diabetic mellitus [5].

Table-1: nanoparticles application in life sciences

Particle class	Material	Application
Natural materials or derivatives	Alginate Chitosan Dextran gelatin Liposome starch	Drug/gene delivery
Dendrimers	Branched polymers	Drug delivery
Fullerenes	Carbon based carriers	Photo dynamics Drug delivery
Polymer carriers	Poly lactic acid Poly acylates Polyethyleinemine Block copolymers polycaprolactone	Drug/gene delivery

POLYELECTROLYTE POLYSACCHARIDE
        Polysaccharides are the polymers of monosaccharide. In nature, polysaccharides have various resources from algal origin (e.g. alginate), plant origin (e.g. pectin, guar gum), microbial origin (e.g. dextran, xanthan gum), and animal origin (chitosan, chondroitin). Polysaccharides have a large number of reactive groups, a wide range of molecular weight, varying chemical composition, which contribute to their diversity in structure and in property. From the viewpoint of polyelectrolyte, polysaccharides can be divided into polyelectrolytes and non-polyelectrolytes; the former can be further divided into positively charged polysaccharides (chitosan) and negatively charged polysaccharides (alginate, heparin, hyaluronic acid, pectin, etc.) [6].

Merits of Polyelectrolytes Polysaccharides (PEP):
        Polyelectrolytes Polysaccharides have various derivable groups on molecular chains; polysaccharides can be easily modified chemically and biochemically, resulting in many kinds of polysaccharide derivatives. As natural biomaterials, polysaccharides are highly stable, safe, non-toxic, hydrophilic and biodegradable. In addition, Polyelectrolyte Polysaccharides have abundant resources in

nature and low cost in their processing. Particularly, most of natural polysaccharides have hydrophilic groups such as hydroxyl, carboxyl and amino groups which could form non-covalent bonds with biological tissues to forming bioadhesion. For example, alginate chitosan, pectin, and so on are good bioadhesive materials.

Nanoparticle carriers made of bioadhesive polysaccharides could prolong the residence time and therefore increase the absorbance of loaded drugs. All these merits endow Polyelectrolytes Polysaccharides a promising future as biomaterials. For the application of these naturally occurring polysaccharides for drug carriers, issues of safety, toxicity and availability are greatly simplified. In recent years, a large number of studies have been conducted on polysaccharides and their derivatives for their potential application as nanoparticle drug delivery systems [7].

Chitosan:

Chitosan (CS) is abundant naturally occurring polysaccharide. Chitosan is made of randomly distributed *β*-(1-4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit) (**Fig-3**). It is produced by deacetylation of chitin extracted from shells of crabs, shrimps and krill. Commercially available chitosan is deacetylated between 66 and 95% and has an average molecular weight between 3.8 and 2000 kDa.
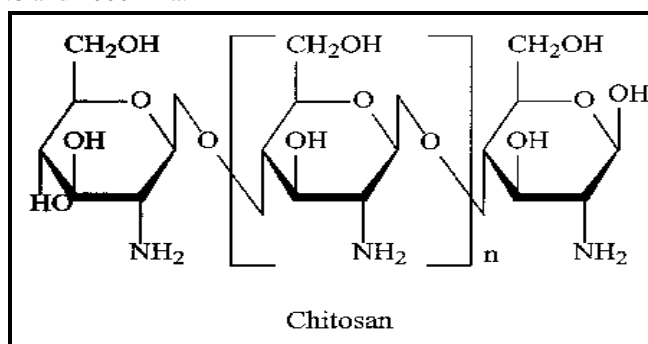

Fig-3: chemical structure of Chitosan

Chitosan is linear, hydrophilic, positively charged and has mucoadhesive property. It is an excellent biopolymer for preparation of microparticles and nanoparticles owing to its excellent biocompatibility and biodegradability. *In vivo*, it is degraded by lysozyme[8]. In addition, the amino groups confer to the molecule a high charge density and are readily available for chemical reactions and salt formation with acids. Chitosan is soluble in various acids, can also interact with polyions to form complexes and gels. These properties are exploited in the fabrication of nanoparticles based either on the spontaneous formation of complexes between chitosan and polyions including DNA or on the gelation of a chitosan solution dispersed in a water-in-oil emulsion [9].

Merits of Chitosan:

Chitosan is a biopolymer is accepted as a biodegradable and non toxic polymer. Despite its biocompatibility, the applications of chitosan are limited due to its insolubility above pH6. Chitosan is a weak base and it is insoluble in water and organic solvents. However, it is soluble in diluted aqueous acidic solution (pH <6.5) which can convert the glucosamine units into a soluble form with protonated amine groups [10]. It is possible to increase the solubility of chitosan in water removing one or two hydrogen atoms from the amino groups of chitosan, and introducing some hydrophilic segments [11]. The non-toxic, biodegradable and biocompatible properties of Chitosan provide potential for many applications. Chitosan is polyelectrolyte nature, can be used in pharmaceutical and biomedical fields for the Delivery of Nanoparticles biocompatibility and biodegradability. It has been assayed as biomaterial for wound healing and prosthetic material, since it can be biodegraded by enzyme action [12]. Also it is reported to find applications as an antimicrobial compound, as a drug in the treatment of hyper bilirubinemia and hyper cholesterolaemia and, also, it has been prepared and evaluated for its anti-tumor activity carrying several anti-neoplastic agents.

Chitosan carrier in nano drug delivery system:

In the field of nanomedicine, Chitosan has attracted attention as a matrix for controlled release due to its reactive functionalities, polycationic character, easily degradation by enzymes and non-toxic degradation products. Over the years, a variety of natural and synthetic polymers have been explored for the preparation of drug-loaded microparticles and chitosan has been extensively investigated [13]. Hydrophobic modification character of CS (**Fig-4**) can be increased by covalent attachment of hydrophobic excipients. Hydrophobic interactions are believed to enhance the stability of substituted CS by reducing the hydration of the matrix thereby resisting the degradation by gastric enzymes[14].

Fig-4: Chitosan derivatives
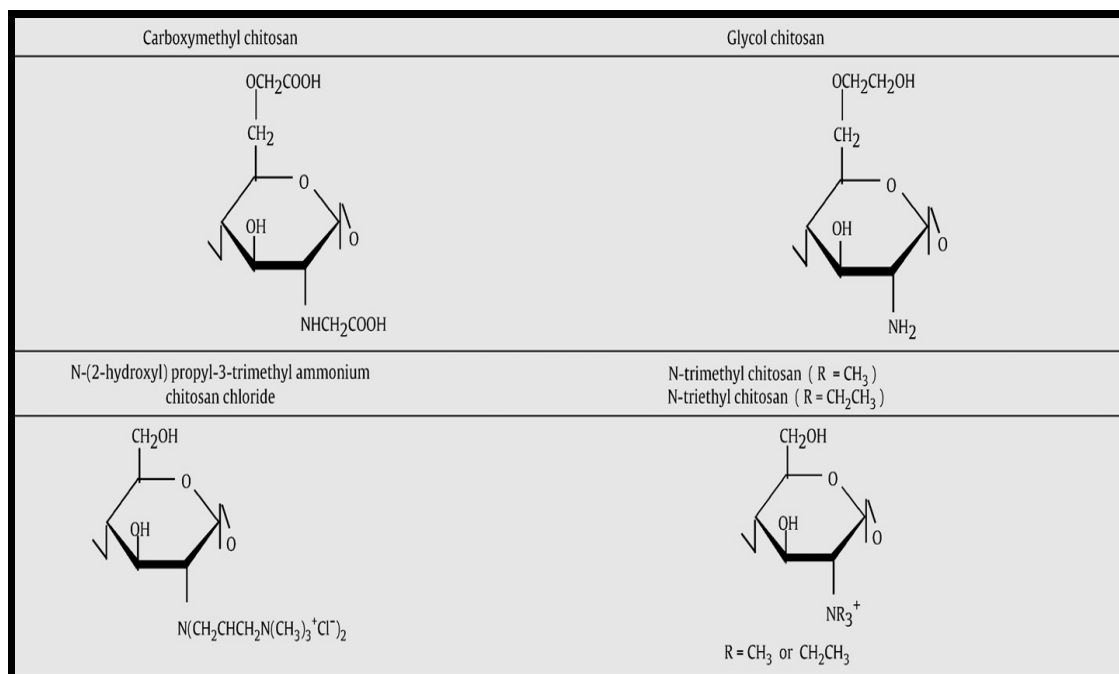
Laurylsuccinyl chitosan:

Laurylsuccinyl chitosan (LSC) particles were found to be highly mucoadhesive, which could be due to the hydrophobic interaction of lauryl groups to the hydrophobic domains of mucosa in addition to its negative Z potential. The strong mucoadhesion of LSC particles might help in the direct delivery of insulin to the intestinal cell surface, thus reducing the susceptibility to the enzymatic degradation and thereby improving the bioavailability [15]. The bioadhesive property of CS can be enhanced by N-acylation with fatty acid chlorides. Fatty acids act primarily on the phospholipids component of the membrane thereby creating disorder and leading to increased permeability. Compared to the CS modified with short chain fatty acids, CS modified with higher fatty acids (e.g. oleoyl chloride) showed better mucoadhesion property [16,17]. From these studies it seems that hydrophobically modified CS will be an interesting system for oral insulin delivery.

Thiolation:

Thiolated chitosans are gaining popularity because of their high mucoadhesiveness and extended drug release properties [18]. Thiolation can be achieved by the immobilization of thiol bearing moieties on the polymeric backbone of CS. Mucoadhesiveness of thiolated polymers is due to the formation of disulfide bonds with cysteine rich sub domains of mucus glycoprotein[19]. The permeation of paracellular markers through mucosa can be enhanced by utilizing thiolated instead of unmodified CS. In addition, thiolated chitosan display *in situ* gelling features. The permeation-enhancing effect seems to be based on the inhibition of protein tyrosine phosphatase, resulting in an opening of the tight junctions for hydrophilic macromolecules. This theory is supported by various *in vitro* and *in vivo* studies where significantly improved pharmacological efficacy and/or bioavailability of insulin were demonstrated [20].

Polyelectrolyte complex formation:

Polyelectrolyte complex formation developed by mixing oppositely charged ions; provide an inexpensive, biocompatible, versatile alternative system to current polymeric delivery strategies that apply organic solvents as reaction environments [21]. The biodistribution study in a rat model showed that some of the orally administered CS polyglutamic acid NPs was retained in the stomach for a long duration, which might lead to the disintegration of NPs and degradation of insulin [22]. To overcome these problems, NPs were freeze dried and filled in an enteric-coated capsule. Upon oral administration, the enteric-coated capsule remained intact in the acidic environment of the stomach, but dissolved rapidly in the proximal segment of the small intestine. Consequently, all the NPs loaded in the capsule were brought into the small intestine, thus enhancing the intestinal absorption of insulin and providing a prolonged reduction in blood glucose levels.

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Trimethyl chitson:

CS is not a suitable carrier for targeting protein drugs to specific sites of the intestine owing to the poor solubility at physiological pH values. Trimethyl chitson (TMC) are drastically more soluble in neutral and alkaline environments of the intestine and hence are more efficient than CS for drug delivery and absorption across the intestinal epithelium. These derivatives are being extensively studied for oral insulin delivery [23]. The permeation-enhancing properties of these CS derivatives have been attributed to the ionic interactions with the tight junctions and cellular membrane components to increase the paracellular permeation of hydrophilic compounds. It was reported that N-[2-hydroxyl] propyl-3-trimethyl ammonium Chitosan chloride, a quaternized derivative of CS could improve the mucoadhesivity owing to the presence of positive charge and hydroxyl functional group on the side chain [24].

Chitosan-inhibitor conjugates

CS, due to its chelating ability with divalent metal ions is expected to inhibit protease degradation. Chelation of calcium further activates protein tyrosine kinases, which ultimately leads to the opening of tight junctions across the intestinal epithelium. Enzyme inhibitors conjugated directly to CS might improve drug bioavailability by localizing the inhibitory effect to the site of drug uptake, as well as by reducing toxicity. The use of such chitosan-inhibitor conjugates may represent a valuable approach to improve protection from drug degradation and achieve more effective oral drug delivery. Recently, Su et al. reported that the immobilization of complexing agents, such as diethylenetriamine pentaacetic acid (DTPA) on CS/ gPGA nanoparticles could significantly enhance the absorption of insulin throughout the entire small intestine, subsequently producing a significant and prolonged hypoglycemic effect [25].

Alginate:

Alginate is a biopolymer and a polyelectrolyte considered to be biocompatible, non-immunogenic, non-toxic and biodegradable, and the composition of the polymer has been reported to affect to its applications. Alginate with high content of guluronic acid block can produce, in the form of calcium salts, cross-links stabilizing the structure of the polymer in a rigid gel form (**Fig-5**). This properly enables alginate solutions to be processed into the form of films, beads and sponges. However, high mannuronic acid alginate capsules are interesting for cell transplantation and for biohybrid organs, because of their less viscosity. In the case of cellular response, some research groups found immunostimulatory activity caused by those alginates with high mannuronic acid content, and immunosuppressive activity caused by alginates with high guluronic acid content.
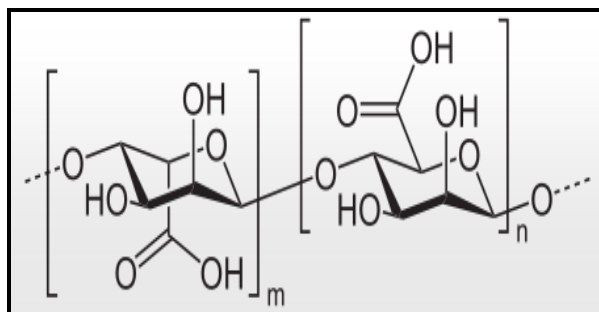

Fig-5: Chemical structure of alginate.

Alginate carrier in nano drug delivery system:

In case of its applications in nanomedicine, alginate has also been extensively investigated as a drug delivery device in which the rate of drug release can be modified by varying the drug polymer interaction, as well as by chemical immobilization of the drug in the polymer backbone using the reactive carboxylate groups [26]. Moreover alginate mucoadhesive and biodegradable and, consequently, it can be used in the preparation of controlled drug-delivery systems achieving an enhanced drug bioavailability [27]. Oral administration of lipoinsulin loaded alginate-chitosan capsules was found to reduce blood glucose level in diabetic rats. Owing to the bioadhesive property of alginate, alginate coated lipoinsulin might anchor the lipoinsulin to the intestinal tract or increase the transit time of the formulation [28]. Thus, the intimate contact with mucosa might help efficient absorption with increased bioavailability of insulin Therefore, the biocompatibility; availability and versatility of this polysaccharide make it an important and hopeful tool in the field of nanomedicine, especially in the preparation of nanoparticulate drug delivery systems.

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Hyaluronic acid:

Hyaluronic acid (HA) also called sodium hyaluronic or hyaluronan is a polysaccharide with a structure composed of repeating disaccharide units of D-glucuronic acid and Nacetyl D-glucosamine linked by β (1-3) and β (1-4) glycosidic bonds (**Fig-6**) [29].

HA can be modified in many ways to alter the properties of the resulting materials, including modifications leading to hydrophobicity and biological activity. There are three functional groups that can be chemically modified the glucuronic acid carboxylic acid, the primary and secondary hydroxyl groups, and the N-acetyl group [30]. HA has a molecular weight that can reach as high as 107Da [31]. It is a biodegradable, bioactive, non immunogenic, non cytotoxic and negatively charged polysaccharide that has been associated with several cellular processes, including angiogenesis and the regulation of inflammation [32]. HA nanoparticles significantly enhanced insulin transport through the duodenum and ileum. Diabetic rats treated with oral insulin-loaded HA nanoparticles also showed stronger hypoglycemic effects than insulin solution. Therefore, these HA nanoparticles could be a promising candidate for oral insulin delivery [33].
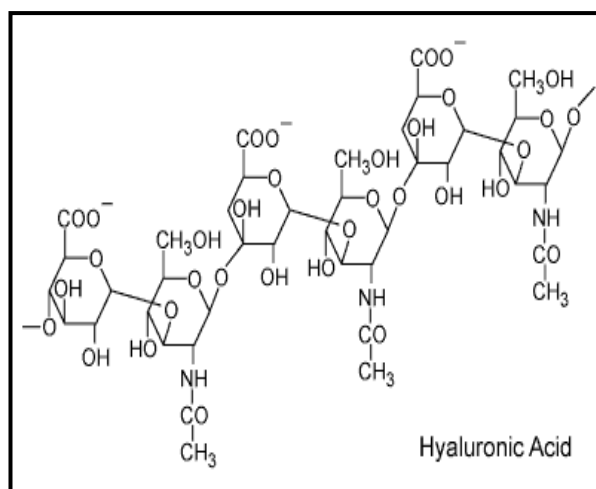

Fig-6: Chemical structure of Hyaluronic acid

Dextran:

Dextran is a polysaccharide made of many glucose molecules composed of chains of varying lengths (**Fig-7**). It has a substantial number of α [1→6] glucosidic linkage in its main chain, and a variable amount of α [1→2], α [1→3] and α [1→4] branch linkages [34]. The degree and type of branching will be determined by the bacterial strain that synthesizes it. Its average molecular weight is as high as 107-108 Da but can be reduce by acidic hydrolysis obtaining molecular weight fractions that also can interest. Dextran is neutral, water soluble, biocompatible and biodegradable.
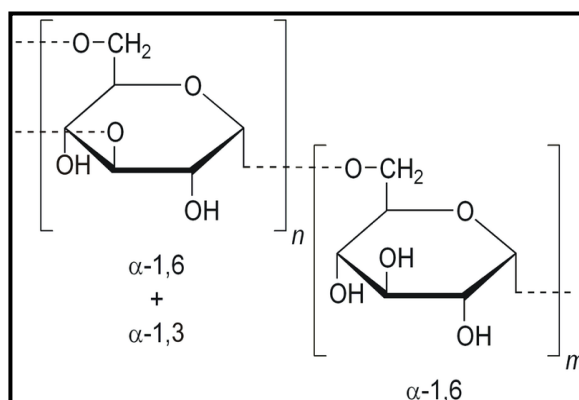

Fig-7: Chemical structure of Dextran

Dextran nanoparticulate systems:

Dextran has wide applications in different areas such as pharmaceutical, chemical, clinical, and food industry. Dextran and its derivatives have potential application for the preparation of modified drug delivery. This negative polyelectrolyte polysaccharide been used to prepare nanoparticulate systems as a carrier, but also it has been employed to cover these systems. It seems that dextran is a very useful tool in the field of nanomedicine, showing also good bioavailavility, biocompatibility and biodegradability, being selected by a lot of researchers as biomaterial in the preparation of nanosystems [35].

The biphasic behaviour of the hypoglycemic effect might be presumed to the diurnal effects feed intake, glucose metabolism and insulin release from the crosslinked cores. The prolonged anti-diabetic activity for many hours might be pre-summed to the possibility that Vitamin-B_{12} dextran system might be trapped at glucose utilizing organs, where either intact conjugate is slowly internalized or releases free insulin. NPs with the low degree of cross-linking were found to be superior carriers, and were more effective with Vitamin B_{12} derivatives of carbamate linkage. The pharmacological availability of carbamate linked Vitamin-B_{12} derivatives was found to be 29.4%, which was superior compared with NP conjugate of ester linked Vit-B_{12} (1.5-fold) and relatively higher cross linked particles [1.1-fold]. These nanoparticle carriers demonstrated a similar oral insulin efficacy in congenital diabetic mice. Significant quantities of plasma insulin were found in both animal models [36].

Pullulan:

Pullulan is a linear bacterial homo polysaccharide produced from starch by the fungus *Aureobasidium pullulans*. The backbone is formed by glycosidic linkages between α-(1→6) D glucopyranose and α-(1→4) D-glucopyranose units into 1:2 ratios (**Fig-8**). The molecular weight of pullulan ranges from thousands to 2,000,000 Da depending on the growth.

The backbone structure of pullulan tends to behave as a random expanded flexible coil in aqueous solution with modelling studies suggesting that this flexibility is imparted by the α- (1→6)linkage. This could be the reason why pullulan is biodegradable and has high adhesion, structural flexibility and solubility [37]. Pullulan is hemocompatible, non-immunogenic, non-carcinogenic; FDA approved it for a variety of applications. The study of nanogels has been intensified over the last decade due to related potential applications in the development and implementation of new environmentally responsive or smart materials, biomimetics, biosensors, artificial muscles, drug delivery systems and chemical separations [38].
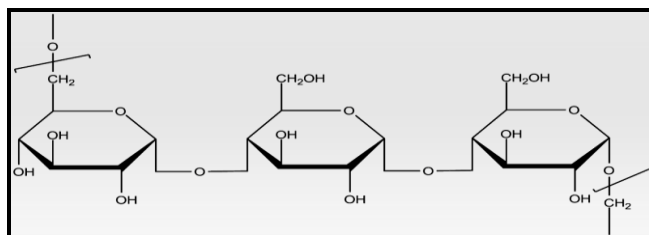

Fig-8: Chemical structure of Pullulan

Pullulan in nano drug delivery systems:

In order to obtain nanostructures that may act as carriers of different drugs, the backbone structure of pullulan is modified with hydrophobic molecules, resulting in a molecule of hydrophobized pullulan that self-assembles in water solutions. Cholesterol, hexadecanol or Vitamin-H is some molecules that are attached to the structure of pullulan in order to obtain micelles in water solution [39]. The thermo-responsiveness of the nanoparticles was related to the partial dehydration of the hydrophobized pullulan upon heating. Insulin was incorporated into the cholesterol-pullulans nanoparticles. The thermal denaturation and subsequent aggregation of insulin were effectively suppressed upon complexation onto the nanoparticles. The complexed insulin was significantly protected from enzymatic degradation. The original physiological activity of complexed insulin was preserved *in vivo* after *i.v*. injection [40, 41].

Guar gum:

Guar gum is a water soluble polysaccharide extracted from the seeds of *Cyamopsis tetragonoloba*, which belongs to Leguminosae family. Also called guaran, it is a non-ionic natural polysaccharide derived from the ground endosperm of guar beans. Its backbone consists of linear chains of (1 → 4)-β-D-mannopyranosyl units with α-D-galactopyranosyl units attached by (1 → 6) linkages, (**Fig-9**) forming short side-branches [42].
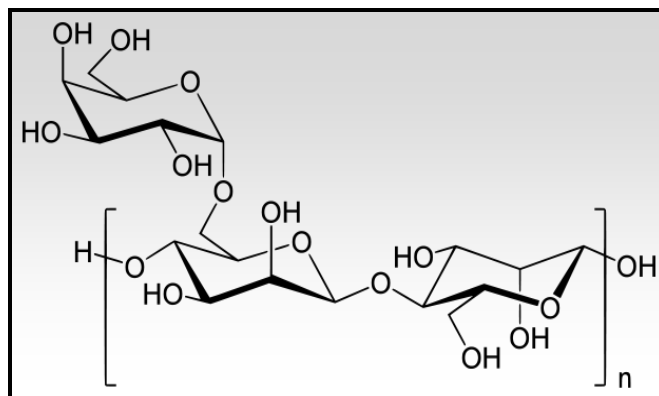
Fig-9: Chemical structure of Guar gum

Guar gum hydrates in cold water to form a highly viscous solution in which the single polysaccharide chains interact with each other in a complex way. Its nine hydroxyl groups are available for the formation of hydrogen bonds with other molecules, but it remains neutrally charged due to the absence of dissociable functional groups. Extreme pH and high temperature conditions (e.g. pH 3 at 50°C) degrade its structure. It remains stable in solution over pH range 5-7. Strong acids cause hydrolysis and loss of viscosity, and alkalis in strong concentration also tend to reduce viscosity. It is insoluble in most hydrocarbon solvents. As the guar gum polymer is a low-cost, easily available and non-toxic polysaccharide, it is widely applied in many industrial fields. Guar gum has been extensively used for colon delivery due to its drug release retarding property and susceptibility to microbial degradation in the large intestine [43].

Little information is available in the literature for the possibility of using guar gum based nano-sized materials as drug carriers due to its solubility in water, what makes difficult to use it as adsorbent in aqueous conditions. Some researchers have incorporated to its structure some compounds like silica, in order to obtain insoluble compounds which could act as adsorbents in aqueous media [44, 45].

Pectin:

Pectin is a structural polysaccharide obtained from the cell wall of all plants, where is implicated in cell adhesion. This natural polymer has a heterogeneous chemical structure based on large amounts of poly (D-galacturonic acid) bonded via α (1 → 4) glycosidic linkage (**Fig-10**). Pectin has a few hundred to about one thousand building blocks per molecule, corresponding to an average molecular weight of about 50,000 to about 180,000 Da [46]. The carboxyl groups are partially in the methyl ester form with different degree of esterification and amidation which determine the content of carboxylic acid in pectin chains.
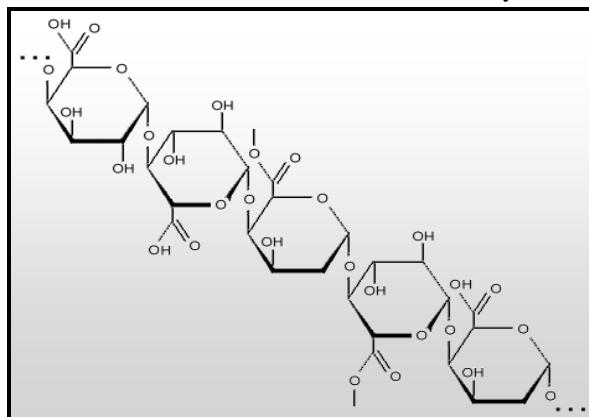

Fig-10: Chemical structure of Pectin

In the beginning, applications of pectin concentrated in food industry, as gelling or thickening agent, but lately it started being also used as excipients for pharmaceutical purposes. Nowadays, some of the uses of pectin in biomedical applications include the facilitation of the delivery of specific sequences of amino acids, anti-inflammatory agents, anti-coagulants, and wound healing substances to tissue sites. Also, pectin remains intact in the physiological environment of the stomach and the small intestine, but is degraded by pectinases, which are secreted by the bacteria inhabitants of the human colon. Due to these properties it is highly possible

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that pectin could function as a delivery vehicle to escort protein and polypeptide drugs from the mouth to the colon. To be used as such, pectin based composites can be formed into membranes, microspheres, scaffolds, or injectable gels [47].

With regard to pectin use in the preparation of drug delivery systems, pectin is not able to shield its drug load effectively during its passage through the stomach and small intestine due to its high water-solubility. Consequently, most of the researching groups focused on looking for water resistant pectin derivatives, which were also enzymatically degradable. For this purpose, calcium salts binding by non-covalent associations with the carbohydrate chains of pectin were investigated, which can reduce the solubility and are stable in low pH solution while resisting extensive hydration *in vivo* in the gastrointestinal tract. Thus, calcium pectinate is a potential candidate as a drug carrier for colon-specific delivery in different formulations such as microspheres, films, gels or droplets. Another derivative of pectin, amidated pectin cross-linked with calcium, was considered for colonic delivery, with retarding drug release and because of its biodegradability, higher tolerance to pH variations and fluctuations in calcium levels [48].

Calcium salts of pectin have reduced solubility and matrix tablets prepared with calcium pectinate showed good potential to be used in colon-targeted drug delivery systems. The main drawback of calcium pectinate gel beads is their macroporous structure, which may cause low entrapment efficiency and fast release of incorporated drugs, especially for those of hydrophilic low molecular weight drugs. In a recent investigation, orally administered, insulin-loaded amidated pectin hydrogel beads produced sustained release of insulin, and also reduced plasma glucose concentration in streptozotocin-induced diabetic rats [49].

Applications polysaccharides nanoparticles on diabetics:
Nanotechnology definitely promises to serve as drug delivery carrier of choice for the more challenging conventional drugs used for the treatment and management of chronic diseases such as cancer, asthma, hypertension, HIV and diabetes. Although the advantages of nanodrug delivery are many as enumerated above, one of the challenges of this technology is safety [50].

In the last decade there has been a great deal of interest in the use of polysaccharides and particularly chitosan and pectin plays the key role in nano drug delivery systems. It is clear that both the polysaccharides either individually or together show great potential on hypoglycemic drug delivery [51].

PERSPECTIVE
Nanomedicine approaches hold great promise in revolutionizing treatment on diabetic mellitus. As pointed out throughout this review, polyelectrolyte polysaccharides show variability and versatility, due to their complex structure, which is difficult to be reproduced with synthetic polymers. Thus, native polysaccharides and their derivatives are emerging in the last years as one of the most used biomaterials in the field of nanomedicine, especially being chosen by a lot of researchers as carriers to be used in the preparation of nanoparticulate drug delivery systems. Polyelectrolyte polysaccharides polymeric nanoparticles are nowadays an attractive option for increasing the bioavailability of diabetic drug.

Polyelectrolyte polysaccharides NP showed to be prospective drug delivery carriers as they offer many advantages (i) safe material as it is natural polymer that possesses biocompatible and biodegradable properties. (ii) Water-soluble in natures which can supreme for drug delivery carriers, therefore, simple and mild preparation methods can be applied. This renders as promising drug delivery carriers that are suitable for a broad category of drugs including macromolecules and labile drugs. (iii) Polyelectrolyte polysaccharides in a wide range of molecular weights and is easily chemically modified by coupling with ligands providing flexibility in formulation development.(iv) Polyelectrolyte polysaccharides provides absorption promoting effect that prolongs the contact time between substrate and cell membrane. In addition, their nano-sized facilitates drug uptake through the cell membrane. Together, the absorption enhancing effect and nano-sized particles exhibited ability to improve drug bioavailability. Polyelectrolyte polysaccharides NP offer versatile routes of administration, especially non-invasive routes, i.e. peroral, nasal, and ocular mucosa, which are preferable routes administration.

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