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RECENT TRENDS IN DIABETES TREATMENT USING NANOTECHNOLOGY

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This review article discusses the potential applications of nanoparticles and BioMEMS as drug delivery systems for diabetes treatment. This manuscript discusses polymeric nanoparticles, oral insulin administration using polysaccharides and polymeric nanoparticles, inhalable insulin nanoparticle formulations, and insulin delivery using BioMEMS. In addition to ceramic and polymeric nanoparticles, studies on gold nanoparticles for insulin delivery and treatment of diabetes-associated symptoms are discussed. There are a few limitations in the use of conventionally available drug delivery systems for diabetes treatment. This article reviews the subject in brief with suitable references to original research articles and review articles on earlier and current research findings about various types of nanoparticles and BioMEMS in diabetes treatment and their limitations.

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Keywords: Nanoparticles; BioMEMS, diabetes; drug delivery systems; insulin; gold and polymeric nanoparticles

1. Introduction

The field of nanotechnology has been undergoing tremendous development in the recent decade. Nanotechnology is the ability to work at the atomic, molecular, supramolecular levels (on a scale of ~1-100nm) in order to understand, create and use material structures, devices and systems with fundamentally new properties and functions resulting from their small structure [1]. In addition to the developments in scientific disciplines such as electronics, material science, space research and robotics, nanotechnology is expected to make significant 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. 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 anti-carcinogenic pharmacological agents, are to mention a few. Biocompatible nanoparticles with optimized physical, chemical and biological properties can overcome these limitations and serve as effective drug delivery systems. These newer generations of drug delivery systems have significant advantages over conventionally available drug delivery systems. This manuscript discusses the need for nanoparticulate drug delivery systems, their advantages, limitations and recent advances in application of such drug delivery systems in the treatment of diabetes.

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2. Diabetes, types and its etiology

Diabetes mellitus, often referred as diabetes is caused by decrease in insulin secretion by pancreatic islet cells leading to increase in blood glucose level (hyperglycemia). Diabetes insipidus is a condition characterized by excretion of large amounts of severely diluted urine, which cannot be reduced when fluid intake is reduced. This is caused due to deficiency of antidiuretic hormone (ADH) also known as vasopressin secreted by the posterior pituitary gland. Diabetes mellitus is characterised by excessive weight loss, increased urge for urination (polyuria), increased thirst (polydipsia) and an excessive desire to eat (polyphagia) [2]. Diabetes mellitus has been classified as Type 1 or insulin dependent diabetes, Type 2 or non-insulin dependent diabetes and Gestational diabetes. Type 1 diabetes mellitus is characterized by loss of insulin-producing beta cells of islets of Langerhans in the pancreas, thereby leading to deficiency of insulin. The main cause of this beta cell loss is T-cell mediated autoimmune attack. Type 1 diabetes in children is termed as juvenile diabetes. Type 2 diabetes mellitus is caused by insulin resistance or reduced insulin sensitivity combined with reduced insulin secretion. The defective responsiveness of body tissues to insulin almost certainly involves the insulin receptor in cell membranes. Gestational diabetes occurs in women without previously diagnosed diabetes who exhibit high blood glucose levels during pregnancy. No specific cause has been identified but it is believed that the hormones produced during pregnancy reduce a woman's sensitivity to insulin, resulting in high blood sugar levels. Control of blood sugar level through modified dietary sugar intake, physical exercise, insulin therapy and oral medications have been advised for control of Type 1 diabetes mellitus. Nanomedicine research over the past few decades have been aimed at the applications of nanoparticles for Type 1 diabetes mellitus treatment through effective insulin delivery and are discussed in the following sections.

3. Nanoparticles for insulin delivery

The various types of nanoparticles that are currently studied for their use as drug delivery systems [3,4] 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.

Polymeric nanoparticles

These are solid, colloidal particles consisting of macromolecular substances that vary in size from 10 nm to 1000 nm [5]. Depending on the methods of preparation [6, 7], nanoparticles can be of two types, nanosphere (Figs. 1(a) and (b)) or nanocapsule (Fig. 2). These nanostructures have completely different properties and release characteristics for the encapsulated drug. A nanosphere is a matrix system [8] in which the drug is physically and uniformly dispersed and nanocapsules are vesicular systems in which the drug is confined to a cavity surrounded by a unique polymer membrane (Fig. 2). 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 [9, 10]. 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 [11]. 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. This feature makes polymeric nanoparticles as ideal candidates for diabetes therapy and delivery of insulin.

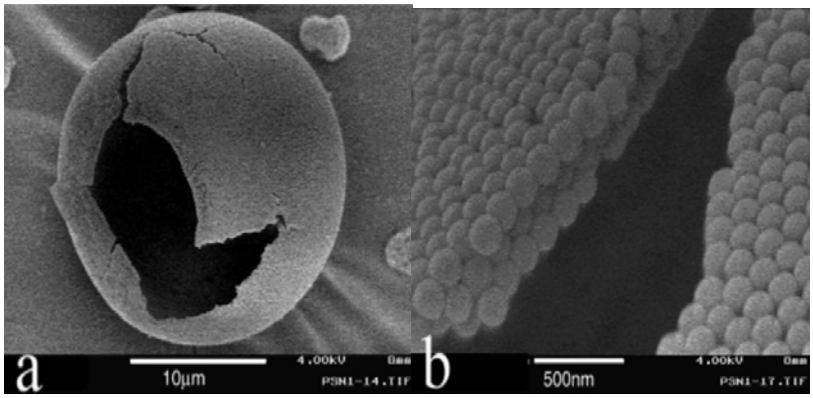

Fig. 1. (a) Scanning electron microscopy image of a hollow nanosphere obtained by spray drying of hydroxyl propyl cellulose and (b) a magnified view of the particle surface in a [6].

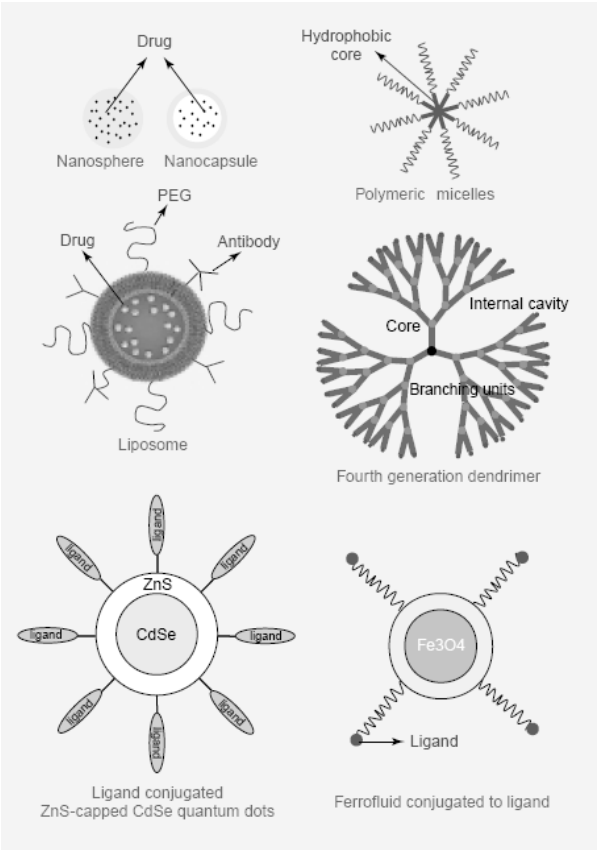

Fig. 2. Schematics of different nanotechnology-based drug delivery systems. Nanoparticles are small polymeric colloidal particles with a therapeutic agent either dispersed in polymer matrix or encapsulated in polymer. Polymeric micelles are self-assembled block co-polymers, which in aqueous solution arrange to form an outer hydrophilic layer and an inner hydrophobic core. The miceller core can be loaded with a water insoluble therapeutic agent. Liposomes are lipid structures that can be made 'stealth' by PEGylation and further conjugated to antibodies for targeting. Dendrimers are monodispersed symmetric macromolecules built around a small molecule with an internal cavity surrounded by a large number of reactive end groups. Quantum dots are fluorescent nanocrystals that can be conjugated to a ligand and thus can be used for imaging purposes. Ferrofluids are colloidal solutions of iron oxide magnetic nanoparticles surrounded by a polymeric layer, which can be further coated with affinity molecules such as antibodies [8].

Polymeric nanoparticles have been used as carriers of insulin [4]. These are biodegradable polymers with the polymer-insulin matrix surrounded by nanoporous membrane containing grafted glucose oxidase. A rise in blood glucose level triggers a change in the surrounding nanoporous membrane resulting in biodegradation and subsequent insulin delivery. The glucose/glucose-oxidase reaction causes a lowering of the pH in the delivery system's microenvironment. This can cause an increase in the swelling of the polymer system, leading to an increased release of insulin. The polymer systems investigated for such applications include copolymers like N, N-dimethylaminoethyl methacrylate [12] and polyacrylamide [13]. 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. 3) [14]. These systems release insulin by swelling caused due to changes in blood pH. The control of the insulin delivery depends on size of the gates, the concentration of insulin, and the rate of gates' opening or closing (response rate). 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.

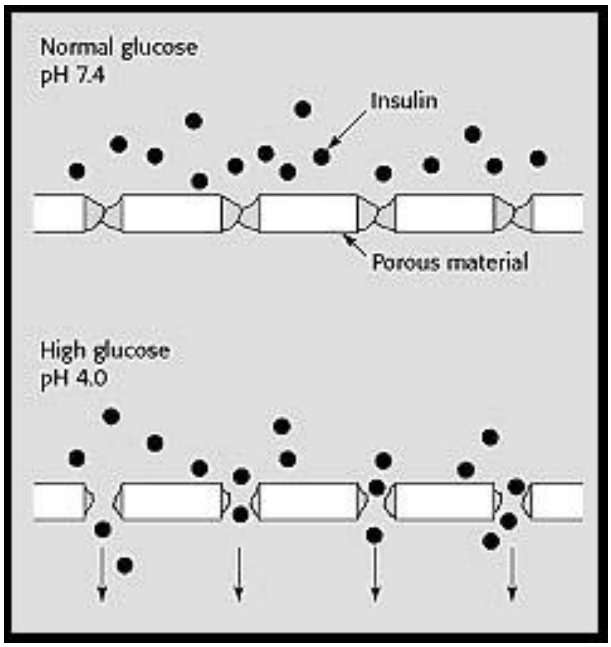

Fig.3. Schematic representation of polymeric nanoparticles with pH sensitive molecular gates for controlled insulin release triggered by the presence of glucose in blood [14].

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. Insulin when administered orally undergoes degradation in the stomach due to gastric enzymes [15]. Therefore insulin should be enveloped in a matrix like system to protect it from gastric enzymes. This can be achieved by encapsulating the insulin molecules in polymeric nanoparticles. In one such study, calcium phosphate-polyethylene glycol-insulin combination was combined with casein (a milk protein) [16]. The casein coating protects the insulin from the gastric enzymes (Fig. 4). 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. In another study, insulin-loaded polymeric nanoparticles were used in the form of pellets for oral delivery of

insulin in diabetic rats [17]. The results showed a significant decrease in blood sugar level following the administration of insulin through the buccal route. Temperature sensitive polymer nanospheres made from poly (N-isopropylacrylamide) and poly (ethylene glycol) dimethacrylate were shown to protect the loaded insulin from high temperature and high shear stress and such polymeric system can be an effective carrier for insulin [18]. Polysaccharides like chitosan, dextran sulphate, cyclodextrin have been used to deliver the insulin molecules with polymeric nanoparticles as carrier systems. Even though chitosan was used for nasal delivery of insulin, it has also been tested for oral delivery [19]. The in vivo results, in a diabetic rat model with insulin-loaded chitosan/poly (gamma-glutamic acid) (gamma-PGA) were shown to effectively reduce the blood glucose level [20]. A combination of dextran sulfate/chitosan nanoparticles were shown to be effective pH-sensitive delivery systems and the release of insulin was governed by the dissociation mechanism between the polysaccharides [21]. Dextran sulphate combined with polyethylenimine (PEI) nanoparticles was shown to exhibit a high level of insulin entrapment and an ability to preserve insulin structure and biological activity in vitro [22]. Cyclodextrin–insulin complex encapsulated polymethacrylic acid based nanoparticles have also been reported as an effective oral delivery system [23]. Over the recent years, different polymeric nanoparticles made of poly (isobutylcyanoacrylate) [24], poly (lactide-co-glycolide) (PLGA) [25], poly (-ε-caprolactone) [26], pluronic/poly (lactic acid) block copolymers [27], PLGA nanoparticles embedded within poly (vinyl alcohol) PVA hydrogel [28] have been reported. Encapsulation of insulin into mucoadhesive alginate/chitosan nanoparticles was a shown to be a key factor in the improvement of oral absorption and oral bioactivity in diabetic rats [29]. These approaches substantiate the potential use of polymeric nanoparticles in oral administration of insulin, thereby bypassing the enzymatic degradation in the stomach.

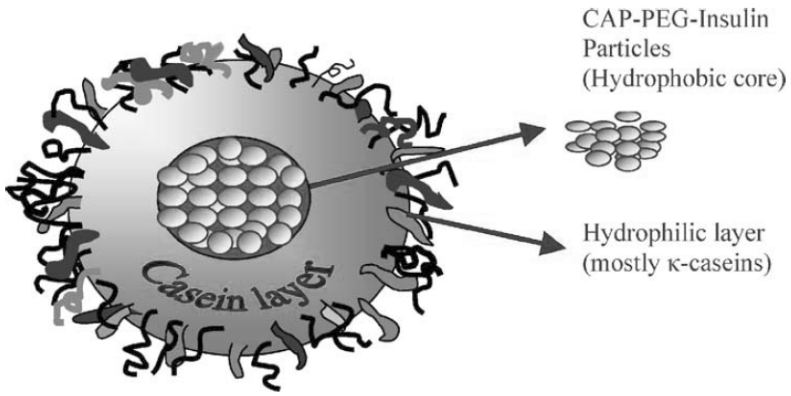

Fig. 4. Schematic representation of calcium phosphate-PEG-insulin-casein (CAPIC) oral insulin delivery system [16].

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 [30]. 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 [31]. 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 [32]. 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 [33, 34]. Calcium phosphate nanoparticle core was used as the

insulin carrier and these particles were characterized and studied *in vivo*. The *in vivo* performance of 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 [35].

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 [33, 34]. Porous hydroxyapatite nanoparticles have also been tested for intestinal delivery of insulin [37]. Preclinical 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 [38]. 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 [39]. 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 [40]. To overcome these limitations, mucoadhesive nanoparticles made of chitosan/tripolyphosphate [41] and starch [42] has been evaluated. These nanoparticles showed good insulin loading capacity, providing the release of 75–80% insulin within 15 minutes after administration.

BioMEMS

Implantable Bio Micro Electro Mechanical Systems (BioMEMS) can be used as insulin pumps for controlled release of insulin when there is an increase in blood glucose level [43]. Another proposed BioMEMS device has a drug reservoir compartment filled with insulin molecules [44]. Biosensors and nonporous membranes with pores of 6 nm in diameter are located in the exterior to detect the changes in blood glucose level and for insulin release. A review about the fabrication of a glucose-sensitive microvalve MEMS device for insulin delivery discusses extensively about the research attempts done in the past few decades [45]. Another implantable polymer-based micropump system with integrated biosensors for optimal insulin delivery without user intervention has been described in a recent study [46]. Microfabrication techniques have taken the miniaturization science to the nanoscale level. Microneedles have also been reported as effective transdermal systems for insulin delivery [47]. The concept of an assembled biocapsule consisting of two micromachined membranes bonded together to form a cell-containing cavity bound by membranes with nanopores was reported earlier (Fig. 5). Microfabricated membranes with 18 nm pore size (Fig. 6) were shown to be sufficiently permeable to small biomolecules such as oxygen, glucose, and insulin [48]. Such biocapsules can be incorporated to BioMEMS devices for insulin delivery and diabetes treatment. While the nanopores were designed to be permeable to glucose, insulin and other metabolically active products, the pores were small enough to prevent the passage of larger cytotoxic cells, macrophages, antibodies, and complement [49] (Fig.7).

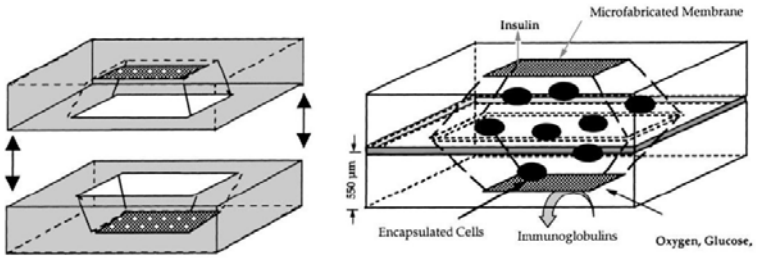

Fig. 5. Schematic of assembled biocapsule consisting of two micromachined membranes bonded together to form a cell-containing cavity bounded by membranes [48].

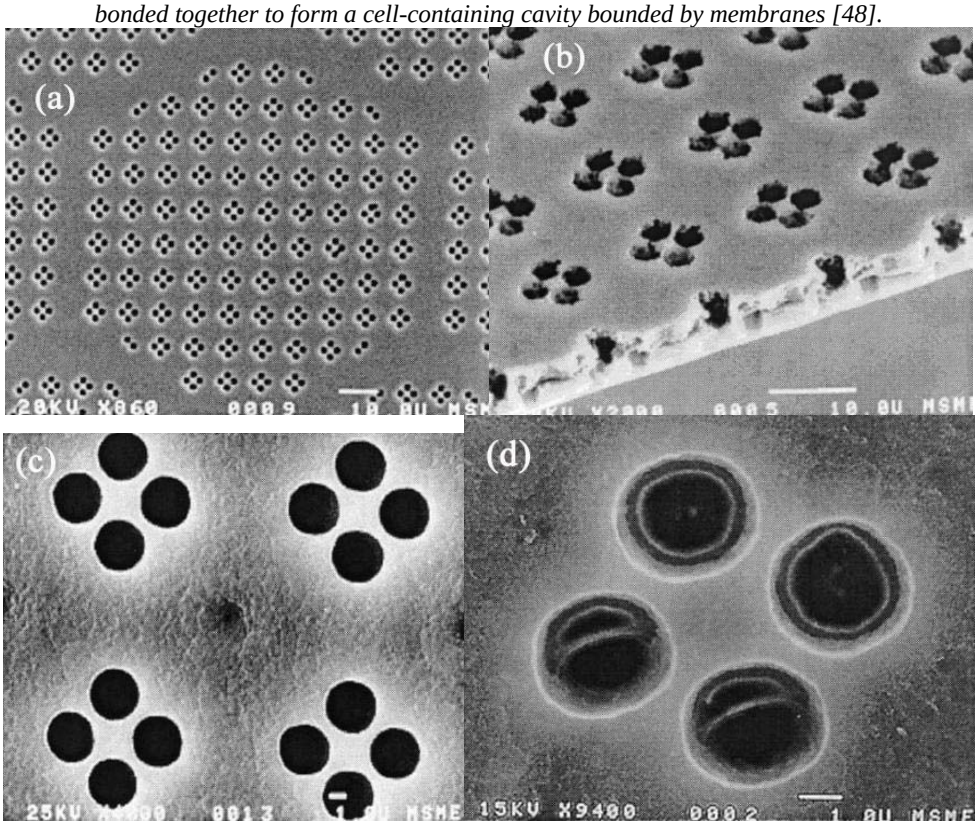

Fig. 6. Scanning electron micrograph of the microfabricated membrane of 18 nm pore size: (a) top-view of pore array; (b) cross sectional view of membrane; (c) cluster of 2x2 micron entry ports; (d) magnified view of 2x2 micron entry ports with 18 nm channels underneath [48].

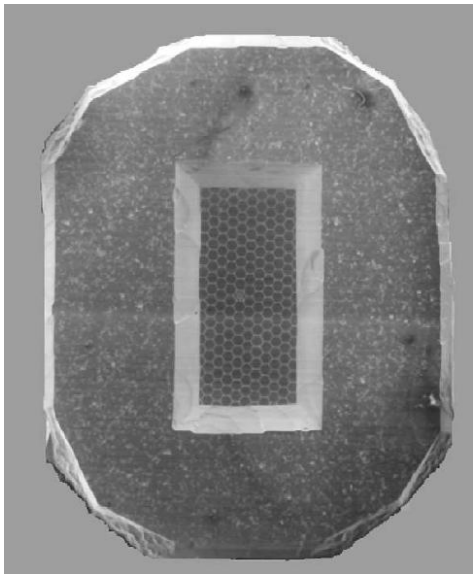

Fig. 7. Micrograph of a biocapsule membrane with 24.5 nm pores [49].

Other nanoparticulate systems for insulin delivery and for the treatment of diabetes associated 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 [50]. 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 [51]. 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 [52, 53]. The recent years have seen the advancement in application of nanoparticles made of polyacrylic acid [54], polylactide [55] and chitosan [56] for ophthalmic drug delivery. The scientific community is working towards utilizing nanoparticle-based drug delivery systems in the treatment of diabetes-associated complications. The advantages and limitations for different types of nanoparticles are discussed in Table.1.

Table. 1. Advantages and limitations for different types of nanoparticles

Types of nanoparticles	**Advantages**	**Limitations**
Polymeric nanoparticles	Degrade 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	Mucoadhesive polymeric nanoparticles may adhere non-specifically to surfaces they are not intended to (gastric mucosa, gut content) or remain trapped within the mucus.
Ceramic nanoparticles	Easy preparative processes; high biocompatibility; ultra-low size (less than 50 nm); good dimensional stability; protect the doped drug molecules against denaturation caused by changes in external pH and temperature; can be manufactured with desired size, shape and porosity; do not undergo swelling or porosity changes	Poor permeability across the mucosal membrane and rapid mucociliary clearance mechanism of non-mucoadhesive formulations for nasally administered insulin
Gold nanoparticles	Long term stability in terms of aggregation and good insulin loading; higher uptake of insulin across oral and nasal mucosa; improved pharmacodynamic activity of insulin	Widespread distribution in organs like liver, lung, spleen, kidney, brain, heart, stomach and joints
Liposomes	Biodegradable, non-toxic and non-immunogenic	Drug loading capacity remains inconclusive; captured by the human body's defense system (reticuloendothelial system (RES)); post-treatment accumulation in skin and eyes

4. Conclusions

The science and knowledge that the scientific community has today about nanotechnology and its potential versatile applications is only based on the research work done in the laboratories. These researches are being conducted to understand how matter behaves at the nanoscale level. Factors and conditions governing the behaviour of macrosystems do not really apply to the nanosystems. The major limitations and technological hurdles faced by nanotechnology and its applications in the field of drug delivery should be addressed [57, 58]. Scientific community hasn't yet understood completely how the human body would react to these nanoparticles and nanosystems, which are acting as drug carriers. Nanoparticles have larger surface area when compared to their volume. Friction and clumping of the nanoparticles into a larger structure is inevitable which may affect their function as a drug delivery system. Due to their minute size these drug carriers can be cleared away form the body by the body's excretory pathways. When these are not excreted, larger nanoparticles can accumulate in vital organs causing toxicity leading to organ failure. Recent study in mice revealed that tissue distribution of gold nanoparticles is size-dependent with the smallest nanoparticles (15-50 nm) showing the most widespread organ distribution including blood, liver, lung, spleen, kidney, brain, heart and stomach [59]. Liposomes have certain drawbacks like being captured by the human body's defence system. The drug loading capacity of liposomes is being tested by researchers and still remains inconclusive. All previous studies resulted in post-treatment accumulation of the nanoparticles in skin and eyes. Gold nanoparticles tend to accumulate in bone joints and organs. Once the nanoparticles are administered into the human body, they should be controlled by an external control preventing them from causing adverse effects. These drug delivery technologies are in various stages of research and development. It is expected that these limitations can be overcome and the discoveries to come into practical use within the next 5-10 years. Diabetes is a rapidly growing global problem, which requires management at the patient level, via blood glucose control to prevent worsening effects of the disease. Given the limited diagnostic tools, there is a need for better methods to measure the blood glucose level. Nanotechnology has proven beneficial in this case by not only increasing the available surface area of the sensor-receptor complex but also by improving the catalytic properties of electrodes and providing nanoscale sensors [60]. There are some other avenues of nanotechnology that may benefit the treatment as well as curing of diabetes in the future. The ability of nanotechnology to enhance numerous regenerative therapies, such as vascular and brain tissue, has been reported in many studies [61]. This specifically would benefit diabetic patients with poor vascularization. In a streptozotocin-induced diabetic rat model Polyethylcyanoacrylate nanospheres in the form of biodegradable polymeric carriers have proven to be successful in insulin delivery [62]. Other technologies included layer-by-layer films, which nano-encapsulate sensors and could revolutionize insulin delivery through enhanced islet encapsulation and oral formulations. [63].

References

[1] Roco, M.C.; Williams, R.S.; Alivisatos, P. Nanotechnology research directions, Kluwer Academic Publications: Boston, 2000.

[2] Kuzuya, T.; Nakagawa, S.; Satoh, J.; Kanazawa, Y.; Iwamoto, Y.; Kobayashi, M.; Nanjo, K.; Sasaki, A.; Seino, Y.; Ito, C.; Shima, K.; Nonaka, K.; Kadowaki, T. Diabetes Res. Clin. Pract., **55**(1), 65 (2002).

[3] Yih, T.C.; Al-Fandi, M. J. Cell. Biochem., **97**(6), 1184–1190. 2006

[4] Attivi, D.; Wehrle, P.; Ubrich, N.; Damge, C.; Hoffman, M.; Maincent, P. Drug. Dev. Ind. Pharm. **31**(2), 179 (2005).

[5] Brigger, I.; Dubernet, C.; Couvreur, P., Adv. Drug. Deliv. Rev. **55**, 329 (2002).

[6] Tsapis, N.; Bennett, D.; Jackson, B.; Weitz, D.A.; Edwards, D.A. Proc. Natl. Acad. Sci., **99**, 12001 (2002).

[7] Si, P.Z.; Zhang, Z.D.; Geng, Y.D.; You, C.Y.; Zhao, X.G.; Zhang, W.S. Carbon, **41**(2), 247 (2003).

[8] Sahoo, S.K.; Labhasetwar, V.. Drug. Disc. Today., **8**, 1112 (2003).
[9] Fujioka, K.; Takada, Y.; Sato, S.; Miyata, T., J. Contr. Rel. **33**, 307 (1995).
[10] Pereswetoff-Morath, L.; Edman, P. Int. J. Pharm. **128**(1–2), 23 (1996).
[11] Kim, Y.S.; Shin, I.G.; Lee, Y.M. J. Contr. Rel. **56**, 197 (1998).
[12] Kost, J.; Horbett, T.A.; Ratner, B.D.; Singh, M. J. Biomed. Mater. Res., **19**, 1117 (1985).
[13] Ishihara, K.; Kobayashi, M.; Shinohara, I.. Makromol. Chem. Rapid Commun. **4**, 327 (1983).
[14] Dorski, C.M.; Doyle, F.J.; Peppas, N.A. Polym. Mater. Sci. Eng. Proc. **76**, 281 (1997).
[15] Morishita, M.; Morishita, I.; Takayama, K.; Machida, Y.; Nagai, T. Int. J. Pharm. **78**(1–3), 1 (1992).
[16] Morcol, T.; Nagappan, P.; Nerenbaum, L.; Mitchell, A.; Bell, S.J. Int. J. Pharm. **277**(1–2), 91 (2004).
[17] Venugopalan, P.; Sapre, A.; Venkatesan, N.; Vyas, S.P. Pharmazie. **56**(3), 217 (2001).
[18] Leobandung, W.; Ichikawa, H.; Fukumori, Y.; Peppas, N.A.. J. Contr. Rel., **80**(1-3), 357 2002
[19] Pan, Y.; Li, Y.J.; Zhao, H.Y.; Zheng, J.M.; Xu, H.; Wei, G.; Hao, J.S.; Cui, F.D. Int. J. Pharm. **249**(1-2), 139 (2002).
[20] Lin, Y.H.; Mi, F.L.; Chen, C.T.; Chang, W.C.; Peng, S.F.; Liang, H.F.; Sung, H.W. Biomacromol. **8**(1), 146 (2007).
[21] Sarmento, B.; Ribeiro, A.; Veiga, F.; Ferreira, D. Coll. Surf. B. Biointerf. **53**(2), 193 (2006).
[22] Tiyaboonchai, W.; Woiszwillo, J.; Sims, R.C.; Middaugh, C.R. Int. J. Pharm., **255**(1-2), 139 (2003).
[23] Sajeesh, S.; Sharma, C.P. Int. J. Pharm. **325**(1-2), 147 (2006).
[24] Mesiha, M.S.; Sidhom, M.B.; Fasipe, B. Int. J. Pharm., **288**(2), 289 (2005).
[25] Cui, F.D.; Tao, A.J.; Cun, D.M.; Zhang, L.Q.; Shi, K. J. Pharm. Sci., , **96**(2), 421 (2007).
[27] Damgé, C.; Maincent, P.; Ubrich, N. J. Contr. Rel. **117**(2), 163 (2007).
[28] Xiong, X.Y.; Li, Y.P.; Li, Z.L.; Zhou, C.L.; Tam, K.C.; Liu, Z.Y.; Xie, G.X., J. Contr. Rel., **120**(1-2), 11 (2007).
[29] Liu, J.; Zhang, S.M.; Chen, P.P.; Cheng, L.; Zhou, W.; Tang, W.X.; Chen, Z.W.; Ke, C.M. J. Mater. Sci. Mater. Med., **18**(11), 2205 (2007).
[30] Sarmento, B.; Ribeiro, A.; Veiga, F.; Sampaio, P.; Neufeld, R.; Ferreira, D. Pharm. Res., **24**(12), 2198 (2007).
[31] Vollath, D.D.; Szabo, V.; Haubelt, J. J. Euro. Cer. Soc. **17**(11), 1317 (1997).
[32] Roy, I.; Ohulchanskyy, T.Y.; Pudavar, H.E.; Bergey, E.J.; Oseroff, A.R.; Morgan, J.; Dougherty, T.J.; Prasad, P.N. J. Amer. Chem. Soc., **125**(26)7860 (2003).
[33] Douglas, S.J.; Davis, S.S.; Illum, L. Nanoparticles in drug delivery. Rev, Ther, Drug Carr, Syst., **3**(3), 233 (1987).
[34] Cherian, A.K.; Rana, A.C.; Jain, S.K. Drug Dev. Ind. Pharm. **26**(4), 459 (2000).
[35] Corkery, K. Inhalable drugs for systemic therapy. Resp. Care., **45**(7), 831 (2000).
[36] Paul, W.; Sharma, C.P. J. Pharm. Sci., **97**(2), 875 (2008).
[37] Pandey, R.; Sharma, A.; Zahoor, A.; Sharma, S.; Khuller, G.K.; Prasad, B. J. Antimicrob. Chemother., **52**(6), 981 (2003).
[38] Paul, W.; Sharma, C. Trends Biom. Artif. Organs., **14**(2), 37 (2001).
[39] Kawashima, Y.; Yamamoto, H.; Takeuchi, H.; Fujioka, S.; Hino, T. J. Contr. Rel. **62**(1-2), 279 (1999).
[40] Zhang, Q.; Shen, Z.; Nagai, T. Int. J. Pharm., **218**(1-2), 75 (2001).
[41] O'Hagan, D.T.; Illum, L. Crit. Rev. Ther. Drug Carrier Syst., **7**(1), 35 (1990).
[42] Grenha, A.; Seijo, B.; Remuñán-López, C. Eur. J. Pharm. Sci., **25**(4-5), 427 (2005).
[43] Jain, A.K.; Khar, R.K.; Ahmed, F.J.; Diwan, P.V. Eur. J. Pharm. Biopharm. **69**(2), 426 (2008).
[44] Maillefer, D.; Gamper, S.; Frehner, B.; Balmer, P. 14th IEEE. Int. Conf. MEMS Tech. Digest., , 413–417. (2001).
[45]http://www.leadershipmedica.com/scientifico/sciesett02/scientificaing/7ferrarie/7ferraring.htm (accessed April 2009)

[46] Ziaie, B.; Baldi, A.; Lei, M.; Gu, Y.; Siegel, R.A. Hard Adv. Drug Deliv. Rev. **56**(2), 145 (2004).
[47] Wong, E.; Bigdeli, A.; Biglari-Abhari, M. Int. J. Sci. Res., **16**, 235 (2006).
[48] Martanto, W.; Davis, S.P.; Holiday, N.R.; Wang, J.; Gill, H.S.; Prausnitz, M.R. Pharm. Res., **21**(6), 947 (2004).
[49] Desai, T.A.; Hansford, D.; Ferrari, M. J. Membr. Sci., **159**(1-2), 221 (1999).
[50] Tao, S.L.; Desai, T.A. Adv. Drug Deliv. Rev., **55**, 315 (2003).
[51] Bhumkar, D.R.; Joshi, H.M.; Sastry, M.; Pokharkar, V.B. Pharm. Res. **24**(8), 1415 (2007).
[53] Chalasani, K.B.; Russell-Jones, G.J.; Yandrapu, S.K.; Diwan, P.V.; Jain, S.K. J. Contr. Rel., **117**(3), 421 (2007).
[54] Zimmer, A.; Kreuter, J. Adv. Drug Deliv. Rev., **16**(1), 61 (1995).
[55] Gurny, R.; Boye, T.; Ibrahim, H. J. Contr. Rel., **2**, 353 (1985).
[56] De, T.K.; Rodman, D.J.; Holm, B.A.; Prasad, P.N.; Bergey, E.J. J. Microencapsul., **20**(3), 361-374. 2003
[57] Bourges, J.L.; Gautier, S.E.; Delie, F.; Bejjani, R.A.; Jeanny, J.C.; Gurny, R.; BenEzra, D.; Behar-Cohen, F.F. Invest. Ophth. Vis. Sci., **44**(8), 3562 (2003).
[58] Enríquez de Salamanca, A.; Diebold, Y.; Calonge, M.; García-Vazquez, C.; Callejo, S.; Vila, A.; Alonso, M.J. Invest. Ophth. Vis. Sci. **47**(4), 1416 (2006).
[59] Neuberger, T.; Schöpf, B.; Hofmann, H.; von Rechenberg, B. J. Magn. Magn. Mater., **293**(1), 483 (2005).
[60] Kayser, O.; Lemker, A.; Trejo, N.H. Curr. Pharm. Biotech., **6**, 3-5. 2005
[61] Sonavane, G.; Tomoda, K.; Makino, K. Coll. Surf. B Biointerf., **66**(2), 274 (2008).
[62] Cash, K. J., & Clark, H. A. (2010). Nanosensors and nanomaterials for monitoring glucose in diabetes. Trends Mol Med, 16(12), 584-593. doi:10.1016/j.molmed.2010.08.002
[63] Khang, D., Carpenter, J., Chun, Y., Pareta, R., & Webster, T. Nanotechnology for regenerative medicine. Biomedical Microdevices, 12(4), 575-587. (2010). doi: 10.1007/s10544-008-9264-6
[64] Martinac K and Metelko Z. Nanotechnology and diabetes. Diabetologia Croatica, **34**(4): 105 (2005).
[65] Pickup, J. C., Zhi, Z.-L., Khan, F., Saxl, T. and Birch, D. J. S. Nanomedicine and its potential in diabetes research and practice. Diabetes/Metabolism Research and Reviews, **24,** 604. (2008), doi: 10.1002/dmrr.893.