Review
Nanotechnology: A Novel Approach for the Treatment of Diabetic Mellitus

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Abstract—Nanotechnology science has been focused on several approaches in the treatment of the common metabolic disorder like diabetes. Insulin has been commercially produced since ages to treat diabetes using animal origin. However, conventional methods are replaced by utilizing microbes for commercial production of insulin. The use of nanomedicine is becoming an eye catching and most promising to overcome the drawbacks of conventional injectable insulin, drugs have been modified through nanocarriers with targeting ligands for their selective and targeted delivery for oral and pulmonary delivery. In diabetic patients, oral administration of insulin can be beneficial not only to overcome the pain and trauma caused by injections, but it can also mimic the physiological fate of insulin as well. Some of the applications of nanotechnology in treating diabetes mellitus are artificial pancreas, instead of pancreas transplantation, use of artificial beta cells for oral delivery of insulin, use of Nano spheres as biodegradable polymeric carriers, etc. Biodegradable Polymeric nanoparticles for parenteral insulin delivery have also been used. Where the insulin matrix surrounded by the nanoporous membrane gets triggered due to rise in blood glucose level which changes the surrounding nanoporous membrane that resulting in biodegradation and subsequent insulin delivery. Inhalable polymeric nano based drug delivery can be directed toward insulin delivery through inhalable nanoparticles. The current statement from this review is to highlight the advancement of nanotechnology for curing of diabetes and also further requirement is needed in nanotechnology for better treatment.

Keywords—Diabetic mellitus, Insulin, drug delivery, Nanomedicine and Nanotechnology.

INTRODUCTION
Diabetes mellitus (DM) is a chronic lifelong metabolic disorder that affects the life of billions of people throughout the world. Over the past 40 years, the status of diabetic mellitus has been changed from mild disorder of the elderly to one of the major causes of morbidity and mortality affecting the youth and middle aged people. It can be classified into two major forms, namely Type 1 DM (T1DM) and Type 2 DM (T2DM). The numbers of diabetic patients are increasing tremendously worldwide, where a recent report has indicated the increase of 422 million patients in 2014 from 108 million in 1980, showing the sharp increase and a total estimate of 1.6 million deaths was directly caused by diabetes in 2016. According to statistics from the Centre for Disease Control (CDC) diabetes is the third leading cause of death among some ethnic populations [1].

Nanomedicine is the medical application of nanotechnology. Nanomedicine ranges from the medical applications of nanomaterials and an offshoot of nanotechnology, refers to highly specific medical intervention at the molecular scale for curing disease or repairing damaged tissues, such as bone, muscle or nerve and etc. It is approximately at this size scale – about 100 nanometers. Nanotechnology is the study of phenomena and fine-tuning of materials at atomic, molecular and macromolecular scales, where properties differ significantly from those at a larger scale. Nanotechnology is the broad scientific field that encompasses nanomedicine.

DIABETES MELLITUS (DM)
Diabetes mellitus, often referred as diabetes is caused by decrease in insulin secretion by pancreatic islet cells leading to increase in blood glucose levels (BGLs) and an inability to maintain BGL homeostasis (hyperglycemia).

Types
Diabetes has been categorized into two types.
1. Type 1 or insulin dependent diabetes.
2. Type 2 or non-insulin dependent diabetes and Gestational diabetes.

Type 1 diabetes is a condition, characterized by deficiency of insulin due to destruction of insulin producing beta cells of Islets of Langerhans by autoimmune system in pancreas, typically caused by autoimmune-induced inflammation and apoptosis. The main cause of this beta cell loss is T-cell mediated autoimmune attack. Type 1 diabetes in children is termed as juvenile diabetes [2].

While, type 2 diabetes is distinguished as disorders of both insulin resistance or reduced insulin sensitivity along with reduced insulin secretion. The defective responsiveness of body tissues to insulin almost certainly involves the insulin receptor in cell membranes [2].
Gestational diabetes occurs in women without previously diagnosed diabetes who exhibit high blood glucose levels during pregnancy. It is believed that the hormones produced during pregnancy reduce a woman's sensitivity to insulin, resulting in high blood sugar levels [2].

In both cases, the loss of homeostasis-regulation mechanisms can lead to chronically high and low BGLs known as hyperglycaemia or hypoglycaemia. Chronic hyperglycaemia can lead to a variety of symptoms including cardiovascular and neurological complications, while hypoglycaemia can lead to lack of energy, unconsciousness, and death. Therefore, management is needed to control diabetes conditions and consequence complications. People are aware for the management of diabetic through planning of balanced meal, exercising regularly or yoga and also medication therapy.

The medications used to control hyperglycemic condition in diabetic are oral medication and parenteral preparations like insulin and glucagon.

**Insulin**

Insulin, is a polypeptide hormone consists of 51 amino acids in two chains (A chain, 21 amino acids; B chain, 30 amino acid), joined together by two disulfide bonds (-s-s) that helps in regulating the uptake and storage of glucose in the liver and muscles. It is produced by β cells of pancreas and released via exocytosis process into the bloodstream to help in utilization of peripheral glucose for generation of energy. The oxidation of glucose gets stimulate and inhibit gluconeogenesis which concurrently gets directed to the hypoglycaemic action of insulin. When insulin directs the glucose transporters (GLUT 4) into the cell membranes, the plasma glucose concentration decreases as a result the transport of glucose in the cell gets increased. However, insulin resistance sometimes may happen during insulin therapy for the management of diabetic conditions. Therefore, nanosize particles have comes out as for a more convenient, safe and non-invasive route for insulin delivery in order to overcome such limitations in diabetes management [3].

**Fig. 1:** Chemical structure of insulin consists of A chain (20 amino acids) and B chain (31 amino acids) are linked together by two disulfide linkages.

**Fig. 2:** Mechanism of action of insulin-activation through phosphatidylinositol-30-kinase pathway, stimulation of translocation of glucose transporter (GLUT 4) on the cell surface.
There are a few limitations in the use of conventionally available drug delivery systems. Lack of target specificity, altered effects and diminished potency due to drug metabolism in the body, cytotoxicity of certain anticancerous pharmacological agents, are to mention a few. Physical, chemical and biological properties are developing the biocompatibility and biodegradability, which are considered as essential criteria for nanoparticles to assist as a carrier molecule in drug delivery systems.

Metabolic disturbances associated with diabetes can lead to:[4, 5, 6, 7] [1]
(1) Activation of the polyol Pathway;
(2) High levels of the cytokine, TNF-α
(3) The formation of advanced glycation end-products (AGEs)
(4) High levels of protein kinase C activation and
(5) Enhanced oxidative stress.

**NANOTECHNOLOGY**

The term nano comes from a Greek word *nanos*, (means one-billionth part of something). “Nano” can be ascribed
to any unit of measure. Nanotechnology offers great solutions in treating diabetes mellitus. Some of them are artificial pancreas or artificial beta cell instead of pancreas transplantation, nanospheres as biodegradable polymeric carriers for oral hypoglycemic agents [8].

The different methods of nanocarriers adopted in drug delivery system are shown in figure 3.

The application of nanocarriers can improve activity against the combating diseases, increase detection sensitivity in medicinal imaging and decrease side effects by functionalizing their surface with synthetic polymers and appropriate ligands due to their small size.

**Nanoparticles for insulin delivery**

From last few years, numerous methods have been proposed for monitoring of blood glucose and it’s made possible through nanotechnology. Several types of nanoparticles presently studied for insulin delivery in DM are:

1. Polymeric biodegradable nanoparticles that include nanospheres and nanocapsules.
Polymeric nanoparticles are observed to be effective and efficient upon traditional oral and intravenous administration procedures. They are biodegradable polymers enclosed by nanoporous membrane and are used as carriers of insulin. pH change swells the polymer system resulting in release of insulin. Copolymers like N,N-dimethylaminoethyl methacrylatem, polyanhydrides, polyurethanes, polycrylic acids and polyacrylamide are being investigated for these applications [9].

Use of nanotechnology in the detection of insulin and blood sugar

The current methods of blood glucose monitoring are the finger-prick test which is painful and has been associated with non-adherence to treatment regimens by diabetic patients because of this, on the other hand it has very limited accuracy as it cannot be performed with other activities and due to its sporadic nature it can miss important and dangerous points in blood glucose test.

The use of nanotechnology is a new method which rapidly measure small amounts of insulin and blood glucose level is to developing the ability to assess the body’s insulin-producing cells. It can be achieved by following ways:

By microphysiometer The microphysiometer is composed of several flat sheets of carbon atoms stacked and rolled into very small tubes called multi walled carbon nanotubes. The nanotubes can conduct electric current and operate consistently at pH of living cells. The current at the electrode is directly related to the concentration of insulin in the chamber. Current detection methods involve periodical collection of small samples and measuring their insulin levels. Insulin molecules are oxidized in presence of glucose which results in continuous electron transfer and generation of current. The current generated in the microphysiometer sensor is directly proportional to the insulin molecules present within the cells and based on this mechanism insulin concentration can be monitored efficiently. When the insulin concentration within the cell increases, the current in the sensor also increases and vice versa, which allows real time monitoring of insulin concentration. This data can be sent wirelessly to a wearable computer via an embedded microchip [10, 11] [12].

By Implantable Sensor (“smart Tattoo”): A polyethylene glycol bead coated with fluorescent molecules to monitor diabetes blood sugar levels is very effective. In this method the beads are injected or implanted under the skin and stay in the interstitial fluid. When glucose in the interstitial fluid drops to dangerous levels, then glucose displaces the fluorescent molecules and creates a glow. This glow is seen on a tattoo placed on the arm. Sensor microchips are also developed to continuously monitor key body parameters including pulse, temperature and blood glucose level. Microchips would be implanted under the skin and transmit a signal that could be monitored continuously, read blood glucose concentrations and signal a warning in case of hypo- or hyperglycaemia [12].

Applications of Nanotechnology for the treatment of Diabetes

Polymeric Nanoparticles

Polymeric nanoparticles are solid, colloidal particles consisting of macromolecular substances size ranges from 10 nm to 1000 nm. Based on the methods of preparation, polymeric nanoparticles can be classified into two types, nanosphere and nanocapsule. In nanosphere the drug to be delivered is physically and uniformly dispersed in a matrix system and in nanocapsules the drug to be delivered is confined to a vesicular cavity surrounded by a unique polymer membrane. The polymers (biodegradable) of these nanoparticles degrade into biologically acceptable compounds (for example lactic and glycolic acids, which are finally reduced to carbon dioxide and water by Krebs cycle) by hydrolysis and delivering the encapsulated drug to the target tissue.

A variety of naturally occurring biodegradable polymers like collagen, cellulose, etc. were used extensively. Recently, chemically synthesized biodegradable polymers such as polyanhydrides, polycrylic acids, polyurethanes, polyesters and poly (methyl ethacrylates) are being explored by researchers. With respect to efficiency and effectiveness polymeric Nano particular drug delivery is more advantageous than traditional oral and intravenous administration.

Fig. 4: Controlling diabetes with a skin patch.

Fig. 5: Polymeric nanoparticles along with active ingredients
Polymeric nanoparticles are made up of biodegradable polymers, with the polymer–insulin matrix enclosed by the nanoporous membrane containing grafted glucose oxidase have been used as carriers of insulin. This “molecular gate” system of polymeric nanoparticle is composed of an insulin reservoir and a delivery rate–controlling membrane composed of poly [meth acrylic acid-g-poly (ethylene glycol)] copolymer. An increase in blood glucose level causes a change in the surrounding nanoporous membrane, resulting in biodegradation and subsequently release of insulin. The glucose/glucose oxidase reaction causes a reduction in the pH in the delivery systems. The polymer swells in size at normal body pH (pH = 7.4) and closes the gates, whereas it shrinks at low pH (pH = 4) when the blood glucose level increases, resulting in opening of the gates and release of insulin from the nanoparticles. The controlled delivery of insulin depends on the insulin concentration, the size of the gates and the rate of gate’s opening or closing [13].

**Ceramic nanoparticles**

Calcium phosphate, silica, alumina or titanium are mainly used to prepare ceramic nanoparticles. Certain advantages of ceramic nanoparticles are easy preparation, high biocompatibility, ultra-low size (less than 50 nm) and good dimensional stability. These nanoparticles prevent denaturation of drug molecules caused by changes in external pH and temperature. In addition, surface modifications of ceramic nanoparticles with different functional groups and conjugation with a variety of ligands or monoclonal antibodies facilitates their targeting to desired sites. Ceramic nanoparticles do not swell or it’s porosity does not change with the variation in surrounding environment. Self-assembling ceramic nanoparticles were explored for the parenteral delivery of insulin. Calcium phosphate nanoparticle has been explored as the insulin carrier which showed better in vivo efficacy as compared to the standard porcine insulin solution. A tricalcium phosphate nanoparticle has recently been found suitable for oral delivery of insulin [14–17] [2] [13].

**Inhalable nanoparticles**

Insulin delivery through inhalable nanoparticles utilizes lung administration route. Lung administration of drugs offer certain advantages over GIT administration such as mild environment, low enzyme concentrations and neutral pH, hence less chances of degradation [13].

In oral delivery of insulin, it is important to protect the insulin against proteolytic enzymes, e.g., pepsin or pancreatin that degrades and inactivates insulin in GI fluid. A study was conducted by Niu et al., the rapid release of calcine (a fluorescent dye) from SGC-Lip was attributed to low pH environment. Then the result indicates that SGC-Lip has certain degree of insulin protection against enzymatic degradation when compared with CH-Lip, then contributed positively to oral bioavailability of insulin [33]. Sodium glycocholate incorporated liposomal formulation is found to be advantageous in increasing efficacy of protease inhibition and permeation. Thus, a study regarding feasibility of glycocholate containing liposomes in improving oral insulin delivery had been conducted by Mengmeng Liu et al [34].

**Nano carrier based approaches in anti diabetic drugs delivery**

**Liposomes based drug delivery system**

Liposomes are small vesicles; consist with one or more phospholipid bilayers that produce from natural nontoxic phospholipids and cholesterol [24–26]. This technology serves as transporters for the active molecules to the site of action. Today’s usage of liposome in investigation in drug-delivery system was mostly their biodegradability, biocompatibility, and low toxicity to entrap both lipophilic and hydrophilic drugs for site-specific/ targeted delivery [27-30]. Liposomal drug delivery also decreases drug toxicity and improve the efficacy and safety. 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 of the article portrayed various liposomal approaches with the antihyperglycaemic drugs. In their research Zhang et al. modified the liposome 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 [31-32].
Niosomes based drug delivery system

Niosomes are synthetic microscopic vesicles, whose size lies in nanometric scale, mostly formed by non-ionic surfactants incorporated with cholesterol as excipient [35-37]. Niosomes can be categorized into large unilamellar vesicles (LUV) (100–3000 nm), small unilamellar vesicles (SUV) (10–100 nm), and multilamellar vesicles (MLV) on the basis of their sizes and bilayers [37].

Niosomes are the potential carriers of drug delivery system for their property of acting as reservoirs for drugs to achieve maximum drug entrapment in sustained and prolonged drug release [37,39,40]. For the presence of hydrophilic, amphiphilic and lipophilic moieties in their structure, niosomes can also accommodate drugs with varying solubility [36, 37]. And also these agents offer excellent biocompatibility and low toxicity due to their non-ionic nature [36, 37, 40].

Niosomes has also been used for vaginal delivery systems of insulin with the niosomal nano carriers were prepared via lipid phase evaporation technique through sonication, consisting two types of vesicles, Span 40 and Span 60.

The investigation of hypoglycemic effects and the pharmacokinetics of insulin were carried out after the vaginal administration of insulin vesicles in ovariectomies (to maintain the vaginal epithelium thickness) alloxan induced diabetic Wistar rats.

The outcomes indicating a maximum reduction of blood glucose with Insulin-Span 40 and Insulin-Span 60 reached to 47.49% and 46.66%, respectively, and the levels were found to be lower even after 6 h of vaginal administration. Further, the bio-availabilities of the two formulations were found to be 9.11% and 8.43%, respectively, higher than that of subcutaneous administration. Prolonged insulin release profile from the niosomes after a day indicated that it can be a promising and effective therapeutic agent in vaginal administration that provides controlled and prolonged drug release in achieving significant hypoglycemic effect [44, 39, 69].

Poly (amidoamine) dendrimer based drug delivery system for anti-diabetic drugs delivery

Dendrimers are nano-sized, polymeric globular hyper branched macromolecules with tree-like morphology in 3D nanostructure which comprises of a central core and branched monomers with different reactive end groups on the surface [42-46]. Dendrimers consists of poly (amidoamine) (PAMAM), poly(propylenimine) (PPI), liquid crystalline (LC), core shell (tecto), peptide, glycol and hybrid dendrimers [47-49]. The main contributing factors are widely usage in pharmaceutical and biochemical applications as an effective carrier for molecules, size and functional end groups of dendrimers can be modified in order to change their hydrophilicity, effective diameter and molecular weight [42, 43, 50].

Zheng et al. The vivo study of pulmonary absorption in peptide and protein drugs (Insulin and calcitonin) were studied in rats, which affects the absorption-enhancing polyamidoamine (PAMAM) dendrimers with various generations (G0 – G3) and concentrations (0.1–1.0% w/v) [51]. The data revealed that PAMAMs had significantly elevated the pulmonary absorption of the entrapped components, thus increased the systemic concentration of calcitonin and insulin. The experimental results further indicate that the absorption enhancing effects are generation dependent. PAMAM G3 has the greatest absorption enhancement effect, followed by G2, subsequently G1 and finally G0 with the least effect [51]. Labieniec et al. determined the ability of PAMAM G4 in scavenging excessive glucose and targeting modulation of declined metabolism of carbohydrate in experimental animals [64]. However, PAMAM G4 was known to be cytotoxic for almost a decade thus, the authors have conducted a study to investigate the degree of cytotoxic effect and evaluated whether this risk would outweigh the benefits of PAMAM G4 on ameliorating the deteriorative implications of oxidative stress, carbonyl stress and hyperglycemia which occurs in chronic untreated experimental diabetes. Labieniec et al. conducted an experiment to evaluate the efficiency of PAMAMs G2 and G4 in non-enzymatic modifications of primary amino groups in polyamine compounds and BSA. Authors clearly demonstrated that PAMAMs at the used concentrations neither interacted with BSA nor affected the protein conformation. In addition, PAMAM dendrimers do not form firm complexes with the proteins while non glycated poly (L-lysine) significantly forms, as evidenced by the decreased fluorescence of BSA [39,52,53].

Artificial Pancreas

The artificial pancreas is a device, first conceptualized in 1974, which would monitor blood glucose levels using an array of sensors, and release insulin from a reservoir into the bloodstream using an infusion pump, whenever it is required. The recent developments made by nanotechnology had changed this simple nanomachine to respond the glucose concentration and release insulin as a result replacing the need of controlling computer unit; this could potentially act as a one-time treatment which would remove all symptoms of diabetes permanently [1, 23, 54, 9].

Artificial pancreas system consists of a continuous glucose monitor, glucose meter, an insulin infusion pump for calibrating the monitor and the needed units of insulin enter the bloodstream from a small reservoir. The entire system, artificial pancreas could be the permanent solution for diabetic patients [1, 55, 57].

In another artificial pancreas system, a small silicon box containing animal’s pancreatic beta cells is incorporated. The box is surrounded by a very specific nanopore size (about 20 nanometers in diameter) material which is used to protect transplanted cells from the immune system. Glucose can diffuse and insulin can pass through these pores, however, much larger immune system molecules cannot pass through these pores. Therefore, the need of eliminating immunosuppressant drugs which may result to serious risk of infection. These silicon boxes can conveniently be implanted under the skin of
diabetes patients which temporarily restore the glucose control level. Yet, practical feasibility of this kind of nano-artificial pancreas is still to be explored [1, 56, 58].

Oral or intestinal insulin delivery
Main aim of Nanoparticulate insulin delivery is to develop the drug preparations which can be orally administered and absorbed in the intestines. Several articles show in the form of physical, enzymatic and protein stability barriers which different insulin nanoparticle preparation for oral and novel strategies developed [60-64]. Some investigation the use of absorption to enhance and enzyme inhibitor to by-pass the first two barriers the gold standard for oral delivery became the mucosa-adhesive particle containing chitosan. So some variety of new nanoparticles was developed with combination of chitosan, for mucosa adhesion with other polymers like hydroxy propyl methylcellulose phthalate for pH sensitivity, alginate for improve loading capacity and activity maintenance, gel formulation with the negatively charged sodium lauryl sulfate or even chitosan [65,66, 59].

![Fig. 7: Mechanism of Artificial Pancreas.](image)

![Fig. 8: (a). Oral insulin treatment of lowering blood glucose level, (b). Significant lowering of blood glucose level by oral insulin (chitosan) nanoparticle delivery.](image)
Table 1: Advantages and limitations for different types of nanoparticles [13]

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<tr>
<th>Types of Nanoparticles</th>
<th>Advantages</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Polymeric nanoparticles</td>
<td>Degraded into biologically acceptable compounds by hydrolysis; lesser cytotoxicity; higher target specificity; high level of insulin entrapment and ability to preserve insulin structure and biological activity; bypassing of the enzymatic degradation in stomach</td>
<td>Mucoadhesive polymeric nanoparticles may adhere non-specifically to surfaces they are not intended to (gastric mucosa, gut content) or remain trapped within the mucus.</td>
</tr>
<tr>
<td>Ceramic nanoparticles</td>
<td>Easy preparative processes, high biocompatibility, ultra-low size (&lt; 50 nm), better dimensional stability and protecting the doped drug against denaturation (like pH and temperature) and also can be developed with desired shape, size and porosity which do not undergo changes the swelling or porosity.</td>
<td>Poor permeability across the mucosal membrane and rapid mucociliary clearance mechanism of non-mucadhesive formulations for nasally administered insulin.</td>
</tr>
<tr>
<td>Liposomes</td>
<td>Biodegradable, non-toxic and non-immunogenic</td>
<td>Drug loading capacity remains inconclusive; captured by the human body’s defenses system (reticuloendothelial system (RES)); post-treatment accumulation in skin and eyes.</td>
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The recent newly develop in chitosan nanoparticle preparations for insulin administrated via the oral/intestinal route in normoglycemic non-diabetic animals is not higher than 50% of that observed by subcutaneous insulin injection.

The main target of intestinal epithelium tissue for oral insulin delivery is characterized by three barriers like the chemical, enzymatic, and absorption barrier [67].

All three barriers are successful and controlled deliveries of insulin Nano drugs. While the chemical environment in the gastrointestinal (GI) tract tend to modify protein drugs like insulin by a broad range of pH (from min. pH 1.3 in stomach to max. pH 8.0 in the intestine) the most severe threat for loss of protein drug is the enzymatic degradation along the way through the GI tract as this is the main function of the intestine [69].

Secondly, the surface of intestinal epithelium is covered with high viscous mucus which is negatively charged and only permeable for nutrients, water and small molecules and to prevent efficiently the entrance of nanoparticles [68].

Finally, the epithelial cells limit to access the blood significantly as tightly connected via tight junctions and suppress any paracellular transport leaving only transcellular route open (Chen39) [67].

In the review by Chen analyzed the influence of size, surface charge and mucosa adhesiveness on particle binding and transcytosis through the different cells of the intestine. Interestingly the affinity and uptake by different cell types depends strongly on the surface charge and size [67].

CONCLUSIONS
Diabetes is a major global problem in the developed country, the regular management required for diabetes patient to control the blood sugar level. Nanotechnology is an application which is widely used in the research work. The main aim is to control the glucose level and improve the treatment of diabetic patient with help of nanoparticles. Although nanotechnology have been widely used in pharmaceutical field. Use of these nanoparticulate drug delivery systems are in infant stage. It involves study of unique properties of nanoparticles as drugs or constituents of drugs or design of the new strategies to controlled release, drug targeting, and deliver drugs with low bioavailability. It is expected that in future, nanotechnology will generate many routes to treatments and cures for diabetes, while some of these technologies are proved to be advantageous over the conventional treatment and management of diabetes.

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