Review on oral hypoglycaemic drugs and nano technology for countering diabetes

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ABSTRACT

At present diabetes has become a global challenge affecting near about 25.8 million people in USA, 62 million people in India and around 382 million people worldwide and these numbers are continuously increasing and it is expected that this number may reach up to 590 million people by the end of 2035. There's a need for the safe agents that can reduce the risk of diabetes.

Number of disadvantages has been associated with subcutaneous administration of insulin as it is an invasive method, requires qualified personal, increased patient non-compliance. Thus, an alternative route for delivering insulin is needed to overcome those drawbacks.

Though there are certain drugs like metformin, orlistat and acarbose that have shown preventive activities for diabetes. Nutraceuticals are known to have significant effect in reducing the risk of diabetes. Natural agents that slow down the carbohydrate absorption mimic the protective effects of acarbose like soluble fibre for example glucomannan, chlorogenic acid can reduce the risk of diabetes associated with heavy intake of coffee and also legume derived α-amylase inhibitors.

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Introduction

Diabetes can be defined as a metabolic disorder and is generally categorize by an elevated blood glucose level which leads to an imbalance in maintenance of blood and glucose homeostasis (1, 2). Patients suffering from the type-1 diabetes areunable to produce insulin due to some auto immune disorders. This leads to complete destruction of β-cells which are present in the pancreas. The production of insulin is carried out by β-cells which help in reduction of glucose level in the blood (3). The patient who suffers from the type-2 diabetes are categorize as they areunable to produce sufficient amount of insulin to maintain normal glucose level in the blood. This leads to increase in the blood glucose level.

At present diabetes has become a global challenge affecting near about 25.8 million people in USA, 62 million people in India and around 382 million people worldwide and these numbers are continuously increasing and it is expected that this number may reach up to 590 million people by the end of 2035 (4, 5). Furthermore, it is expected that diabetes will become the 7th largest cause of death worldwide.

The main care for the patients suffering from the type-1 and advanced type-2 diabetes involves regular subcutaneous insulin injections for maintaining the normal glucose level along with regular pricking of fingers to check the glucose level in the blood (6). Daily injection and pricking of fingers are painful measures for the patient leading to patient non-compliance.

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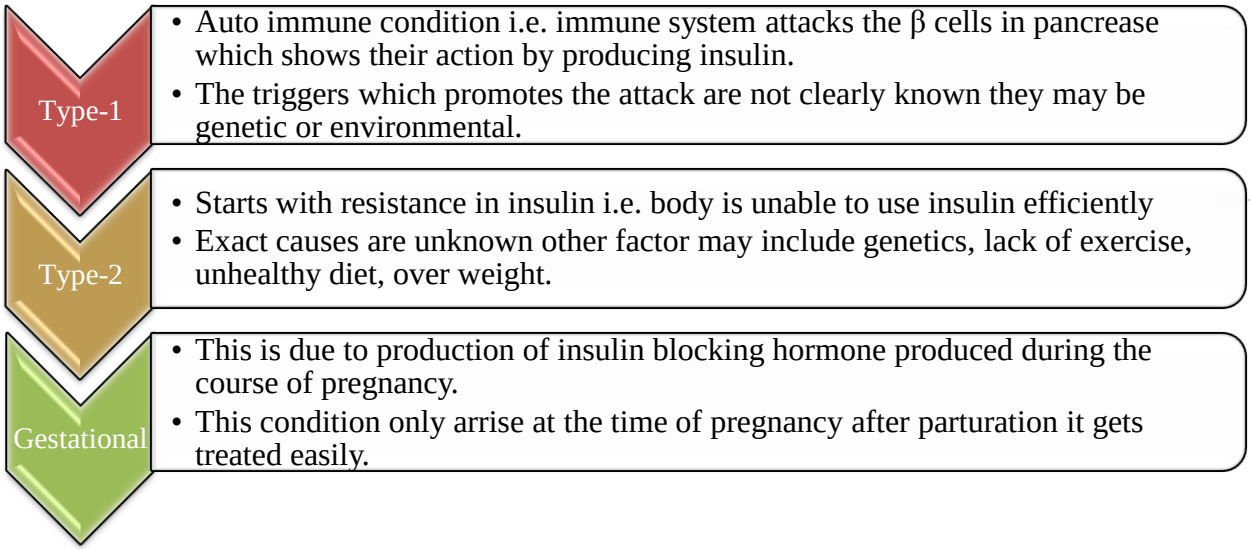

Fig 1-Types of diabetes

Pathophysiology of Diabetes:

Diabetes type-2 is a progressive disorder categorized by deficit in insulin secretion and action (insulin resistance). In diabetes type-2 a decreased level of insulin in plasma along with insulin resistance is present due to which desired action cannot be produced. As a result, due to decreased insulin level and insulin resistance by the cells there is marked increase in glucose level in the blood.

Pancreas is present in the abdomen directly connected with stomach and intestine. It contains clusters of cells called as the pancreatic acini these acini contain the exocrine cells which release enzymes that helps in digestion process. Around the pancreatic acini bunch of cells named as Islets of Langerhans are present and these cells are endocrine cells and are responsible for the secretion of insulin in blood. Insulin possesses various functions in the body i.e. in general insulin is responsible for storing the energy in adipose tissues and skeletal muscles and also responsible for the process glycolysis. Insulin also shows its effect on liver by increasing protein synthesis,lipogenesis, glycolysis andglucogenesis. All in all, insulin promote glucose uptake and storage of energy and inhibit the release of glucose into the blood.

Islets of Langerhans are composed of various cells i.e. β-cells which are known for the production of amylin and insulin, glucagon is produced by α-cells, δ-cells are better known for the production of somatostatin. Glucagon shows opposite action to insulin.

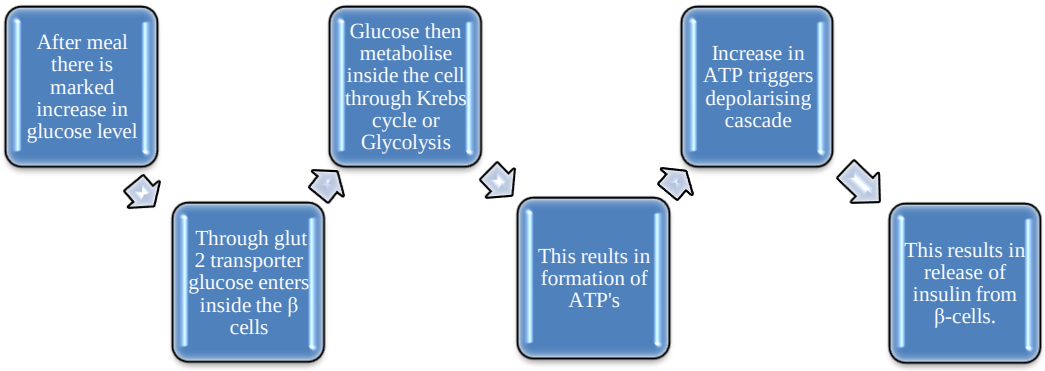

Fig 2-Steps involved in release of insulin

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When insulin released into the bloodstream, it is targeted to the site of action(cells) where it binds with insulin receptors which results in storage of glucose inside the cell. Thus glucose level is reduced inside the blood by the action of insulin.

However, this whole process gets disturbed in type-2 diabetes which shows marked increase level of glucose inside the blood stream.

Persistent high blood glucose level results in clinical manifestations of patients having diabetes. Common signs and symptoms include

- Regular infections
- Fatigue
- Blurred vision
- 4 P's (Polyphagia, Polyurea,Parasthesia and Polydipsia)

Diabetes include various of risk factors like

- Older age
- Obese
- Gestational diabetes
- Polycystic ovary syndrome

If diabetes is progressive and is untreated it can lead to various complications

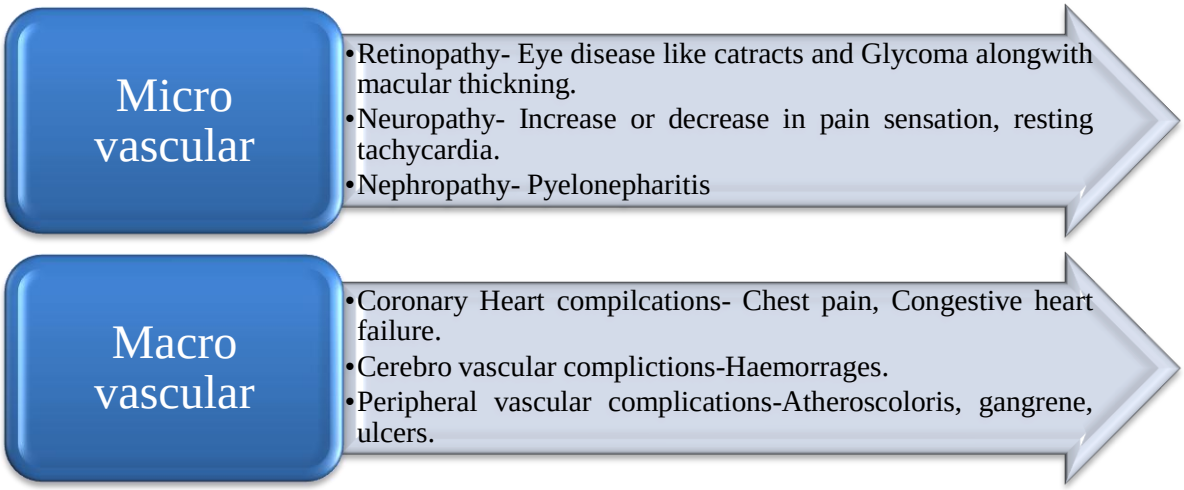

Fig. 3- Complications associated with Diabetes

Insulin delivery methods

Continuous subcutaneous, insulin pen, vials and syringes are some of the common methods through which a patient can administer insulin for the treatment of diabetes. List of advantages and disadvantages are enlisted below

Table 1- Various insulin delivery methods

Methods	Advantages	Disadvantages
Pen devices	More convenient, less painful than syringes, more precise, accurate, easier to use	More expensive than syringes, cannot mix two different insulins
Inhaled insulin (Exubera, Technosphere, Dexcome G4)	Noninvasive, high patient compliance, rapid onset of action	Less bioavailability, inhalational devices are used for this, may interfere with lung function
Oral	Noninvasive, patient friendly,	Less bioavailability
Nasal (nasulin)	No interference with	Local irritation, reduced

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	pulmonary function	mucous secretion
Transdermal (microneedle, ionotophoresis, electrophoresis, sonophoresis)	Needle free	Skin irritation, inflammation, pain at the site of administration
Vial and syringes	Less expensive compared to pen devices	Invasive method, less patient friendly, less accurate if compared with pens
CSII (continuous subcutaneous insulin infusion)	Continuous delivery of insulin, high patient acceptance	High cost

Vials and syringes

The word syringe is originated from the Greek word "syrinx" which means "tubes". The syringes are developed from mid-1800. The first syringe was the Fergusson Syringe which gave an idea to researchers to make the modern syringe which we use for injecting insulin. (7) Intravenous route was considered as the first parental route for delivering drug with the help of syringe. Subcutaneous route was developed in early 19 century. Becton, Dickinson and company made specially designed syringes for delivering insulin in 1924, two years after the discovery of insulin. (8) In earlier days' syringes are made up of metals which were reusable and they have to be sterilized in hot boiling water after every use. To overcome the transmission of infections through continuous use of same needle, disposable syringes came into the existence. BD Hypack was the first glass disposable needle made by BD in 1954. (9)

Insulin pen

The major disadvantages of syringe and vials were found to be inaccurate and inconvenient as we have to prepare a perfect insulin dose for injection. (10) This disadvantage led to the development of insulin in 1985. The first insulin pen was manufactured by NovoNordisk. (11) In past 30 years several advancements can be seen in these insulin pens. The new insulin pens are reusable, more accurate, having audible click sound system to reduce the human error while delivering the insulin. (12) Recent advancement in insulin pen is found to be an inbuilt recording system of time and date of last 16 injections which gives proper idea to the patient regarding the dose which he/she is taking along with the accurate time. (13)

If compared with vials and syringes insulin pens are less painful, easy to use, patient friendly, more accurate but associated with higher costs. The use of insulin pens widely differs between countries i.e. Europe (about 75%) diabetic patients use insulin pen and less in USA and India (about 15-20%) as a result of physician and patient related factors. (14)

Recent advancement in insulin pen includes shorter and thinner needles which are less painful and requires less thumb force and time for injecting insulin. Nowadays these pens guide patients about the dose of insulin by means of inbuilt calculator. They are also equipped with the memory function so as to maintain the record of dose and time of past 16 days. (15)

Continuous subcutaneous insulin infusion

In early 1960's the first insulin pump was invented by Kadish, however, it was limited to its technical issues and size. (16) Since then several modifications have been done to make it much comfortable to the patient and make it more efficient. In 1979 USA was the first country in which the first commercial insulin pump was used. Insulin pumps which we are using currently are smaller in size having smart features such as alarms, built-in-dose, and calculator. (17)

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Study of clinical trials indicates the effectiveness of the CSII over MDI (Multiple Dose Insulin) therapy in achieving reduction in insulin dose, improved patient satisfaction and quality of life, achieving glycaemic goals.

The main disadvantages of CSII are

- Costly therapy as compared to MDI
- Higher risk for diabetic ketoacidosis
- In convenience of being attached to a device (18)

Table 2-Types of insulin preparations

Types	Onset	Peak	Duration
Rapid acting insulin analogue	5-15 min	30-60 min	2-5 hrs
Short acting	30 min	1-3 hr	4-8 hrs
Intermediate or long acting (isophane or zing insulin)	1-2 hrs	4-8 hrs	8-12 hrs
Long acting insulin analogue	30-60 min	No peak	19-24 hrs

Novel approaches to deliver insulin

Number of disadvantages has been associated with subcutaneous administration of insulin as it is an invasive method, requires qualified personal, increased patient non-compliance. Thus, an alternative route for delivering insulin is needed to overcome those drawbacks.

Different routes for administration of insulin is are discussed below and till date only pulmonary route of delivering insulin is approved.

Inhaled insulin

Inhaled insulin was reported to be the first alternative for subcutaneous injection. It has been clearly seen that insulin is delivered in the aerosol form reduces the blood glucose level to a greater extent. (19) Early studies show that insulin obtained from bovine and porcine administered in aerosol form with the help of nebulizer shows marked reduction in glucose level in the patient. (20)

Advantages of pulmonary route for inhaled insulin

- Provides larger perfuse absorptive surface
- By pass the first pass metabolism
- Non-invasive method
- High patient acceptance (21)

The exact mechanism of insulin absorption through pulmonary epithelium is unknown but researchers think that it acts through paracellular or transcytosis mechanism.

Exubera was the first inhaled product which got certification from the USFDA in 2006. It was a dried formulation which comes in 1 and 3 mg doses which is combined with the inhaler for administration (22).

It was found that Exubera shows similar pharmacokinetics and pharmacodynamics with respect to insulin with a faster onset of action of around (10-15) min (23). In clinical trial studies it was seen that Exubera significantly reduced blood glucose level in those patients who were suffering from the uncontrolled T1DM and T2DM (24). Exubera was strictly contraindicated in those who smoke as it increases the risk of hypoglycemia due to greater absorption of drug when compared to non-smokers. Patient should undergo various tests before starting treatment. Despite of non-invasive method and high cost, was unable to do well in pharmaceutical market and in 2007, this

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product was revoked from the market by Pfizer (25).

Afreeza is another promising inhaled insulin dry powdered formulation manufactured by Sanofi and MannKind. Onset action of Afreeza is about 15 min and duration lasts for about 2-3 hours, and is said to be an ideal for controlling the glucose level. Despite of its long lasting duration Afreeza also have some drawbacks such as persistence of cough while using and moderate decrease in normal lung functioning. This device is in the process of FDA approval (26).

Oral Insulin

Oral route can be the most promising route of administration for insulin as it can closely mimic the physiological insulin delivery. However, the major challenges which occur in formulating oral insulin include

- Protecting insulin for proteolytic enzymes present in GI tract
- Low permeability of insulin through GI
- Low bioavailability

Major pharmaceutical companies are developing these kinds of carriers which can prevent the deterioration of insulin in GI tract by the action of proteolytic enzyme and to ease intestinal transport of insulin so as to directly deliver into the circulation with ample of bioavailability (27, 28).

For making the carriers' natural and synthetic nanoparticles have been used such as chitosan, various polymeric hydrogels, polymeric nanovesicles, polylactides. Oral insulin preparation such as Capsulin, OMRD-0801, IN-105 gives promising results in phase 1 and phase 2 clinical trials (29).

Nasal insulin

Due to less disadvantages when compared to other routes i.e. oral (by pass first pass metabolism), inhalational route (does not suppress the normal lung functioning), subcutaneous route (non-invasive method) makes this route prominent for delivering the insulin (30). Bovine and porcine insulin has been investigated in patients suffering from T1DM through intra nasal route. Till date Nasulin (CPEX pharmaceuticals) and Nasal insulin by (Nastech pharmaceutical) are in investigation procedure. Both of the insulin preparations show bioavailability around 20-25% with onset of action 10-20 min. Results of clinical trials are yet awaited. Substances such asfatty acid derivatives,bile salts, and surfactants can be used to increase the mucosal permeability of insulin. They can also produce local irritation along with the decrease in nasal secretion and burning sensation inside nasal cavity (31, 32).

Buccal insulin

Buccal delivery of insulin shows similar benefits of oral insulin but buccal has the advantage that it by passes the GI degradation. Furthermore, the large surface area results in better and higher bioavailability (33). Generex biotechnology developed Oral-lyn^{TM} which is a liquid formulation of insulin and is administered by using metered dosage aerosol. Eli- Lilly along with Generex conducted the phase-1 and 2 clinical trials on patients suffering from T1DM and T2DM which gave promising results (34).

Transdermal insulin

Problem associated with needle and syringes can be overcome with the use of transdermal delivery of insulin, in which large surface area makes it more convenient route for insulin delivery. However, the penetration of insulin is prohibited by the outermost layer of the skin (stratum corneum) (35).

Various methods can be applied to reduce the barrier of stratum corneum which are enlisted below-

- Use of electric current Iontophoresis
- Use of ultrasound waves Sonophoresis, phonophoresis
- Disruption of stratum corneum

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Various lengths of micro needles having diameter of 1µm can deliver insulin in an effective and accurate manner. Microneedle technology can be combined with transdermal patch (36). This technique is limited by skin injuries, blisters, can also cause pain and discomfort at the site of administration. These are evolving as a technology of long term utility; however, effectiveness and safety are not clearly known today.

Emerging opportunities (nanotechnology based systems)

Nanometer in metric systemis define as unit of length which is equal to the one billionth of the meter and is too small that it cannot be seen under conventional or regular microscopes. Size scale of nanoparticles is between 100 nanometer and less. Nano science can be defined as the study of structures and materials on ultra-small scale (atomic or molecular scale) (37). Nanotechnology is basically related to the production and application of structure, design characterization, device and system by regulating or changing the shape and size on the nanometer scale. Nowadays nanotechnology has become very important in fields like engineering, electronics, agriculture, health care sector etc. Extensive use of nanotechnology can be seen in the field of health care sector as it has been used in treatment and diagnosis of various diseases. Using nanotechnology quicker and cheaper treatment can be provided to the patients (38).

Pharmaceutical nanotechnology can be defined as use of nanotechnology in pharma sector for making devices for drug delivery along with diagnosis of disease with the help of imaging and biosensors (39).

Nanomedicine is a branch of medicines in which knowledge and tools of nanotechnology have been applied for prevention and treatment of disease. They include nano scale materials such as biocompatible nanoparticles or nano robots for delivering, sensing, diagnose purpose (40).

Use of Nanotechnology in diabetes

- **Detection of blood glucose levelandinsulin**

Several new methods and technologies have been discovered in past few years to measure the minute amount of insulin as well as the blood glucose level, those are enlisted below

- **Microphysimeter**- Microphysimeter is made up of carbon nanotubes which consist multi walled flat sheets of carbon atom which were stalked and rolled over in a small tube.
  - These tubes are electrically conductive and concentration of insulin in chamber directly relate to current at the electrode and pH at which these tubes are reliable to do work in normal cell.
  - Current detection methods used to detect the level of insulin production at several intervals by regularly collecting the small sample and measuring the amount of insulin in it.
  - This method is used to detect the insulin level by measuring the transfer of electrons that are produced at the time when insulin molecule gets oxidized in the presence of glucose molecule.
  - When cell produces more amount of insulin, the current intensity increases and vice versa, which allows monitoring insulin amount in real time (41, 42).
- **Implantable sensors-** These sensors are made up of polyethylene glycol

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coated with the fluorescent molecules having bead like shape.

- They are injected under the lining of the skin and stay in the interstitial fluid
- When there is a rapid decrease in the glucose level inside the interstitial fluid glucose displaces the fluorescent molecule from the sensor which results in the glow. This glow can be seen easily at the site where that implant has been implanted.
- Microchips having sensors have also been developed to monitor the change of glucose level inside the body by determining the key parameters of the body such as body temperature, pulse rate, glucose level etc.
- Chip is implanted inside the skin which gives regular signal to the detector which monitors the level of insulin and glucose (42).

- **Contact lenses**- Jin Zhang professor at university of Western Ontario has developed the contact lenses which changes its colour when there is a disturbance in the level of glucose.
  - These contact lenses are made up of nanoparticles which are embedded in the standard hydrogels.
  - These particles react with the glucose present in the tears and change its color.
  - The effect is slight but it can alert the patient about the condition so as he/she can take earlier measures (44).

Nanotechnology in treatment of diabetes

- **Oral insulin-** Insulin when administered via oral route do not get absorbed as the main barrier is intestinal epithelium which reduces the absorption of hydrophilic drug, as they are unable to diffused across the membrane (lipid bi layer) to the blood stream.
  - Therefore, the focus has been given to improve the paracellular transport of hydrophilic drugs, which requires a carrier system that protects the drug from the harsh environment of stomach and small intestine, if administered orally.
  - Chitosan polymer is used as the intestinal permeation enhancer.
  - Mucoadhesive chitosan is coated over the insulin nanoparticles that has the property to prolong the resistance time in small intestine, infiltrate into mucus layer and subsequently mediate the transient opening of the tight junctions between epithelial cells while becoming unstable and broken apart due to pH (45, 46).
  - The insulin released from the broken nanoparticles permeates through paracellular pathway into the blood stream.

Microsphere for oral insulin production- Microsphere system is the most promising strategy to be used for oral insulin. Basically it is a microsphere which acts both as a protecting layer (encapsulates insulin to avoid it from enzymatic degradation within its matrix) and as a permeation enhancer (which

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effectively crosses the epithelial membrane after oral administration) (47).

Use of nanoparticles for delivery of insulin-

Enlisted type of nano particles are used-

- Polymeric nanoparticles
- Ceramic nanoparticles
- Liposomes (48.49)

Polymeric nanoparticles- These are macromolecular substances which are solid or colloidal in nature having a size range of 10 nm-1000 nm (50). Depending upon the method of preparation these particles can be classified into two categories-

- Nanocapsules
- Nanosphere

These nanoparticles are completely different in their properties and also in release characteristics for the encapsulated drugs. Nanosphere is a matrix system in which the drug is uniformly dispersed while in case of nanocapsule drug is confined into a particular cavity which is surrounded by polymer membrane (51). These particles degrade inside the body through hydrolysis and results in the delivering the drug to target cells or tissue. Polymeric membrane degrades into lactic and glycolic acid which is further converted into carbon dioxide and water through Krebs cycle. Earlier researchers focused on the use of collagen and cellulose as these are natural polymers and are biodegradable with a non-toxic property (52,53).

Polymeric nanoparticles have a great advantage over oral and intravenous administration of drug in terms of efficacy and effectiveness. They can deliver higher concentrations of pharmaceutical ingredient at a desired site. Thus, this feature makes polymeric nanoparticles as an important and desired substance in diabetes therapy.

These particles have been used as the carrier for insulin and are biodegradable in nature. The polymer insulin matrix is surrounded by nano porous membrane containing glucose oxidase. Raise in blood glucose level initiate change in the surroundings of nano porous membrane which results in biodegradation and subsequent release of insulin. The reaction between glucose/glucose oxidase lowers the pH and results in swelling of polymers which leads to higher release of insulin at the site. The polymers used for this method are actually co-polymers like N,N-dimethylaminoethyl methacrylate and polyacrylamide (54).

Ceramic nanoparticles- These particles are made up of silica, aluminium or titanium along with calcium phosphate. Ceramic nanoparticles possess enormous advantages such as preparation which is easy, are highly biocompatible, very low size (>50 nm) more stable etc. (55). These particles generally protect the drug from degradation generally caused by change in external pH and temperature.

These nanoparticles can be manufactured in desired size and shape. They do not possess the tendency to undergo changes like swelling which is caused by change in surrounding environment. For delivering the parenteral insulin self-assembling ceramic nanoparticles are used (56). Core made up of Calcium phosphate is used as a carrier for insulin as the in vivo result of this delivery system is far better than the result of efficacy of porcine insulin. Recent studies showed that tricalcium phosphate nanoparticle can be used for oral delivery of insulin (57).

BioMEMS

Bio Micro Electro Mechanical Systems (BioMEMS) are implantable devices. These are used as insulin pumps for controlled release in case of rise in blood glucose level (58). 6 nm diameter pores and nano porous membrane are located in the exterior part of the bio-sensors which detect the change in blood glucose level thus resulting in the release of insulin. Micro needles can also be used for

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effective transdermal administration of insulin.

Biocapsules consists of two micro machined membranes which form a cavity bounded with nano porous membrane. Reported pore size was found to be 16 nm thus providing an easy permeability for biological matters like insulin, oxygen, glucose etc. Such biocapsules can be incorporated as BioMEMS devices for insulin delivery (59).

Table 3-Advantages and disadvantages for different types of nano particle

S.No.	Types of nanoparticle	Advantages	Disadvantages
1	Polymeric nanoparticles	Degrades easily by hydrolysis, have less cytotoxicity, high level insulin entrapment, bypass enzymatic degradation via stomach	As it is mucoadhesive it may adhere to the non-specific site in gastric mucosa
2	Ceramic nanoparticles	Protects the degradation of drug by the action of change in pH and temperature, desirable size and shape can be obtained, having easy preparation	Shows poor permeability across the membrane, having rapid mucociliary clearance
3	Liposomes	Immunogenic, biodegradable and non-toxic	Easily detected by defense system of the body, can accumulate in the skin, no specific drug loading capacity

Nanoparticle based delivery system for hypogylcemic drugs

Maximum of the hypoglycemic drugs are available in the form of capsules or tablets. Regular use of these drugs leads to serious adverse effects like systemic toxicity, complex dosing schedule, and longtime treatment (60). To overcome these limitations researchers have developed new drug delivery systems which improved their therapeutic efficacy. Novel drug delivery systems have been designed so as to deliver the anti-diabetic drug safely & efficiently to the desired location for better control and treatment of diabetes mellitus.

In past few decades, nanoparticle based drug delivery systems have gained a huge popularity. They show numerous potential advantages like controlled drug release profile, highly biocompatible in nature, show low toxicity, targeted drug delivery, proper embodiment of both lipophilic as well as hydrophilic drugs at a time etc. include few advantages that gained researchers' interest thus the need for nanoparticles in delivery systems has come to light (61).

Few nanoparticle formulations of oral hypoglycemic drugs are enlisted below-

Metformin solid lipid nanoparticle- Sharma et al.,havedeveloped (M-SLNs) and incorporated them in transdermal patches.

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These M-SLNs were prepared via solvent diffusion technique zeta potential for this preparation comes out to be +27mv and drug content was found to be 1.45mg/patch. The further ex vivo studies have shown that the cumulative release of drug from the patch was high and these results have given a clear idea to develop transdermal metformine patches for human use (62).

Rosiglitazone- loaded PLGA nanoparticles- Behera et al., have prepared nanoparticles by using emulsification solvent evaporation technique in which they used polymer which is biodegradable PLGA i.e. (poly D L-lactic- co-glycolic acid)carrier for sustain release. In this the drug release pattern was found to be in two phases i.e. in first phase(fast releasing) drug releases about 40% (within 24 hours) followed by slow releasing pattern/phase in which it releases about 90% within next 48 hours (63).

Pioglitazone Hydrochloride loaded chitosan nanoparticles- Borkhataria and Patel haveprepared and evaluated these nanoparticles. Method of preparation includes nanoparticle formation by ionic gelation of chitosan using tripolyphosphate anions at different concentrations. Particle size range found to be around 250-503 nm with +30.70-+40.50 mv zeta potential. Encapsulation efficiency and drug loading capacity were found to be 54-77% and 29-52% respectively and in-vitro study results have shown sustained release of drug from the nanoparticles over a period of 20 hrs. This test shows that it can be used in the management of Diabetes mellitus (64).

Repaglinide loaded ethyl cellulose nanoparticles- Lekshmi et al., have prepared these nanoparticles via solvent evaporation method. The prepared nanoparticles have shown 9.61% of drug loading and encapsulation efficiency was found to be 86.4%. The in-vitro studies were characterized by delayed drug release phase. Thus through this it was stated that nano encapsulation of drug in biocompatible and biodegradable polymer will improve its pharmacological significance by a large extent (65).

Repaglinide loaded SLN's- Ebrahimi et al.,prepared nanoparticles via solvent diffusion method. The zeta potential was found out to be -17$\pm$3 mv and mean size of nanoparticles was around 210 $\pm$ 16 nm. In vitro studies of these particles have shown the drug release profile for at least 24 hours with mild burst release(66).

Nateglinide loaded ethyl cellulose nanoparticles- Naikprepared nanoparticles which shows sustained release. These nanoparticles were prepared via using oil in water single emulsion evaporation technique. Particle size along with encapsulation efficiency was found to be 248.37 nm and 91.16% respectively. Nanoparticles formed were spherical in shape having a uniform size distribution. The obtained nanoparticles possess low crystallinity than pure drug (Nateglinide). The end result was found to be 61.1 $\pm$ 1.76% drug release up to 24 hours (67).

Gliclazide loaded chitosan nanoparticles- Alkem et al, have prepared nanoparticles by salting out chitosan with sodium citrate method. High drug loading capacity and encapsulation efficiency can be seen in the prepared particles. The results of these particles showed a prolonged action of drug for 24 hours an immediate (burst release followed by sustained release of it). The study also revealed that the drug release decreased with the increase in amount of polymer. (68)

Gliclazide- loaded Eudragit(L100 and RS) nanoparticle- Devaranjan and Sonavanehaveprepared gliclazide loaded Eudragit nanoparticles with a sustained release carrier for enhancing efficacy. The Eudragit nanoparticles have shown high drug loading capacity and high encapsulation efficiency. The prepared nanoparticles have shown a increased bioavailability, sustained

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release when compared to simple Gliclazide. This test has been done on streptozotocin induced diabetic rats. Eudragit nanoparticles can reduce dosing frequency, increase patient's compliance and can be useful to reduce ADRs (69).

Glimepiride- loaded nanoparticles- Mokale et al., prepared glimepride loaded nanoparticles using PLA as a polymer and method of preparation was o/w solvent evaporation. Encapsulation efficiency and drug content was found to be 80.55% and 40.27% respectively. These particles were spherical and uniform in size (442 nm). In-vitro drug release of these particles was found to be 78.12 % up to 12 hours (70).

Glibenclamide- loaded Eudragit L100 nanoparticles- Dora et alprepared these nanoparticles by solvent evaporation method. In this preparation method it was clearly seen that drug concentration increased with respect to polymer drug loading and encapsulation efficiency was also found to be increased. Dissolution studies of these nanoparticles clearly showed that there was an increase in the release of Glibenclamide. Significant change in solubility can be seen with respect to pure drug. There was an enhanced bioavailability which makes these nanoparticles superior to pure drug (Glibenclamide) as pure drug's bioavailability in the alloxan induced diabetic rat model was quite low when compared to the former (71).

Nutraceuticals in diabetes

'Nutraceutical' is a term derived from two terms i.e. nutrition and pharmaceutical which was named in early 1980s by the founder and chairman of the "foundation for innovative medicine", Stephen DeFelice. [1,2]

Nutraceuticals can be defined as the components or nutrients that have been isolated from or purified from nutritious substances that are edible and have natural benefits like providing health and nutrition with their actual functions along with the benefit of preventing the occurrence of a disease or use in treatment of particular disease. These are generally sold in medicinal or dosage forms and are not associated with foods from where these nutraceuticals are derived or isolated.[1,2]

Nutraceuticals are successful due to their properties of imparting various desirable therapeutic effects and benefits along with enormous reduction in side effects that are associated with the direct use of pharmaceutical ingredients in treatment and prevention of various diseases or disorders. (3)

Though there are numerous nutraceuticals to treat many diseases, over past few years' phytochemicals such as herbal polyphenols have become attractive components for researchers and consumers not only due to their potential health, physiological benefits and ability of preventing and treating numerous diseases but also due to their beneficial effect in improvement of immunity. [1,2,3]

By conducting appropriate experiments and research over the past years, researchers have proved that nutraceuticals provide much protection against numerous diseases like diabetes, cancer, cardiovascular diseases, neurodegenerative disorders etc. [1,2,3]

There's a need for the safe agents that can reduce the risk of diabetes. Though there are certain drugs like metformin, orlistat and acarbose that have shown preventive activities for diabetes. Nutraceuticals are known to have significant effect in reducing the risk of diabetes. Natural agents that slow down the carbohydrate absorption mimic the protective effects of acarbose like soluble fibre for example glucomannan, chlorogenic acid can reduce the risk of diabetes associated with heavy intake of coffee and also legume derived α-amylase inhibitors. (4)

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Though there are no natural lipase inhibitors that are functionally equivalent to orlistat, poorly documented claims regarding this are found in *Cassia nomame*extracts. The efficacy of metformin is found to be the activation of AMP-activated kinase. Preliminary evidence about certain compounds that are found in barley malt has shown that there are similar activities of metformin without the side effects associated with it. (4)

Generally, biotin activates are soluble in guanylate cyclase directly and a particular amount of biotin intake exerts its effect on β cells, liver and skeletal muscle thus favouring glucose tolerance and maintenance of β cell function effectively. Sufficient intake of chromium picolinate seems to promote the sensitivity of insulin in many of the individuals and also improved glycemic control in few diabetics was found. (4)

Some of the other natural agents like extracts of cinnamon and bitter melon are found to have a potential for treating and preventing diabetes. (4)

Researchers at the University of South Australia, in a review found on efficacy of nutraceuticals have statedthat nutraceuticals like *cinnamon, curcumin* (turmeric) and *resveratrol* (from grapes) were all effective in combatting various elements of diabetes like regulating glucose levels, improving insulin resistance and also reducing cholesterol.

They stated that “they have found that cinnamon can reduce fasting blood glucose levels in type 2 diabetes; curcumin can improve insulin resistance in pre-diabetic and Type 2 diabetes, and resveratrol can reduce glucose levels and improve insulin resistance”.

Though phytochemicals have efficient activity, majority of them are associated with low bioavailability, poor solubility in gastrointestinal fluids or undergoes first pass metabolism. This leads to diminished absorption of them from GIT and thus resulting in reduced or no biological activityand giving rise to the nanotechnology in this field that helps to overcome these drawbacks. Various researchers have used the principles of nanotechnology for delivering nutraceuticals very efficiently and also for enhancing their bioavailability and their biological activity. (3)

Various formulations like micelles, nanoemulsions, nanoparticles, nanocpchleats, nanocapsules, nanocrystals etc. are utilised for the delivery of encapsulated or entrapped nutraceutical. Thus, these nano formulations not only aid the encapsulated nutraceutical for targeted delivery but also help in sustained release of nutraceutical from the formulation thus improving bioavailability and therapeutic efficacy. (3)

Both organic and inorganic materials can be used in preparation of nanoparticles and nowadays various natural/nature-based biodegradable biopolymers are most frequently used for encapsulation. (5,6,7)

Nanoparticles can be produced by various methods like top-down methods like fluidisation, dispergation, homogenization or emulsification techniques or bottom-up methods like evaporation, condensation or precipitation techniques or through sol-gel synthesis. (8,9,10) Nanoparticles that are produced by using mechanical techniques are generally in a range of 100-1000 nm and for producing them in a size range of 10-100 nm bottom-up or chemical methods are used. [11,12,13].

Curcumin has drawbacks like poor bioavailability, low solubility, rapid metabolism, poor absorption which causes diminished use of it in clinical applications though it has efficient medical uses. (14,18). Curcumin when conjugated with metal oxide nanoparticles or encapsulated in lipid nanoparticles, nanogels, dendrimers, polymeric nanoparticles improves solubility

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and thus aiding the increment in its bioavailability and pharmacological effects are quite improved. [16,19].

In recent studies, found that in different formulations of curcumin only a hydrophilic carrier containing formulation mostly provide good therapeutic levels of curcumin in retina of rabbit. [15,17,20].

Resveratrol is another phytochemical derived from grapes has also similar drawbacks of curcumin like poor bioavailability, poor solubility and also low photostability thus diminishing its use. Oral administration of resveratrol undergoes high intestinal and hepatic metabolism. [21].

To overcome these drawbacks, different nanoformulations of resveratrol have been prepared and tested. These nano formulations include liposomes, polymeric nanoparticles, solid lipid nanoparticles, cyclodextrins etc. Thus, the use of nanotechnology in preparing nano formulations of curcumin, resveratrol etc. helps in the enhancement of solubility, bioavailability, physical stability, chemical stability and also controlled release of these nutraceuticals [22– 25].

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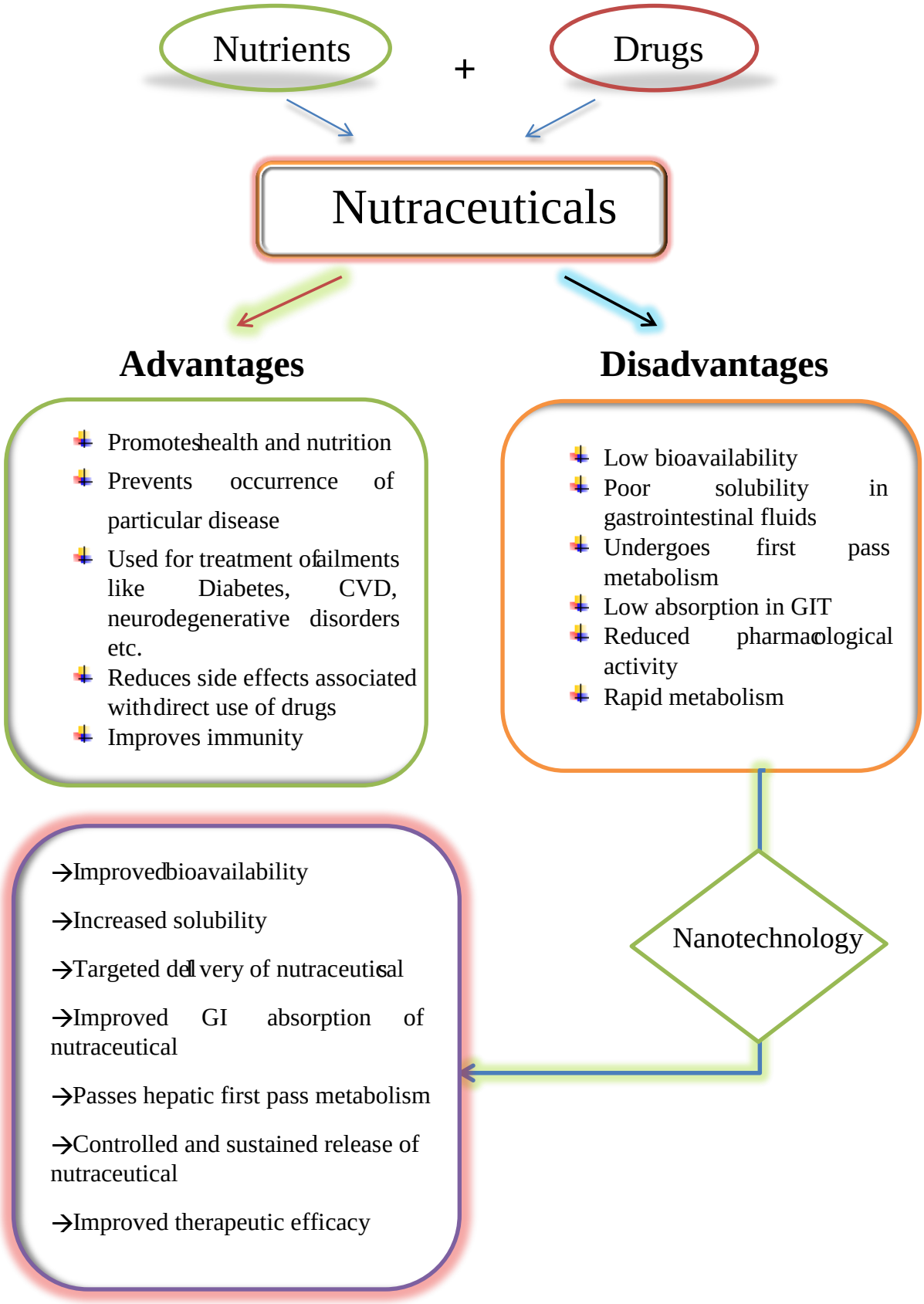

Encapsulated nutraceuticals in sodium alginates can be used for treatment of type 2 diabetes, obesity, GIT disorders, hypertension etc. Naringin is a flavonoid found in citrus fruits and has a role in prevention of diabetes and cardiovascular diseases. [26].

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Mahmoud et al. have studied that when STZ (streptozotocin) induced diabetic pregnant mice is administered with camel whey protein as a dietary supplement, found that the immune system of offspring was very efficient and verified that it played an efficient and protective role in diminishing the tendency of developing diabetes in the offspring. [27]

Comparison of prophylactic effects found in diabetic rats when induced with α- eleostearic acid rich nano and conventional bitter gourd seed oil emulsion showed that in supressing the oxidative stress, maximum efficacy was achieved when the diet is supplied with 0.5% (*w/v)* NE along with bioactive lipid conjugated α- LNA. Thus, this type of nano formulations can be used as nutraceuticals for supressing the effects of diabetes mellitusby reducing the adverse effects of excessive reactive oxygen species (ROS). [28].

When the nano sized natural clinoptilolite or nano sized metformin induced directly in high fat diet or streptozotocin induced diabetic rats, there were no efficient results in the serum glucose level, minerals and in lipid profile. But when clinoptilolite is co-treated with the drug, there was an increase in HDL cholesterol (high density lipoprotein) and Ca and Cu levels have increased only in metformin groups. [29].

When nano sized clinoptilolite is administered in streptozotocin induced diabetic rats, there was a drastic change in blood glucose level as it was found to be decreased nearly to normal levels but there was no significant effect on oxidative stress markers. [30].

Leaf extract of *Stevia rebaudiana*with Chitosan nanoparticles has given efficient results test groups of diabetic rats like enormous decrease in mean fasting blood glucose level when compared with control group of diabetic ratsand also the serum levels of some antioxidants and various enzymes like reduced GHS (glutathione), catalase, SOD (superoxide dismutase) were found to be much closer to normal level in test groups treated with nanoparticles when compared with control group. [31].

When selenite and ascorbic acid redox system has been added with *Catathelasmaventricosum*polysaccharide (CVP),a size range of approx. 50 nm spherical *Catathelasmaventricosum*polysaccharide-selenite nanoparticles (CVP-Se NPs) were formed. When these were administered and by considering the results of serum profiles as well as enzyme antioxidant levels it can be said that CVP-Se NPs have a higher antidiabetic activity (*p<0.05)* when compared with selenite nanoparticles, selenocysteine and Na_2SO_3. [32].

Fisetin is a nutraceutical which is an anti-hyperglycaemic agent and to control its release rate, an orally controlled releasing system containing polymeric nanoparticles having a size range of 140-200 nm are prepared. Generally they may containfisetin encapsulated with poly-(ε-caprolactone) and also poly-(lactic-*co*—glycolic acid)-polyethylene glycol-COOH. These nanoparticles have shown a preserved release of the API in simulated gastric conditions and a controlled release in intestine and have shown good improvement in α-glucosidase inhibiting activity of the fisetin when compared with commercial acarbose formulation. [33].

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Table 4- Pharmacotherapy

S. No.	Category of drug	Name of the drug	Brand Name	Dose	Mechanism of action	Route of administration	Dosage form	Limitation	References
1	Biguanide	Metformin	Fortamet Glucophage Glucophage XR Glumetza Riomet Riomet ER	500mg 750mg 850mg 1000mg	Decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves peripheral glucose uptake and utilization	Oral	Tablet ER Tablet Suspension Solution	Induce Infections, Nausea, Vomiting, Chest discomfort, flushing , palpitations, Diaphoresis	Drugs.com https://www.drugs.com/ppa/metformin.html USFDA https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020357s037s039,021202s021s023lbl.pdf
2	Sulfonylurea	Glimepiride	Amaryl	1mg 2mg 4mg	Stimulate the release of insulin from functioning pancreatic beta cells	Oral	Tablet	Induce Hypoglycemia, Headache, Nausea, Dizziness Increase Serum ALT	Drugs.com: https://www.drugs.com/ppa/glimepiride.html USFDA: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020496s021lbl.pdf

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3	Dipeptidyl Peptidase 4	Sitagliptin	Januvia	25 mg, 50 mg, 100 mg	Acts by slowing the inactivation of incretin hormones	Oral	Tablet	Results in upper respiratory tract infection, nasopharyngitis and headache, hypoglycemia	Drugs.com: https://www.drugs.com/ppa/sitagliptin.html USFDA: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021995s019lbl.pdf
4	Insulin Inhalation	Insulin	Afreeza Exubera	4 unit, 8 unit and 12 unit	Acts by stimulating peripheral glucose uptake and by inhibiting hepatic glucose production	Oral Inhalation	Inhalational Powder	Leads to and by inhibiting hepatic glucose production, Hypoglycemia, and may result in Lung Cancer	Drugs.com: https://www.drugs.com/pro/afrezza.html USFDA: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022472lbl.pdf
5	DPP-4 Inhibitor	Saxagliptin	Onglyza	2.5 mg, 5 mg	Saxagliptin is a competitive DPP4 inhibitor that slows the inactivation of the incretin hormones,	Oral	Tablet	Results in Peripheral edema, Headache, Hypoglycemia, UTI,	Drugs.com: https://www.drugs.com/ppa/saxagliptin.html USFDA: https://www.access

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								Lymphocytopenia etc.	data.fda.gov/drugsatfda_docs/label/2009/022350lbl.pdf
6	Meglitinide Analog	Repaglinide	Prandin	0.5 mg, 1 mg, 2 mg	Depolarizes the ß-cell and induces insulin secretion	Oral	Tablet	Induce hypoglycemia, upper respiratory infection, arthralgia, , and back pain	Drugs.com: https://www.drugs.com/ppa/repaglinide.html USFDA: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020741s041s042lbl.pdf
7	SGLT2 Inhibitor	Canagliflozin	Invokana	100 mg 300 mg	Reduces reabsorption of filtered glucose and increases urinary glucose excretion	Oral	Tablet	female genital mycotic infections, urinary tract infection, and increased urination	Drugs.com: https://www.drugs.com/ppa/canagliflozin.html USFDA: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204042s000lbl.pdf

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8	Thiazolidinedione	Pioglitazones	Actos	15 mg 30 mg 45 mg	Decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output	Oral	Tablet	upper respiratory tract infection, headache, sinusitis, myalgia, and pharyngitis	Drugs.com: https://www.drugs.com/ppa/pioglitazone.html USFDA: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021073s043s044lbl.pdf

Table 5-Preclinical studies on nanoformulation for diabetes

S8.No.	Formulation	Drug	Dose	Animal selected	Conclusion of study	Reference
1	Chitosan NPs	Insulin		Diabetic Rats	Prolonged the hypoglycemia and exert TJ opening effect	1. https://www.researchgate.net/profile/Ezharul_Chowdhury/publication/253329769_Oral_nano-insulin_therapy_Current_progress_on_nanoparticle-based_devices_for_intestinal_epitheliu

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						m-targeted_insulin_delivery/links/00b49521eabfbd7be900000 00.pdf 2. https://pubmed.ncbi.nlm.nih.gov/21925726/
2	CS/γPGA-DTPA NPs	Insulin		Diabetic Rats	CS/γPGA-DTPA NPs can promote the insulin absorption throughout the entire small intestine BA 20%	1.https://www.researchgate.net/profile/Ezharul_Chowdhury/publication/253329769_Oral_nano-insulin_therapy_Current_progress_on_nanoparticle-based_devices_for_intestinal_epithelium-targeted_insulin_delivery/links/00b49521eabfbd7be900000 00.pdf 2. https://pubmed.nc

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						bi.nlm.nih.gov/22243802/
3.	Dipalmitoyl-phosphatidylcholine (DPPC)/cholesterol liposomes	Insulin	0 to 8 units	Normal & Diabetic Rats	Prolonged hypoglycemic effects	https://www.researchgate.net/profile/Ezharul_Chowdhury/publication/253329769_Oral_nano-insulin_therapy_Current_progress_on_nanoparticle-based_devices_for_intestinal_epithelium-targeted_insulin_delivery/links/00b49521eabfbd7be900000.pdf https://pubmed.ncbi.nlm.nih.gov/61498/#:~:text=Hypoglycaemic%20effect%20of%20liposome%2Dentrapped%20insulin%20administered%20intragastrically%20into%20rats.,-Dapergolas%20G%2

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						C%20Gregoriadis&text=1%2D3%20units%20of%20insulin,77%25%20of%20those%20before%20treatment.
4	NaTC liposomes	Insulin		Normal mice	Significantly decreased blood glucose levels	1.https://www.researchgate.net/profile/Ezharul_Chowdhury/publication/253329769_Oral_nano-insulin_therapy_Current_progress_on_nanoparticle-based_devices_for_intestinal_epithelium-targeted_insulin_delivery/links/00b49521eabfbd7be900000.pdf 2.https://pubmed.ncbi.nlm.nih.gov/15464833/

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5	Cetyl palmitate-based solid Lipid nanopartoiicles (SLNs)	Insulin	2.5 IU of insulin/kg	Diabetic Rats	Prolonged Hypoglycemia (24 hours)	1..https://www.researchgate.net/profile/Ezharul_Chowdhury/publication/253329769_Oral_nano-insulin_therapy_Current_progress_on_nanoparticle-based_devices_for_intestinal_epithelium-targeted_insulin_delivery/links/00b49521eabfbd7be900000.pdf 2.https://www.researchgate.net/publication/5648991_Oral_insulin_delivery_by_means_of_solid_lipid_nanoparticles

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6	VB12-dextran NPs	Insulin		Diabetic rats	Prolonged hypoglycemia (54 h); 70-75% blood glucose reduction; Pharmacological Availability 29.4%	1https://www.sciencedirect.com/science/article/abs/pii/S0168365907002635 2.https://www.researchgate.net/profile/Ezharul_Chowdhury/publication/253329769_Oral_nano-insulin_therapy_Current_progress_on_nanoparticle-based_devices_for_intestinal_epithelium-targeted_insulin_delivery/links/00b49521eabfbd7be900000.pdf 3.https://pubmed.ncbi.nlm.nih.gov/17239471/

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Table 6-Clinical studies conducted on nano formulation for diabetes

S.No.	Formulation	Drug/Dose	Subjects enrolled	Duration	Status of study (withdrawn,completed)	Result	Reference
1	Capsulin	Insulin			Phase IIA for T1DM Completed & Phase II in T2DM is completed	Not available	https://journals.sagepub.com/doi/pdf/10.1177/193229681300700228
2.	ORMD 0801	Insulin/ 1 capsule ORMD 0801 3 times a day	12	July 2008 to August 2008	Phase II Completed	potentially slowing disease progression and delaying or even eliminating late-stage complications	ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT00867594?term=ORMD-0801&cntry=IL&draw=2&rank=1 2.https://journals.sagepub.com/doi/pdf/10.1177/193229681300700228 3.https://www.oramed.com/pipeline/ormd-0801-type-2/
`3.	NN1952	Insulin aspart/Single Dose of NN1952	84	November 2009 to June 2010	Phase 1 Completed but discontinued after Phase II		ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT01028404?term=NN1952&draw=2&rank=1 2.https://journals.sagepub.com/doi/pdf/10.1177/193229681300700228

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4	NN1953	Insulin Lispro	51	27 march 2014 to 1 July 2014	Phase 1 Completed	Positive Phase 1 Results	Clinical trials.gov: https://clinicaltrials.gov/ct2/show/NCT03392961 2. https://www.biocon.com/biocon_research_pipeline.asp
5	HDV-1	LiposomalIns ulin/ 2 doses of Oral HDV-1	230	Decem ber 2008 to Octobe r 2009	Phase II-III undergoing with unknown status	Unknown	1.https://clinicaltrials.gov/ct2/show/NCT00814294?term=HDV-I&draw=2&rank=1 2. https://www.diasome.com/breakthrough-hdv-technology
6	NN1953;NN 1954	Insulin Glargin	83	May 2012 to Octobe r 2012	Phase I Completed		1.https://clinicaltrials.gov/ct2/show/NCT01597713?term=NN+1954&draw=2&rank=1 2.https://journals.sagepub.com/doi/pdf/10.1177/193229681300700228

Table 7-List of patents

S. No.	Patent ID	Patentee	Patent for
01	CN1362143A	Yang Mengjun	Nano diabetes treating medicine and its preparation

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02	US9539210B2	Harvard College Brigham and Women's Hospital Children's Medical Center ,Corp Massachusetts Institute of Technology	Vaccine Nanotechnology targeting immunomodulatory actions
03	WO2010113177A2	RangaswamyVidhya, MalleshappaAminabhaviTejraj, Ramesh BabuVadde, ChaluvayyaMundargiRaghavendra, HiremathAnand	Oral insulin delivery systems for controlling diabetes incorporating nanotechnology
04	US8859004B2	Nano and Advanced Materials Institute Ltd	pH-sensitive nanoparticles for oral insulin delivery
05	WO2014160175A1	Brian Jay FELDMAN, HongjieDaiRajiv Kumar, Bo Zhang	Plasmonic substrate for multiplex assessment of type 1 diabetes
06	WO2015087329A1	Yoav David Livney	Pectin based nanoparticles
07	WO201417944A1	Daniel G. Anderson, Zhen GU, Alex Arthur AIMETTI, Robert S. Langer	Injectable nano-network gels for diabetes treatment

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