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Novel Technologies Mark the Future of Insulin

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ABSTRACT

Diabetes mellitus is a chronic disease that is characterized by inadequate pancreatic insulin secretion or poor insulin directed mobilization of glucose by target cells. Population affected with diabetes has increased from 108 million in 1980 to 422 million till date. So, it is clearly evident that the rate is alarming and diabetes has now become a global problem. Diabetes is seventh leading cause of death globally. Insulin therapy in diabetes is the commonest and the most effective therapy. Conventional methods like subcutaneous or the oral route are having several shortcomings like the pain and invasion associated with injections, oral degradation of insulin, infection, etc. Among all the demerits hypoglycemia is the major issue especially nocturnal hypoglycemia as the patient cannot monitor the level of glucose at night. To overcome these detriments there is a need for insulin delivery through novel technologies. Many novel technologies have been proposed like the painless smart patch, Clicksoft microinjection device, pens, pumps, modified oral delivery oral delivery, inhaled insulin, etc. for the delivery of insulin. Many other novel devices and routes are being developed. This review discusses the glimpse of these novel technologies with their pros and cons.

Keywords: Diabetes Mellitus, Insulin, Smart Patch, Clicksoft microinjection device, Afrezza.

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INTRODUCTION

Diabetes mellitus is a chronic disease that is characterized by inadequate pancreatic insulin secretion or poor insulin directed mobilization of glucose by target cells. This disorder basically arises because of the inability of the body to metabolize proteins, carbohydrates and lipids due to the impaired function of insulin. It is characterized as a heterogeneous disease because, as the disease progresses there are severe complications like retinopathy, neuropathy, nephropathy and other cardiovascular issues. [1,2]

Diabetes mellitus can be classified into three types i.e., type I diabetes mellitus, type II diabetes mellitus and gestational diabetes. [1]

The number of people with diabetes has increased from 108 million in 1980 to 422 million in 2014. The rise has been equally dramatic in India. India has been stated as the diabetes capital by WHO with a rise in diabetic population from 11.9 million in 1980 to 64.5 million till date and it has been predicted that by 2025 every 4th person in the world suffering from diabetes will be an Indian. [2]

Insulin therapy in diabetes is the commonest and the most effective therapy. Insulin was discovered in 1920s at the university of Toronto and later was used successfully in a 14-year-old patient named Leonard Thompson. Fredrick banting and J.R.R Macleod received Nobel prize for the same and shared the prize with Charles Best and James Colip respectively. In 1950s basal insulin was developed and in 1990s more rapid acting insulin was developed. Basal insulin was lente, ultralente and protamine hagedorn for extending the time action profile of insulin while the more rapid acting insulin improved the post prandial glucose levels and reduced the nocturnal hypoglycemia. [3,5]

But, despite the development in basal and prandial insulin there lies many challenges regarding insulin delivery. The conventional forms of insulin fail to have therapeutic index due to their degradation in gastro-intestinal tract because of lack of stability. The most widely used form of insulin are insulin injection given subcutaneously but has many disadvantages like pain or hypertrophy at injection site, infection due to improper administration, cost-effectiveness, etc. Hypoglycemia and especially nocturnal hypoglycemia is the major problem. There is even the fear of missed meals and if then prandial insulin is taken then it leads to hypoglycemia. Many techniques of insulin administration are even invasive which reduces patient compliance. [1,3,4]

Because of the shortcomings associated with conventional insulin, there is a need for non-invasive and longer acting insulin with reduced side effects. Much work and research has been done in the

different routes and technologies for administration of insulin. These new insulins have proved to be more effective in managing diabetes with lesser side effects. This review will discuss all the novel technologies for insulin administration with their pros and cons.

Painless smart patch

People from the North Carolina state university, Raleigh have designed insulin delivery device based on microneedle array patches integrated with hypoxia sensitive hyaluronic acid (HS-HA) vesicles containing insulin and glucose oxidase (GO_x) which is claimed to be first of its kind. It contains live beta cells and delivers insulin when the level of glucose in blood increases. There are glucose responsive vesicles(GRV_s) which are formed by the combination of hypoxia sensitive hyaluronic acid and a hydrophobic component called 2-nitroimidazole which gets converted into a hydrophilic molecule called 2-aminoimidazoles. The complex of hyaluronic acid and 2-nitroimidazole is called HS-HA and this complex forms the glucose responsive vesicles. Insulin and glucose oxidase is entrapped into the vesicles. Under hyperglycemic conditions, glucose undergoes oxidation catalyzed by GO_x and this forms a microenvironment of hypoxia which leads to dissociation of the vesicles and release of insulin. [6] In this system, no chemical is used to sense the rise in glucose in blood instead the oxygen which is consumed in the reaction of glucose and GO_x leads to hypoxia and ultimately dissociation of vesicles. [6]

Chief advantage of this system is that it is painless as the GRV_s are loaded into an array of microneedles(MN_s) and these MN_s are made up of hyaluronic acid, which makes the MN_s stiff and reduces the loss of GRV_s. In the presence of high interstitial glucose, the MN_s disassemble. This patch was tested on mouse model of type 1 diabetes. [6] The schematic diagram of smart patch is shown in figure 1.

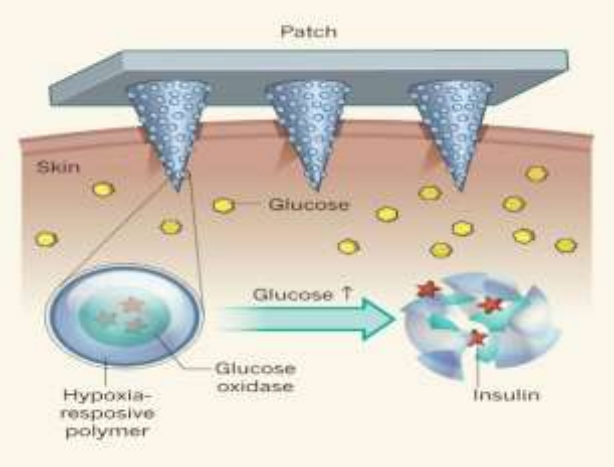

Figure 1: Schematic of the glucose-responsive insulin delivery system using hypoxia-sensitive vesicle-loading MN-array patches. [7]

This system has the following advantages:

i) Fast responsiveness and close similarity of pharmacokinetic parameters to pancreas.

ii) Ease of administration

iii) Biocompatibility [6]

Among many advantages of this smart patch, one is that it is using glucose oxidase which is an enzyme for detecting the presence and amount of glucose without any limitations which makes it unique in comparison to other insulin patch pumps or pumps available. There are many insulin pumps which sense the glucose with the help of chemical moieties, but the accuracy of dose is still in question. These glucose sensing moieties have certain limitations like phenylboronic acid(PBA) will interact with glucose and the interaction will be more efficient in basic environment which doesn't matches to the physiological pH. Another glucose sensor called conA precipitates in-vivo toxicity. [6]

The fluorescence microscopy and SEM of MN array loaded $GRV_{(s)}$ is shown in figure 2.

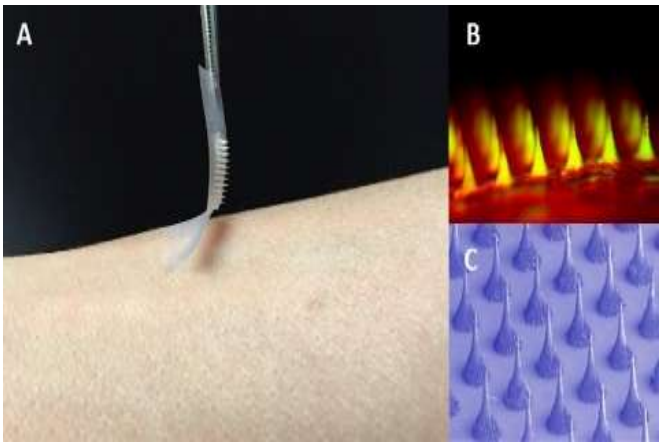

Figure 2. A) Photograph of the smart insulin patch with an MN array. B) Fluorescence microscopy image of MN-loaded GRVs with FITC labeled insulin. C) SEM image of MN array. [8]

Painless intradermal delivery of insulin: The novel Clicksoft microinjection device

Clicksoft is a spring loaded micro needle intradermal injection system. Patient does not experience pain while taking insulin from this device as this design makes the use of microneedles. [9] The functioning of the device can be explained as when the trigger of the device is pressed by the patient, the microneedles project out of the device and pierces into the skin and the drug is passed into an ultrafine needle in a fine stream of liquid medication from the drug chamber into the layers of the skin. After the trigger is released the needle is retracted back into the device ensuring safe disposal. [9]

There are wide range of advantages associated with the clicksoft technology which are listed as follows:

1. Clicksoft has the proficiency to deliver 100 plus units of insulin in a single dose.
2. This device is suitable for rapid acting insulin. It has a faster onset of action when compared to any of the rapid acting insulin presently available in the market.
3. It reduces the needle force by 60% because of the use of microneedles and ultimately minimizes the pain experienced by the patient.
4. It has a prefilled fixed dose chamber which is color coded for different doses.
5. No patient to patient contamination is found while using this device and there is no hazardous needle disposal as it is retracted back into the device.
6. No refrigeration is required as it is using stabilized insulin.
7. Cost effective. [9]

This device has been proved to be effective in dogs and almost painless. [9] Schematic diagram of clicksoft microinjection device is shown in figure 3.

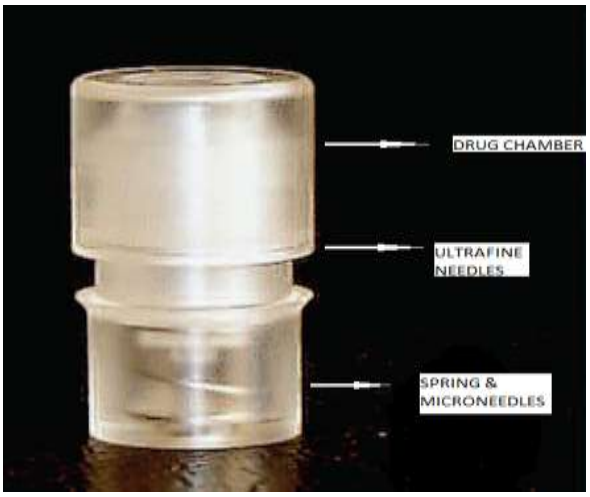

Figure 3: Clicksoft Microinjection device with drug chamber [9]

Insulin pen technology

As the name suggests, in this system a pen is there, which contains a cartridge of insulin and it can be used multiple times a day by a single patient by using a disposable syringe every time. This device also reduces the risk of cross contamination between the patients.

First pen devices were introduced by Novo Nordisk in 1987. [4]

There are basically two types of pens that is Prefilled pen and Reusable pen. [11, 12] Prefilled pens can be easily understood as a “use and throw pen”. This contains a prefilled cartridge of insulin which when ends up the pen has to be disposed off. These pens have single unit dosing increments,

audible clicks when dialing the dose, a large magnifying window that shows unit dose, two-way dose setting that allows the user to decrease the dose without taking the pen apart or discharging the insulin from the pen, and the end dose click indicates delivery of the complete dose. These type of pens are suitable for the people who cannot manage changing the cartridge but these type of pens can be expensive. First prefilled syringe was Novolin70/30 in 1993 and the latest ones are Humalog and Humulin by Eli Lilly. [11, 12]

Reusable pens are those which have replaceable cartridges and once the insulin ends up the patient can insert a new cartridge. This is suitable for the patients with changing regimens so they can change the type of insulin without having to change the pen. This system is economical but this may lead to the loss of sterility and damage to the pen over the course of time. In reusable pens first injection is screwed into the pen, then the dose is dialed, then injection is inserted subcutaneously and after pressing the plunger the injection is kept inside for 5 sec. Generally, the capacity of these pens is 1.5ml or 3ml. cartridge should be refrigerated and after it is inserted into the pen temperature should be maintained below 86^0F. [11, 12]

Innolet is a novel pen and it looks like an oven timer. It is appropriate for elderly patients as it can be easily manipulated. It has an easy to read large clock like dial to adjust the dose and an easily press able button. It can deliver insulin upto 1-50 units with 1 unit increments. This pen can also be used by the people having vision or motor disability. [12] Schematic diagram of innolet is shown in figure 4.

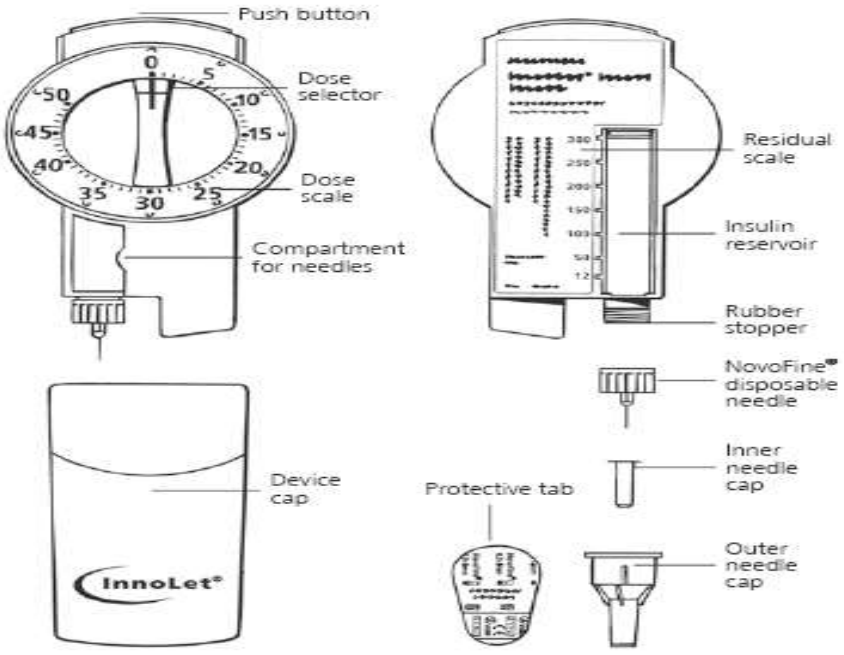

Figure 4: Innolet device. Schematic of different parts of the device [15]

There are many advantages of pen technology like these are more convenient, more accurate, less painful because of the use of small gauze needles, provide more flexibility, convenient for elderly, children, adolescents and pregnant women. [11]

Photographs of novopen, autopen and flexitouch is shown in figure 5., figure 6. and figure 7. respectively.

Figure 5: Novopen 4 [14]

Figure 6: Range of autopens of various capacities [16]

Figure 7: Flex touch [17]

Many examples of the insulin pens present in the market are mentioned in table no.1.

Table 1: Commercially available insulin pens in the market [12]

Sr. no.	Name of the insulin pen	Manufacturer	Special features
1.	Humapen memoir	Eli Lilly	Patient can review date, time and amount of last sixteen doses.
2.	Novopen Junior	Novo Nordisk	Available in vibrant colors. Gives 0.1 increments.
3	BD pen classic BD pen mini	Becton Dickinson	Dark dosing number on light background and audible click when dialing.
4.	Autopen AN 3000 Autopen AN 3001	Owen Mumford	Insulin cartridge is compatible with all pen needles. Unique side firing mechanism for easy injection and handling. Less force required to inject.

Insulin pump technology

First portable insulin pump was invented by Kadish in 1963 while first commercial pump introduced in US was in 1979. There are three mechanisms in our body by which the insulin achieves its functions. First is the presence of background insulin which is present all the time except during starvation. Secondly, secretion of insulin in response of the glucose. Thirdly, the adjustment in the secretion of the insulin by beta cells according to the release of glucose. There is burst release of insulin every 13 minutes in the blood. Insulin pump achieves all these three functions by ultra-short acting insulin. Insulin pumps are also known as continuous spontaneous insulin infusion(CSII). This system is recommended for kids above the age of 12 years failed treatment with injections, more HbA_{1c} level with failed Multiple dose injections(MDI) therapy. It is specially recommended for children below 12 years and 5 years. [18] Pumps can be allocated into the following classes:

Insulin patch pumps:

Now-a-days insulin pumps and insulin patch pumps are coming with glucose sensors. Patch pumps were developed to overcome the demerits of pumps. A patch pump consists of an insulin reservoir, delivery system and cannula and these are all integrated into a small wearable disposable or semi disposable device. In this device tubing has been eliminated and it is easy to use as compared to pumps. Omnipad is the only patch pump available in the market and is marketed by Ypsomed. It is a tube free disposable device which is applied with the help of adhesive and is changed every three days. It has an integrated infusion set and automated inserter and it wirelessly communicates with the personal data manager(PDM) which controls the delivery of insulin. As it is water proof so can be worn during shower. [19]

There is other patch pump also called Solo Micro pump and Calibra Finesse patch pump. Both of them are approved by the FDA but are not yet available commercially. The micro pump is small and slim and consists of 2ml of insulin reservoir and a cannula which need to be replaced every 2-3 days. [19]

Different patch pumps which are under development are the “cellnovo pump”, “Vgo pump”, jewel pump, Cequr pump, the passport transdermal system, nilipatch disposable system, freehand system. [19]

Insulin pumps coupled with glucose sensors:

First type of devices in this system are called the non-automated or open loop systems. This system consists of a glucose sensor and an external pump. The glucose sensor senses the glucose and it is displayed on the pump screen. Then the patient can adjust insulin release from the pump. Recent

system in the market is Minimed Paradigm REAL-Time system. Soon Animas vibe™ will also be in the market. [19]

In case of these non-automated system there was a major demerit that as the patient had to regulate the delivery of the insulin depending upon the level of glucose being displayed on the screen, so there were cases when patients did not react to the hypoglycemic alerts as they were mostly during the night time. This problem was most common in elderly and children. Due to this hindrance arises the need of automated system. This type of system delivers the insulin by connecting to the glucose sensor and so there is no need of monitoring the value of glucose. [19]

Example of this type of system is Medtronic and is used in Europe for around two years. [19] photograph of Medtronic insulin pump is shown in figure 8.

Figure 8: Medtronic insulin pump [20]

V-go:

V-go is a FDA approved device which delivers insulin every hour for an interval of 24 hours. This system uses the patch technology and is non-electric and does not requires batteries or tubing. V-go uses rapid acting analog insulin. It can be worn while having shower. The dimensions of the device are 2.4*1.3 inches. Every 24 hours a new insulin cartridge has to be placed inside the device. The pros of this device are that needle phobia is eliminated, reduces multiple dose injections, can be taken outdoors adheres to the skin with colostomy adhesive and auto inserts 30 gauze needle that results to minimized pain. [21]

Shortcoming of the device was found out that it only has three predetermined basal delivery options and it is mostly recommended for type-2 diabetic patients. [21] A well labelled diagram of V-go pump is shown in figure 9.

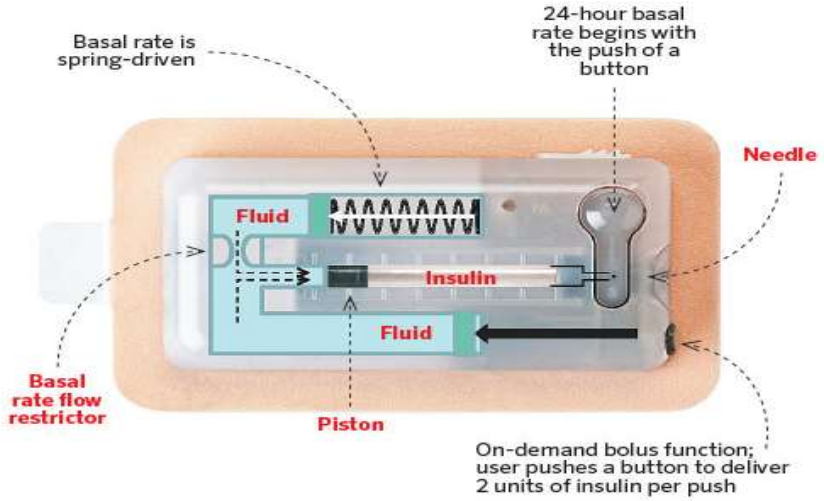

Figure 9: V-go pump. Schematic of various parts of the pump. [22]

Calibra finesse device:

This device was approved by the FDA in 2010 and was acquired by J&J in 2012. [23] It is a slim plastic device which has to be worn on the skin for 3 days and it contains 200 units of insulin. The wearer can take boluses in two unit increments by pressing two buttons simultaneously on the device. [23]

Its key benefit is its small size that is 0.25*2*1 inches which leads to patient compliance. [23] Demerit of the system is that it is not able to deliver basal dose of insulin so multiple dose injections(MDI) has to be taken. [23] Photographs of omnipod, solo, calibra finesse, cellnovo and jewel pump is shown in fig 10.

Figure 10: Various pumps used for spontaneous infusion of insulin. OmniPod pump, Solo Pump, Calibra Finesse pump, Cellnovo pump and Jewel pump.

Many examples of the pumps present in the market are given in table 2.

Table 2: Commercially available insulin pumps in the market [25]

Sr. no.	Name of insulin pump	Manufacturer	Special features
1.	Animas Vibe insulin pump	Animas corporation	Only integrated continuous glucose monitoring(CGM) system approved for children of 2 years of age.
2.	Accu-check combo	Roche insulin delivery systems	Water tight upto 8 feet for 1 hour. Compatible with windows except windows 8.
3.	Omnipod	Insulet corporation	No tubing required. Compatible with all windows except windows 8. Waterproof.
4.	Dana diabecare IIS	Sooil development	

Transdermal insulin

Skin provides a barrier for large and hydrophilic peptides like insulin. But, it has been found that if we overcome this drawback then skin can prove to be an excellent media for the delivery of insulin. This route is having several rewards like the large surface area of the skin, this route escapes the first pass metabolism by the liver, checks drug degradation, gives good patient compliance. The penetration of insulin through the skin can be boosted by several physical and chemical methods like iontophoresis, sonophoresis, microdermabration, etc. [5, 30]

0.25In iontophoresis the insulin molecules were charged and they were facilitated into the skin with the help of a small electric current. The basic underlying principle of iontophoresis can be stated as the current provides the external energy to the ions present in drug move across the skin. An iontophoretic system comprises of an anode, a cathode and two reservoirs, out of which one contains the drug ions while the other contains the biocompatible salt. There can be anodal or cathodal iontophoresis. In the anodal system, the cationic drug ions are placed under the anode at the site of application and the cathode is placed on a different site on the skin. In the cathodal system the arrangement of the anodal system is reversed. [30]

According to a patent numbered US5681580A, a patch type device was mentioned for iontophoretic delivery of insulin. They have disclosed a patch type device which can provide a releasable attachment between the container of the insulin and a power supply for supplying electric current to insulin. This was economically effective as compared to the prior art. [32]

The prior art of this patent was a Korean patent no. 92-2264. It stated that the device comprised of an insulin solvent filled reservoir and a water swellable and insulin carrying polymeric supporting layer on which insulin is dispersed as a powder, and needles are there which expand on discharge of insulin and an electrode is present in the reservoir for supplying electricity to the reservoir and

the skin. When this patch was pressed over the skin, the needles expanded and penetrated the skin passageways. The passageways close for a while due to swelling of the perforated skin. Then electricity is applied to the electrode housed in the reservoir and so the ionized insulin moves towards the opposite electrode. Due to the phenomenon there is shrinkage of skin and enlargement of the pores so the insulin gets delivered. [32] A photograph showing iontophoresis is shown in fig 11.

Figure 11: Iontophoresis [31]

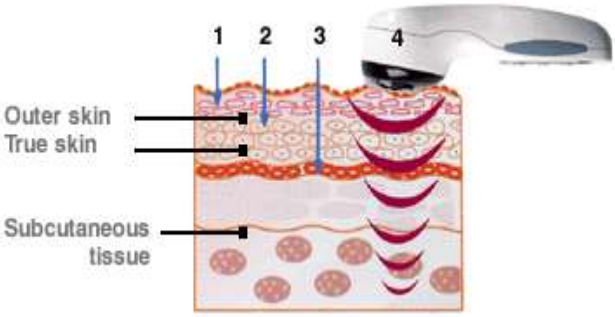

Figure 12: Sonophoresis [31]

Sonophorosis is another technique which can be used for the delivery of insulin. In this ultrasound waves are used to increase the penetrability of the skin when insulin is applied as an aqueous solution or is mixed with a hydrogel. The frequency which is used is generally 3MHz. [5] A photograph demonstrating sonophoresis is shown in fig 12.

A technique called microabration stated that the penetrability of the skin could be increased by damaging the upper layer of the skin or startum corneum. [1]

Inhaled insulin

This route is appropriate for the delivery of insulin because of the large surface area provide by the alveoli and the rapid absorption of the drug into the blood stream. [34]

Afrezza is a product present in the market which is a rapid acting inhaled form of the human insulin. Afrezza was approved by the USFDA in 2014. The mechanism of action of afrezza is similar to that of other devices that is it increases the absorption of glucose by the skeletal muscle and lessens the production of hepatic glucose. [33]

Afrezza is available with 4 and 8 unit cartridges which is tailored in the inhaler. The content of the cartridge comprises of dry powder of insulin which becomes aerosolized when the patient breaths through the inhaler. Respiratory issues are commonly associated with afrezza. [33]

Another inhalational powder known as Exubera was approved by USFDA and later was taken up by Pfizer but later in 2007 all the inhalational products were withdrawn from the market. [1, 4]

One more of these inhalational products called TI was approved in 2010 and the inhaler used was called DreamBoat but the whole system was known as Gen2. TI is regular human insulin which is formulated by absorbing it onto the technosphere microparticles. [4]

Absorption of inhaled insulin decreases if the person is suffering from Chronic obstructive pulmonary disorder(COPD) and the absorption was altered in smokers. [33]

There are many products which are present in the market for pulmonary administration of insulin. Some of them are described below.

AER_x iDMS was developed NovoNordisk. This system uses a liquid formulation of insulin and expels a single dose of aerosol of insulin through the nozzle. [4] A diagram of AeRx device is shown in figure 13.

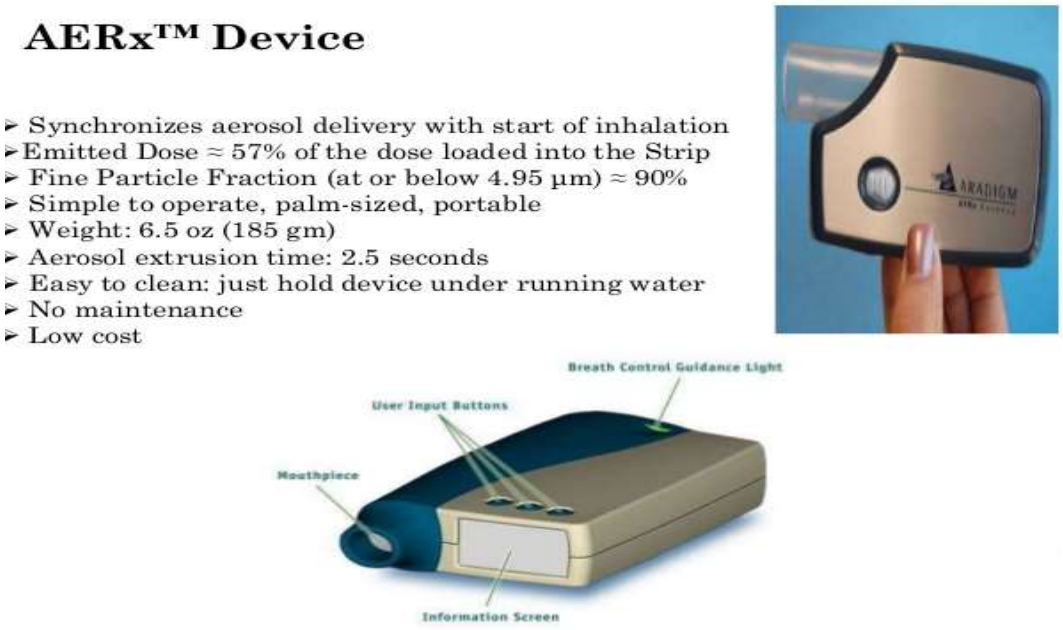

Figure 13: AERx™ device with its characteristics and different parts.

Advanced inhalation research(AIR) was developed by Alkermes and Eli Lilly. It contains dry capsules of insulin and it is a breath activated system. The aerosol of this system consists of large, porous particles that contain insulin. [4]

Technosphere insulin is a crystallized form of insulin which is encapsulated in gelatin capsules and then it is filled in high impedence inhaler. [4]

Spiro system was introduced by Elan corporation and it is dry powder formulation of insulin delivered by self-breath inhaler. [4] The advantages of afrezza over exubera is mentioned in table 3.

Table 3: Advantages of Afrezza over Exubera [37]

Afrezza	Exubera
Lower bioavailability and slower clearance	Higher bioavailability and faster clearance
Large device	Small device
Complicated titration system	Easy to use
Doses were in milligrams	Doses are equivalent to insulin units
Time consuming in-office training	Less training required
Device required weekly cleaning	No cleaning required

A well labelled diagram of afrezza inhaler is shown in figure 14.

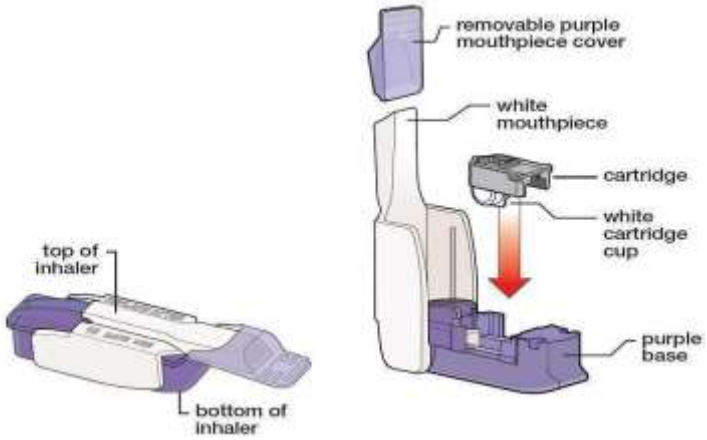

Figure 14: Afrezza inhaler. Schematic of different parts of the inhaler. [35]

Insulin delivery by oral route

There are many challenges faced in the delivery of insulin like digestion by proteolytic enzymes in the intestinal lumen, rapid enzymatic degradation in the stomach and due to its high molecular weight, there are permeability issues. these detriments can be overcome by the mentioned solutions:

i) Modifying the physicochemical properties

ii) Addition of novel functions

iii) Use of improved carrier systems [39]

Among the many approaches for the delivery of insulin, some are elaborated below:

Enzyme inhibitors:

Enzymes which are responsible for the degradation of the insulin are serine protease trysin, α-chemotrypsin and thiol mettaloproteinase IDE. So, researchers have aimed to give protease inhibitors in order to slow the rate of degradation of insulin and thereby increase the concentration of insulin for absorption. Examples of trypsin inhibitors are pancreatic inhibitor, soyabean trypsin inhibitor, camostat mesylate and aprotinin. Examples of inhibitors of insulin degrading enzymes are 1,10 phenanthroline, p-choromericuribenzoate. [39]

Permeation enhancers:

permeation of peptides can be improved by increasing paracellular or transcellular transports. Paracellular transport can be increased by modulating tight junctions of the cells with the help of calcium chelators. These act by inducing calcium depletion, disrupting actin filaments and adherent junctions and thereby diminish cell adhesion. Transcellular transport can be increased by increasing the fluidity of cell membrane with the help of surfactants and these act by exfoliating the intestinal membrane. Example of permeability enhancers are sodium laurate, cetyl alcohol, sodium cholate, EDTA and zonula occludens toxin. [39]

Hydrogels:

These are ideal candidates for oral delivery of insulin due to their ability to responds according the changing pH of gastrointestinal tract and is responsible for protection of insulin. [39]

Insulin delivery by nanoparticle carrier:

When insulin is delivered by the oral route, it is degraded due to its instability in the gastrointestinal tract. This limitation can be overcome with the help of nanoparticles. Nanoparticles are the submicron particles with the size range of 100nm or less. These are used as carriers of insulin for oral delivery as they are highly stable, feasible for incorporation of hydrophobic and hydrophilic substances, can release drug in a controlled rate from the polymeric matrix. When the nanoparticles reach the system they are taken up by the payer's patches of intestine. Many nanoparticle carriers were tried for the delivery of insulin. [41]

For eg: alginate, chitosan, etc.

Enteric coated capsules were filled with freeze dried chitosan nanoparticles which functioned as carrier of insulin and these capsules facilitated the oral delivery of insulin. Capsules were protected from the proteolytic enzymes against degradation while they were in the stomach and the shell dissolved when it reached the intestine and therefore the drug was released. [41]

Resealed erythrocytes for delivery of insulin:

Erythrocytes can prove to be potential carriers for the oral delivery of many peptides including insulin as they are biodegradable, biocompatible and inert in nature. These erythrocytes can deliver the encapsulated material in sustained zero order release and have prolonged circulation time. Encapsulation will prevent the degradation of the drug in the gastrointestinal tract so the bioavailability will increase. [5]

For the synthesis of resealed erythrocytes, first blood has to be collected from a living organism. Then the blood is centrifuged and the RBCs are separated. Now these RBCs are placed in

hypotonic solution which leads to the rupturing of the RBCs and the drug solution is diffused on it. Later these erythrocytes are placed in isotonic solution which again leads to sealing of the RBC. [5] The merits of this system are that it can release the drug in a steady state in the therapeutic window with reduced side effects. But this technology stands back due to some issues like storage of these RBCs is not easy, contamination of the RBCs when they come in contact of the environment, etc. [5] Lot of work is being done on the resealed erythrocytes and soon our researchers will come out with affirmative results. [5]

Buccal delivery of insulin

This route is having similar disadvantages as the oral route ie. Degradation due to stomach acids. Many products for buccal delivery were developed like Oral-lyn^{TM} by Generex Biotechnology which is liquid formulation of short acting insulin administered by generex metered dose aerosol applicator. It is under phase II clinical trials. Another molecule called Recosulin by Shreya Lifesciences Pvt Ltd. is under phase 2 and 3 trials. [5, 39]

Another method of delivering insulin by the buccal route is by using insulin in fast dissolving film. Midaform insulin was developed by Monosol Rx and Midatech company for insulin delivery. Another formulation of insulin loaded orally dissolvable film is undergoing pharmacokinetic/pharmacodynamics investigation(NCT01446120). [5, 39]

FUTURE TRENDS

Presently diabetes is a burning topic and countless number of studies are going on. There is a bright future of the technologies being developed for the delivery of insulin. Many techniques are under study and will become a reality in future which now are merely a dream. One of these many technologies is the encapsulated cells used for insulin delivery. In patients with Type-I diabetes autoimmune cells attack the islet of pancreas thereby impairing the release of insulin. For such patients, answer to their problem can be transplantation of islet cells but these cells also had the risk of being attacked by the immune system. Scientists have come up with a resolution for this problem. Researchers from MIT, Boston Children School developed a technology of encapsulating the cells to be transplanted. Alginate gel is used for encapsulation of the cells as they do not harm the cells and allow the movement of glucose and other peptides so that cells can sense the presence of glucose and release insulin. But it was found that there was scar tissue build up around the transplanted cells. So 800 derivatives of alginate were prepared by adding different groups. Out of these triazolethiomorphine dioxide(TMTD) was found to be successful. They tested TMTD in the mice with strong immune system and implanted these cells into the intraperitoneal cavity. It was

found that cells were actively producing insulin for complete length of the study ie. 174 days. [46]

Another technique was put forward by the researchers of Niagara University. They proposed that insulin can be delivered orally with vesicles. This technology is known as Cholestosomes™. Cholestosomes are neutral lipid based particles, simple lipid esters are used to prepare the vesicles which trap the drug molecules inside. When these lipids assemble into spheres, they form neutral particles which are resistance to stomach acids. When cholestosomes reach the intestine, body identifies it as something to be absorbed. So, the cells take them in and break them apart to release the insulin. These findings were presented in the American Chemical Society. [48]

Researchers from University of California Santa Barbara presented their findings in American Association of Pharmaceutical Scientists(AAPS) of insulin capsule. They have designed an intestinal patch contained in a capsule. The patches are made up of mucoadhesive polymers loaded with insulin contained in an enteric coated capsule. When it reaches the intestine the capsule dissolves and the patches adhere to the intestinal wall and release insulin. [44]

Many other studies are going on which will minimize or even end the use of multiple dose injections.

CONCLUSION

Due to the pain and other shortcomings of the conventional methods for the delivery of insulin, people are hesitant to commence the insulin therapy. So, more acceptable, painless technologies for insulin delivery have been searched and worked upon for many years. Many technologies are under trials, while many of them are available in the market. The highlight of the methods used for delivery of insulin is the painless smart patch designed by the people of North Carolina university. It is a patch with live beta cells and delivers insulin according to the level of glucose present in the blood stream and is painless due to the inclusion of microneedles. Painless smart patch will mark the start of a revolution in the field of insulin delivery. Novel technologies in insulin delivery will prove to be a blessing for the mankind. These novel technologies will define the future of insulin delivery.

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