IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

"Novel drug delivery system for insulin''

Santosh Negi*, Parul Bisht[1], Dr.Shivanand Patil [2]

Deparatment of pharmacy, Shree Dev Bhoomi Institute of Education Science and Technology, Dehradun

Abstract

A metabolic condition called diabetes mellitus is characterised by hyperglycemia, glycosuria, and hyperlipidemia. The current medication delivery techniques for the management of diabetic mellitus (DM) make it difficult to deliver medications to the target site in a reliable and secure manner. Therefore, research into new delivery methods for diabetes medications is Novel drug delivery system, followed by the commercialization of these medications. The goal of the current review is to compile the most recent research on Novel drug delivery systems (NDDSs) for diabetics, with a focus on particulate, vesicular, and other systems. It is studied from this review that, to overcome the issues with the conventional dosage forms and to gain the end users' trust in the higher acceptability, it is discovered that the curiosity to develop NDDSs of anti-diabetic drugs with special attention to the nanoparticulate system followed by microparticulate and lipid-based system is gradually emerging. It was summerised that the unique potential of providing physical stability, sustained, and sitespecific drug delivery for a scheduled period of time can open new vistas for precise, safe, and effective treatment of diabetes mellitus in the current scientific landscape where the field of novel drug delivery system has been recognised for its tangible benefits.

Key Words: "nanoparticle", "microparticle", "liposomes", "niosomes", "transdermal systems", "insulin", "antidiabetic drugs" and "novel drug delivery systems".

Introduction

A metabolic condition called diabetes mellitus is characterised by hyperglycemia, glycosuria,hyperlipidemia, negative nitrogen balance, and occasional ketonemia. The thickening of thecapillary basement membrane, an increase in the vessel wall matrix, and cellular proliferation arecommon pathological changes that lead to vascular complications like lumen narrowing, earlyarthrosclerosis, glomerular capillary sclerosis, retinopathy, neuropathy, and peripheral vascularinsufficiency.[1] Over 150 million people have diabetes worldwide, and by 2025, that figure isexpected to reach 300 million or more as a result of an increase in sedentary behaviour, theconsumption of calorie-dense foods and obesity. A set of illnesses with diverse aetiologies thatare defined by chronic hyperglycemia and other metabolic abnormalities make up diabetesmellitus. Type I, type II, those caused by certain mechanisms or diseases, and gestationalDiabetes is categorized according to its etiological causes. Destructive lesions of pancreaticbeta cells caused by an autoimmune mechanism are a hallmark of type I diabetes mellitus.Reduced insulin secretion and sensitivity are the two characteristics of type II diabetes mellitus. In the past, daily subcutaneous injections of human insulin have been used to try to achieve rigorous glucose when controlling for diabetes. Although it has improved glycemic control, this approach falls short of accurately replicating the typical, diurnal plasma profile of endogenous insulin[2] Thecreation of innovative, non-invasive insulin administration methods holds the potential to further advances the management of diabetes. The need for frequent insulin injections, concerns about the Pain associated with insulin injections and other factors can act as barriers to starting insulin therapy. [2] Currently, diabetes mellitus is one of the most deadly non-communicable diseases, causing a high death and morbidity rates occur alongside cardiovascular disease and cancer. Diabetes mellitus, one

of the most prevalent chronic diseases, is an endocrine and metabolic condition characterized owing to hyperglycemia and several consequences. Genetic, environmental, microbial, immune system, and mental variables that lead to inadequate insulin production and insulin resistance are main cause of diabetes mellitus. Diabetes mellitus patients have long been plagued by lifethreatening complications that could drastically reduce their quality of life and even put their lives in danger. Chronic progressive lesions and multi-system and multi-organ focused damage are the results of long-term metabolic diseases,[3] such as diabetic retinopathy [4], diabetic nephropathy [5], and diabetic hypertension [6]

Types of Diabetes Mellitus[1]

Two major types of diabetes mellitus are as follows:

1. Type I or Insulin dependent diabetes mellitus (IDDM)

2. Type II or Non insulin dependent diabetes mellitus (NIDDM)

1. Type I or Insulin dependent diabetes mellitus (IDDM) : It is also known as juvenile onset diabetes mellitus. The majority of cases of pancreatic islet beta cell loss are caused by autoimmune antibodies that may be identified in the blood, although some cases are idiopathic and no beta cell antibodies are found. Circulating insulin levels are always low or very low in type 1 individuals, and they are more likely to go into ketosis. This type is less prevalent and has a low hereditary propensity.

2. Type II or Non insulin dependent diabetes mellitus (NIDDM): It is often referred to as diabetes mellitus with maturity onset. There is no beta loss or only a slight reduction in beta cell mass; insulin levels are low, normal, or even high; anti-cell antibodies cannot be shown; there is a high degree of hereditary predisposition; and start is typically delayed.

The Globe Health Organization (WHO) has designated India as the Diabetic Capital of the world due to an alarming increase in the incidence and prevalence of diabetes. According to studies,increasing patient understanding about the condition and its complications has a considerable positive impact on both patient adherence to treatment and the number of problems related to the disease. In light of this, we wanted to measure the level of knowledge regarding several topics relating to the prevention and treatment of associated problems in a population of diabetics visiting our clinic. [8]

Despite the proliferation of drugs on the market, there is currently no complete and effective treatment for diabetes mellitus (DM) due to their numerous side effects, which include nausea, vomiting and gastrointestinal irritation. As a result, these drugs eventually cause patients to become non-compliant, necessitating the need for highly skilled medical knowledge. [7,10] It might be more advantageous to find stable/non-invasive medication delivery methods that also have controlled release. Pharmaceutical researchers have primarily worked to change the physical and biological barriers that restrict access of drugs to the therapeutic targets, even though precise and safe drug delivery to the specific site for the scheduled period of time to get controlled and Sustained release remains a touchstone.
Because they provide tangible advantages in terms of decreased dosing frequency, increased bioavailability, prevention from degradation specifically against the harsh gastric environment, site specificity, and decreased side effects, novel drug delivery systems (NDDSs) have gained popularity in recent years. Numerous experiments conducted around the world's in vitro, ex vivo, and in vivo results strongly suggested that NDDSs are a new and promising approach to treat serious ailments and diseases. [11]

Problems by the antidiabetics

Antidiabetics are easily accessible on the international market. The majority of oral
Hypoglycemic agents are offered as tablets and capsules. However, these dosage forms come with a number of undesirable side effects and restrictions, including gastrointestinal degradation-related lactic acidosis in patients with abnormal kidney or liver function and water insolubility They do not adhere to patient safety and efficacy requirements. The limited accessibility of

conventional dose forms at the intended site of action, increased systemic toxicity, a small therapeutic window, and a complex dosing regimen for long-term treatment were all indicated by these side effects. [12]

The drugs' ideal concentration at the intended site of action and sustained effective concentration for a longer period are the two essential components for drugs to be effective. Oral hypoglycemics travel toward the site of action after instantaneous release from the biological membranes. But it takes roughly two to three dosages to deliver the therapeutic concentration into blood samples for the entire day. [13]

Additionally, DPP-4 inhibitors (vildagliptin, (Galvus), sitagliptin, (Januvia), and saxagliptin, (Onglyza)) and peptide analogues are available on the global market as tablets. Insulin and peptide medications, specifically GLP-1 and GLP1RAs, are generally available as subcutaneous (SC) injections. In the past ten years, they have received approval from the USFDA and EU for the treatment of DM. GLP-1 receptors, which are located in the brain, lung, pancreatic islets, stomach, heart, intestine, and kidney, are how Liraglutide, Exenatide, and Albiglutide work. They are used less commonly for oral delivery because of their vulnerability to proteolytic breakdown in gastric environments and shorter plasma half-life. Exenatide injections produce nausea, vomiting, and the development of antibodies when administered twice daily, whereas liraglutide injections only cause moderate, temporary nausea and vomiting when administered once daily. [14]

Another restriction is pain at the injection site and the resulting injection fear. It is difficult to increase these analogues' oral bioavailability. As a result, significant research is necessary in the field of drug delivery, which might be accomplished by looking at novel and more focused drug delivery carriers. [15]

Insulin

The INS gene in humans encodes insulin, a peptide hormone generated by beta cells of the pancreatic islets. It is regarded as the body's primary anabolic hormone. It promotes the uptake of glucose from the blood into liver, fat, and skeletal muscle cells, which controls the metabolism of carbs, lipids, and protein. The absorbed glucose in these tissues is either turned into glycogen by glycogenesis or into fats (triglycerides) through lipogenesis, or in the case of the liver, both. When there are high levels of insulin in the blood, the liver's ability to produce and secrete glucose is severely hindered. [16]

Structure of Insulin

A polypeptide with an estimated molecular weight of 6000, insulin. It is made up of a B-chain (basic) with 30 amino acids joined by two disulfide (-S-S-) bridges, and an A-chain (acidic) with 21 amino acids. Proinsulin, which has the A and B chains connected by the "connecting" peptide (Cpeptide), which in humans has 31 amino acids, is the immediate precursor of insulin in pancreatic cells. The molecular weight of proinsulin is 9000. Despite being fully synthesised, the majority of the current supply of insulin are still made from the pancreas of cattle (bovine).[35]

Mechanism of Action of Insulin [1,17]

The insulin receptor is a protein hormone that is implanted in the plasma membrane, just like other protein hormone receptors. Two alpha subunits and two beta subunits make up the insulin receptor, and they are joined together by disulfide bonds. While the connected beta chains pass through the plasma membrane, the alpha chains, which are completely extracellular and include insulin binding domains, do not. An example of a tyrosine kinase is the insulin receptor. In other words, it acts as an enzyme that phosphorylates tyrosine residues on intracellular target proteins by transferring phosphate groups from ATP. The enzymatic activity of the receptor is activated when insulin binds to the alpha subunits, causing the beta subunits to phosphorylate themselves (autophosphorylation)[1] . A biological reaction is then generated as a result of the activated receptor's subsequent phosphorylation of several intracellular proteins. The insulin interacts with a particular receptor made up of two extracellular and two transmembrane subunits connected by disulfide bonds. The subunits have tyrosine protein kinase activity, whereas the subunits have insulin binding sites. The active receptor subsequently phosphorylates a number of intracellular proteins, altering their activity and initiating a biological reaction. The particular receptor for insulin is made up of two extracellular and two transmembrane subunits that are joined by disulfide connections. Insulin binding sites are

present on the subunits, whereas tyrosine protein kinase activity is present on the subunits. Insulin binding to subunits causes the receptor to aggregate and internalise along with the attached insulin molecules. Tyrosine residues of the subunits undergo autophosphorylation as a result of this activation of tyrosine kinase activity, increasing the activity of this subunit to phosphorylate tyrosine residues of insulin receptor substrate proteins (IRS1, IRS2). This sets off a series of phosphorylation and dephosphorylation processes, which in turn stimulate or inhibit the enzymes involved in insulin's quick metabolic effects. By increasing the activity of the glucose transporters GLUT4 AND GLUT1, as well as by causing them to move to the plasma membrane, insulin promotes the transport of glucose across cell membranes. Over time, it also encourages the expression of the genes that control the production of GLUT. [17]

Needle free Technology of Insulin[2]

This issue is appropriate because, by its very nature, the diabetes market, and notably the development of insulin, is a breeding ground for novel approaches to medication administration. It is challenging to name another therapeutic field, let alone another single disease, where such a confluence of variables has fueled the creation of innovative delivery methods. The benefits of needle-free insulin injection include:
i. Increase adherence to the insulin regimen.
ii. Enhance the health and wellbeing of the patient.
iii. Prevents needle stick injuries and eliminates the need for sharps disposal.
iv. Quick injection; regardless of dose, insulin is administered in less than 0.3 seconds.
v. Large doses can be supplied without the need for additional pressure.

Novel drug Delivery System

Novel drug delivery system is used provide a therapeutic amount of drug to the appropriate site in the body to accomplish and then maintain the desired drug concentration.
Advantages of novel drug delivery system:
1. Protection from physical and chemical degradation.
2. Sustained delivery.
3. Improved tissue macrophages distribution.
4. Enhancement of stability.
5. Enhancement of pharmacological activity.
6. Protection from toxicity.
7. Increased bioavailability.
8. Enhancement of solubility [18].

1. **Microparticulate systems**

   The formulation of different drug-polymer combinations and targeted drug release to the precise treatment site are both made possible by microparticle-based therapy. By regulating their release, microparticulate systems assist in preserving the therapeutic concentration of medications (with a shorter half-life) in plasma for longer periods of time. Microparticles, which are tiny in size and have higher surface-to-volume ratios, can be created to increase the pace at which essentially insoluble medicines dissolve. Additionally, factors like dose and release kinetic are periodically changed as needed by using microencapsulation techniques, adjusting the drug-polymer ratio, etc. in order to get the ideal therapeutic concentration of the medication in systemic circulation. Microparticulate systems have been developed for oral, topical, parenteral, and nasal, routes. Concept of microencapsulation has been used to modify drug release pattern and to enhance in vivo hypoglycemic effect of Glipizide and Gliclazide. According to reports, the processes of release of pharmaceuticals that are microencapsulated are erosion or diffusion for matrix types and diffusion for reservoir types. [19]

2. **Nanoparticulate systems: [20,21]**

The carriers of choice for delivering antidiabetic medicines are nanoparticulate systems due to their relatively increased intracellular absorption. Additionally, they cover a wide spectrum of structures (1-1000 nm in size), including nanospheres, nanocapsules, nanodiamonds, and nanofibers. They can be divided into four categories: biological NPs, lipid-based NPs, metalbased NPs, and polymeric NPs. Methods used to create these nanostructures include ionic gelation, free radical precipitation/dispersion, solvent displacement, emulsion solvent evaporation, diffusion solvent evaporation, polyelectrolyte complexation, ionotropic polyelectrolyte pre-gelation, and dispersion polymerization. They have unquestionably increased the blood glucose-lowering potential of drugs like insulin even up to 22 days, protected actives from harsh gastric pH, increased bioavailability, and reduced dosing frequency have reflected the potential benefits of nanoparticulate systems. This is primarily due to their tiny size and explicit morphology, which allows them to pass through very fine blood capillaries and protect peptide/peptide surrogate or other contents from deterioration.

3. **Niosomes [22]**

Niosomes are non-ionic surfactant vesicles with a lamellar structure that are created by the molecules of the surfactant self-assembling. Niosomal vesicular systems are created to lessen the frequency of dosing and the dose-dependent toxicity of medications with shorter halflives, such as metformin. These medications include Glibenclamide, which is poorly water soluble. The production of bilayer vesicles is primarily influenced by the hydrophiliclipophilic balance of the surfactants, the chemical makeup of the contents, and packaging characteristics. Niosomes have been used as a system to increase the bioavailability of medications with extremely poor aqueous solubility and to extend the time that the active medication is available for action at the intended spot.

4. **Liposomes [23,24]**

Liposomes are vesicular structures that have been created artificially and are mostly made of a lipid bilayer. Various classic liposome types, including unilamellar (ULV) and multilamellar vesicular systems, are described in the literature (MLV). Liposomal systems have been used to encapsulate cytotoxic, anti-diabetic, anti-cancer, proteinaceous, and genetic material, and it has been shown to be a reliable method for delivering drugs to the target site of action. Such liposomes are created employing a range of polymers and a number of formulation processes, such as thin film hydration and membrane dialyzing method, two-step double emulsification modified reverse phase evaporation, etc. Studies on their in vitro and in vivo pharmacodynamic release indicated that they would continue to release over several weeks. A different strategy has also been tried, such as the triggered release of insulin using liposomal delivery to the lungs, which ensured an extended hypoglycemic impact, lasting up to 72 hours, with a lesser degree of adverse effects and improved efficacy.

Devices used in Insulin drug delivery System

1. **Jet Injectors: [9,25]**

A jet injector is a kind of medical injectable syringe that punctures the epidermis with a high-pressure, narrow jet of the injection liquid rather than a hypodermic needle. It is driven by compressed air or gas, either from an internal gas cartridge or small cylinder or through a pressure pipe from a large cylinder. Some are single shots, while others are multi-shots. Instead of using needle syringes, diabetics use them to inject insulin.

2. **Insulin Infusion Pumps: [26]**

An insulin pump, sometimes referred to as continuous subcutaneous insulin infusion therapy, is a medical device used to administer insulin in the management of diabetes mellitus.

3. **Insulin Pen: [9]**

The insulin bottle and syringe are combined into one modular unit in pen devices, which makes them innovative. Carrying insulin and syringes is no longer necessary thanks to insulin pens. In 1987, Novo Nordisk introduced the first insulin pen (NovoPen®). Since then, a wide range of pen types and shapes have become available. Pens can be divided into two primary categories: reusable ones and ones with prefilled ink. In the first scenario, a patient needs to fill an insulin cartridge before using it. Both types of pens can hold cartridges that range in size from 1.5 ml to 3 ml and contain U100/ml insulin. With reusable pens, different pen device manufacturers have varied requirements for the steps needed to change an insulin cartridge. Prefilled devices are widely used in type 2 patients' bedtime insulin regimens. Reusable insulin pens have a number of benefits, including longevity, the capacity to carry a three- to five-day supply, and the removal of the requirement for cartridge refrigeration. The size and weight of the refilled insulin pens have been reduced. They employ the shortest and finest disposable insulin needles, which results in less pain. Additionally, because they resemble a fountain pen, they are quick and simple to use and are thought of being discrete. The pen device's creators advise keeping the needle separate and only attaching when ready to use. Reusing insulin pen needles has been demonstrated to reduce the economic burden of diabetes without causing needle tip deformity or greater pain, according to a study. Pen needles come in a variety of gauges and lengths, ranging from 8 mm to 12.7 mm (from 29- to 31-gauge; the larger the gauge number, the smaller the diameter of the needle bore). The gadgets may improve glycemic control and increase lifestyle flexibility. For type 2 diabetics, many of the newest generation pens can deliver 60 U at once. In some nations, such as France, where more than 50% of insulin-treated patients use insulin pens, they have become quite popular.

4. **Insulin micropump: [25,27]**

Small molecule drugs may be delivered gradually and over an extended period of time thanks to a controlled release system developed by Flamel Micro Pumps. It is acceptable in the top portion of the small intestine's rather narrow window of absorption. The Flamel Micro Pump Technology uses numerous capsules or tablets that each contain microparticles. The 200–500 mm diameter size microform in the stomach and pass into the small intestine, where each microparticle, operation delivery system releases the medication via osmotic pump at a variable rate (micro pump first or delayed for micro pump second) and over an extended period of transit time. The micro particle design can be adopted to be each drug specifically modifying the coating thickness and composition include the expedients, allowing extended transit time enough plasma mean resident time extended up to 24 hrs, which is spatially suited drug known to be absorbed only in small intestine (encapsulation) reduce toxicity and/or C max, or peak plasma drug concentration (an improve patients regimen).

5. **Insulin Nanopump [28]**

The Insulin Nanopump delivers unmet improvement in diabetes treatment and is based on Nanopump technology. Its goal is to significantly improve patients' quality of life. It was created with the help and assistance of diabetic patients, nurses, and endocrinologists. It was designed as a patch pump without tubing to provide the patient more flexibility and freedom. Its incredibly small size and light weight allow for wear under clothing, its ultra-precision enables accurate insulin delivery even at very low delivery rates and regardless of Novel Drug Delivery System for Insulin Shree Dev Bhoomi Institute of Education, Science & Technology 23 | P a g e environmental conditions, its integrated functional monitoring ensures complete safety while being used, and its design as a whole makes it more patient-friendly.

6. **Insulin port[29,30]**

   A medicine delivery pathway into the subcutaneous tissue is what an insulin port does. A soft cannula, a short, flexible tube, is inserted under the skin to apply the injection port. The soft cannula serves as the entrance to the subcutaneous tissue once the insertion needle has been inserted and removed. The needle from an insulin pen or syringe is used to administer medication through the insulin port. The drug is promptly injected into the subcutaneous tissue through the soft cannula while the needle stays above the skin's surface.

7. **Transdermal patches: [31]**

   Recently, Ozin and Landskron revealed that they have developed an unusual substance utilising dendrimers, which are synthetic molecules. It functions as a new kind of patch in that it can store medications and, when applied to the skin as a film, allow them to diffuse into a patient's bloodstream. The issue with present drug delivery systems is that the drugs are either injected too little so that they are ineffective or administered too much so that they reach a dangerous concentration and remain in the system. The brand-new substance, called Periodic Novel Drug Delivery System for Insulin Shree Dev Bhoomi Institute of Education, Science & Technology 24 | P a g e Mesophorus Dendrisillicus (PMD), would allow medications to permeate a person's epidermis in the ideal quantity and maintain that level.

Novel Approaches to deliver Insulin

Many problems, including injection discomfort, annoyance, erratic compliance, and difficulties establishing postprandial blood glucose control, are connected to the subcutaneous technique of administering insulin. In addition, compared to physiologic distribution to the portal vein, subcutaneous insulin injection causes peripheral hyperinsulinemia. As a result, there is interest in using alternative noninvasive delivery methods for insulin. The pulmonary route of administration is currently accepted and debated, along with alternative routes that are being looked into. [32]

Inhaled Insulin[33]

As an alternative to subcutaneous injection, insulin delivery to the lungs was first documented. The fact that insulin delivered through aerosol lowers blood glucose has long been understood. Early research demonstrated that both diabetic and non-diabetic participants had an immediate hypoglycemia after receiving bovine or porcine insulin by nebulizer.

Oral Insulin [34]

The oral approach of administering insulin may be the most convenient for patients and more closely resemble natural insulin delivery (more portal insulin concentration than peripheral). The difficulties in producing oral insulin, however, include: Inactivation by proteolytic enzymes in the GI tract and low permeability across the intestinal barrier as a result of insulin's greater size and hydrophobicity, resulting in poor bioavailability. In order to deliver insulin to the circulation with adequate bioavailability, several pharmaceutical companies are working to create carriers to shield insulin from GI breakdown and promote intestinal transport of insulin.

Colonic Insulin Delivery [35]

Currently, oral colon administration is regarded as important for the treatment of systemic therapeutic objectives as well as local diseases, especially inflammatory bowel disease. Drug absorption processes are best suited for the small intestine, however the large intestine has several advantages over the small intestine, including a longer transit time, lower levels of peptidases (which prevent peptide synthesis), and a higher response to permeation enhancers.

Nasal Insulin Delivery [36]

The distribution of insulin through intranasal method is appealing because it has various advantages over other routes, including oral (bypasses GI peptidases), subcutaneous (noninvasive and painless), and inhalation (no issues with lung function). However, intranasal administration has drawbacks like inconsistent absorption caused by quick mucociliary clearance and restricted penetration of a big molecule via the nasal mucosa.

Buccal route delivery [37]

Buccal administration of insulin has similar benefits as oral insulin with the advantage of bypassing GI breakdown. Additionally, the surface area's relative size leads to improved bioavailability. Oral-lynTM, a liquid version of short-acting insulin that is administered using Generex's metered dosage aerosol applicator (RapidMistTM), was first created by Generex Biotechnology. Phase 1 and Phase 2 trials by Eli-Lilly and Generex in people with T1DM and T2DM have encouraging outcomes.

Intra Peritoneal Delivery [38]

As previously mentioned, peripheral hyperinsulinemia is linked to the intravenous and subcutaneous routes of insulin delivery, which are regarded as nonphysiological. The high portal insulin concentration is simulated by administering insulin directly into the portal vein. Since the 1970s, research has been done on this method of delivering insulin. Under general anaesthesia, the pump (The MIP 2007C Medtronic/Minimed, Northridge, CA, USA) is implanted in the lower abdomen beneath the subcutaneous tissue. The peritoneum is opened from this subcutaneous pocket, and the catheter's tip is cautiously inserted and pointed in the direction of the liver. Depending on the patient's specific insulin needs, the pump reservoir is replenished in the outpatient clinic transcutaneously at least every three months after implantation. Intraperitoneal insulin administration has been found to be both safe and effective in clinical trials.

Conclusion

There is a long history of study devoted to finding an insulin administration method that is least intrusive or noninvasive, efficient, safe, practical, and economical for patients. Every route and delivery technique has potential benefits and drawbacks of its own. Alternative delivery methods, however, could transform the management of diabetes mellitus and enhance the quality of life for patients if they are successful. Novel drug delivery systems serve to boost therapeutic value by decreasing toxicity, enhancing bioavailability, and other factors. They also lessen the need for repeated administration to overcome non-compliance. Through the use of these Novel delivery methods, natural medicines will exhibit improved bioavailability, decreased toxicity, sustained release action, and protection from GI degradation.

References

1.Tripathi KD, Essentials of Medical pharmacology, 5thedition, 2004, New Delhi, pp. 235-236., 246.

2.Verge D. Insulin: New molecules and routes of administration-Biotechnological innovations in insulin therapy, Medical Science 2004, 20, 986-998.

3.Wu, T., Xie, G. X., Ni, Y., Liu, T., Yang, M., Wei, H. F., et al. (2015). Serum metabolite signatures of type 2 diabetes mellitus complications. J. Proteome Res. 14, 447–456.

4.Cheung, N., Mitchell, P., and Wong, T. Y. (2010). Diabetic retinopathy. Lancet 376, 124–136.

5.Mauricio, D., Alonso, N., and Gratacòs, M. (2020). Chronic diabetes complications: the need to move beyond classical concepts. Trends Endocrinol. Metab. 31, 287–295.

6.Yamazaki, D., Hitomi, H., and Nishiyama, A. (2018). Hypertension with diabetes mellitus complications. Hypertens. Res. 41, 147–156.

7.Tuomilehto J, Lindström J, Eriksson JG, et al. (2001). Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. New Engl J Med 344:1343– 1350

8.Gulabani M, John M, Isaac R, Indian Journal of Com-munity Medicine, Vol. 33, Issue 3, July 2008, pp. 204.

9.Gulabani M, John M, Isaac R, Indian Journal of Com-munity Medicine, Vol. 33, Issue 3, July 2008, pp. 204.

10.Ensign LM, Cone R, Hanes J. (2012). Oral drug delivery with polymeric nanoparticles: the gastrointestinal mucus barriers. Adv Drug Deliver Rev 64:557–70

11.Dash TK, Konkimalla VB. (2011). Poly-ϵ-caprolactone based formulations for drug delivery and tissue engineering: a review. J Control Release 58:15–33

12.Sutradhar KB, Sumi CD. (2014). Implantable microchip: the futuristic controlled drug delivery system.

13.Pradhan SK. (2011). Microsponges as the versatile tool for drug delivery system. Int J Res Pharm Chem 1:243–58

14.Kalra S. (2013). Glucagon-like peptide-1 receptors agonists (GLP1 RA). J Pak Med Assoc 63:1312–15

15.Schmid MH, Korting HC. (1996). Therapeutic progress with topical liposome drugs for skin disease. Adv Drug Deliver Rev 18:335–42

16.Voet D, Voet JG (2011). Biochemistry (4th ed.). New York: Wiley

17.Evans JL, Goldfine ID, Maddux BA, Grodsky GM. Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes. Endocrine reviews. 2002 Oct 1;23(5):599- 622.

18.Muller RH, Runge SA. Solid lipid nanoparticles (SLN) for controlled drug delivery. In: Benita S, editor. Submicron emulsions in drug targeting and delivery. Harwood Academic Pub, 22(7), 1998, 219-234.

19.Soppimath KS, Aminabhavi TM, Kulkarni AR, Rudzinski WE. (2001). Biodegradable polymeric nanoparticles as drug delivery devices. J Control Release 70:1–20.

20.Peng Q, Zhang ZR, Gong T, et al. (2012). A rapid-acting, long-acting insulin formulation based on a phospholipid complex loaded PHBHHx nanoparticles. Biomaterials 33:1583–8

21.Dash TK, Konkimalla VB. (2011). Poly-ϵ-caprolactone based formulations for drug delivery and tissue engineering: a review. J Control Release 58:15–33

22.Kumar GP, Rajeshwarrao P. (2011). Nonionic surfactant vesicular systems for effective drug delivery: an overview. Acta Pharma Sin B 1:208–19

23.Misra GP, Singh RS, Aleman TS, et al. (2009). Subconjunctivally implantable hydrogels with degradable and thermoresponsive properties for sustained release of insulin to the retina. Biomaterials 30:6541–7

24.Bi R, Shao W, Wang Q, ZhKoda-Kimble MA, Young LY, Kradjan WA, Joseph B, Allodredge BK ; Diabetes Mellitus ; In: Applied Therapeutics- The clinical use of drug, Philapedia, Corelli Lippincott and Willkins:2004 ;13,50.

25.Panchal A, Shah V, UM U. Insulin drug delivery systems: a review.

26.islet.isletsofthope.com/pic/zzpic insulin pen .jpg

27.wikipedia.org/wiki/insulin-port.

28.port=images.google.co.in/images?gbv=2&hl=en&q=insulin+port&btnG=Search+iages.

29.pharmainfo.net/reviews/recent_progress_active_transdermal_drug_delivery

30.Soares S, Costa A, Sarmento B. Novel non-invasive methods of insulin delivery. Expert Opin Drug Deliv. 2012;9:1539–58

31.Gänsslen M. Über inhalation von insulin. Klin Wochenschr. 1925;4:71.

32.Arbit E, Kidron M. Oral insulin: The rationale for this approach and current developments. J Diabetes Sci Technol. 2009;3:562–7.

33.Maroni A, Zema L, Del Curto MD, Foppoli A, Gazzaniga A. Oral colon delivery of insulin with the aid of functional adjuvants. Adv Drug Deliv Rev. 2012;64:540–56.

34.Yaturu S. Insulin therapies: Current and future trends at dawn. World J D

35.Kumria R, Goomber G. Emerging trends in insulin delivery: Buccal route. J Diabetol. 2011;2:1– 9.

36.Gin H, Renard E, Melki V, Boivin S, Schaepelynck-Bélicar P, Guerci B, et al. Combined improvements in implantable pump technology and insulin stability allow safe and effective long term intraperitoneal insulin delivery in type 1 diabetic patients: The EVADIAC experience. Diabetes Metab. 2003;29:602–7

37. Kumareswaran K, Evans ML, Hovorka R. Closed-loop insulin delivery: Towards improved diabetes care. Discov Med. 2012;13:159–70

38. Sinha VR, Singla AK, Wadhawan S, et al. (2004). Chitosan microspheres as a potential carrier for drugs. Int J Pharm 274:1–33