Needle free injection technology biology essay

Science, Biology

ABSTRACT:

Needle free injection systems are innovative ways to introduce a variety of medicines in patients without piercing the skin with a traditional needle. This systems work by the mechanism in which liquid medication is forced at a high speed through a tiny orifice that is held against the skin. Due to this an ultrafine stream of high pressure fluid is created, that penetrates the skin without the use of a needle, thus faster administration of drug occurs as compared to conventional needles. They are present in the form of power sprays, edible products, inhalers, and skin patches. Needle free systems are designed to solve the problems created due to conventional needles making them safer, less expensive, and more convenient. It is expected that these systems will augment the rate of vaccination and reduce the amount of antibiotics prescribed. Moreover, they should decrease the number of needle stick accidents that have been seen in some health care workers contracting diseases. Today, they are a increasingly rising technology that promises to make the administration of medicine more efficient and less painful. Companies are not only working on developing devices that are safer and easier to use, but also on alternatives which can deliver even more types of medicines. Keywords: Needle, Free injection, drug delivery.

INTRODUCTION:

Generally injections are given to people to protect them from various diseases such as influenza, tetanus, cholera, typhoid, and other diseases. When a needle is inserted through the skin, the vaccine or drug it carries provides systemic immunity. This is due to the fact that the vaccine gets into

the bloodstream and provokes the body to generate antibodies that are carried throughout the entire body. Unfortunately, there are a variety of problems related with the hypodermic needles used for these injections. One of the most significant drawbacks is the relatively high cost of the needles. The cost results in a lower vaccination rate, especially for children in developing countries. Another problem with traditional needles is the lack of reusability. If a needle syringe is not sterilized, reusing it can lead to the spread of disease. Additionally, many people have a fear of needles which causes them to avoid treatment. These drawbacks have led to the development of alternative delivery systems to needle injections. Needle free systems are designed to solve the above problems making them safer, less expensive, and more convenient. It is expected that these systems will increase the incidence of vaccination and reduce the amount of prescribed antibiotics. Moreover, they should reduce the number of needle stick accidents that have resulted in some health care workers contracting diseases. More than a dozen companies have developed alternatives to needle injections. Some of the different designs include nasal sprays, nose drops, flavored liquids, skin patches, air forced and edible vaccine packed vegetables. The needle free systems that are most like traditional injections involve the direct transfer of the medicine through the skin. Nasal sprays, suppositories, and eye and nose drops are forms of needle free systems that deliver medications through the mucous membrane, where 90% of all infections occur. The mucous membrane is found throughout the body and includes the lining of the respiratory tract, digestive tract, and urinary and genital passages. These needle free systems prompt the body to produce

both antibodies at the mucosa surfaces and system wide. The nasal shot may be the first needle free flu shot. It is a syringe like device that has an aerosol sprayer substituted for the needle. It delivers a weak flu virus directly to the nasal passages and creates immunity to the flu with minimal side effects. Inhalers are another type of needle free delivery system.

HISTORY

As long as drugs have been known to alleviate diseases, people have searched for enhanced methods of delivering them. During the early nineteenth century researchers made several discoveries that ultimately led to the development of the hypodermic needle by Alexander Wood in 1853. This device was used to give morphine to patients who were suffering from sleeping disorders. In following years, the hypodermic needle underwent major changes which made them more convenient to use, safer, and more consistent. However, needles still have major drawbacks which prompted researchers to find needle free alternatives. The first air powered needle free injection systems were developed during the 1940s and 1950s. Over the years, these devices have been modified in order to improve the amount and types of medicines delivered, and the effectiveness and the ease of use.

STRUCTURE OF HUMAN SKIN

Knowledge of the structure of skin is essential for successful administration of drugs through needle free injection systems as these drugs are administered beneath the skin. Human skin is generally made of two layers i. e., epidermis and dermis. Epidermis: It is the outermost layer of the skin. A waterproof, protective wrap over the body’s surface is formed due to the

epidermis; it is made up of stratified squamous epithelium with an underlying basal lamina. The epidermis has no blood vessels, and cells in the deepest layers are nourished by means of diffusion from blood capillaries which extend to the upper layers of the dermis. Merkel cells, keratinocytes, melanocytes and langerhans cells are the main type of cells which form the epidermis. The epidermis can be further subdivided into various strata such as (beginning with the outermost layer): corneum, lucidum (only in palms of hands and bottoms of feet), granulosum, spinosum, basale. Dermis: The dermis is the layer of skin below the epidermis and it consists of connective tissue and protects the body from stress and strain. The dermis is tightly connected to the epidermis by a basement membrane. It also harbors many mechanoreceptors (nerve endings) that provide the sense of touch and heat. It consists of the hair follicles, sweat glands, sebaceous glands, apocrine glands, lymphatic vessels and blood vessels. The blood vessels in the dermis supply nourishment and waste removal not only from its own cells but also from the stratum basale of the epidermis. Hypodermis: It is not the part of the skin, and lies below the dermis. Its function is not only to put together the skin and the underlying bone and muscle but also supplying it with blood vessels and nerves. It mainly consists of loose connective tissue and elastin. It consists of main cell types such as fibroblasts, macrophages and adipocytes (the hypodermis contains 50% of body fat). Fat mainly acts as padding and insulation to the body.

Fig 1: Human skin

NEEDLE FREE TECHNOLOGY: ORIGIN AND METHODOLOGY

Needle free technology (Jet injectors), were developed in the 1930s and used widely over 50 years in mass vaccination programs in patients suffering from smallpox, polio, and measles. Mechanical compression is used to force (generated by a compressed gas typically air, CO2 or nitrogen) fluid through a small orifice, these devices created a high pressure stream that could easily penetrate the skin, subcutaneous tissue and underlying shallow muscle in order to deliver the vaccine in a fraction of a second. One major problem to needle free injections has been the wetness related with residual vaccine on the skin surface that may cause the vaccine administrator to think that the vaccine was not properly administered. Needle free injection technology has been designed to deliver antibiotics, iron dextran or vaccines comfortably, accurately, easily and rapidly without the application of a needle. Needle free injection is precise, reliable, and virtually the same every time. There are 3 stages in needle free delivery: Stage 1, the peak pressure phase, in which optimal pressure is used to penetrate the skin (< 0. 025 sec); Stage 2, the delivery or dispersion phase (~ 0. 2 sec); and Stage 3, the drop-off phase (< 0. 05 sec). This pressure profile is steady with each administration of vaccine which ensures that each animal is vaccinated at the proper tissue depth. The needle free injection technology enhances the dispersion of medication throughout the tissue. As the fluid stream forces its way through the tissue, a path of least resistance is followed, resulting in a broadly dispersed, and spider web like distribution of the medication.

Types of Needle Free Injection Systems:

Needle free technologies are of three types: 1. Powder injections2. Liquid injections3. Depot or projectile injection.

1. Powder Injections

For delivery via skin, the particles must only pierce the outermost barrier, the stratum corneum. So, drugs delivered with powder injection technology or Needle Free Injection (NFI) reach the circulatory system faster than those administered by subcutaneous injection, because it is an intradermal delivery and the capillary blood supply is immediately nearby to the site of administration. The powder injection system for particle delivery is the combination of a device with a specially formulated powdered drug. Exclusive devices have been configured for injection into any physically accessible tissue, normal skin or mucosal sites. Some systems have been designed for single use and are entirely disposable and others, intended for longer courses of therapy, have some reusable elements. For convenience and economy, reusable systems have only the drug and pressurized helium energy source in a single cartridge that is replaced for each injection. The principle of all the devices is the same; i. e. the harnessing of the energy of a transient gas jet to accelerate a premeasured dose of particulate drug formulation. The most common orifice size is 0. 127mm, compared to a 25 gauge needle, which is about 1mm. So, process is completely painless. The powder injection systems are powered by a manufactured helium gas aluminum microcylider of ampoule design and make use of a drug cassette or package to introduce the powder into the gas flow. In operation, the microcylider tip can be broken when the device is pressed against the tissue

site that is to be treated. This releases the compressed helium suddenly to open the drug cassette for delivery of its payload to the tissue. The gas does not actually penetrate the skin, instead, it is reflected back in to the device through a silencer. The silencer is essential because the flow is rapidly supersonic. The other components of the device are manufactured from medical grade plastics using standard injection molding techniques.

Ideal characteristics of powder particles

Powder is an essential component of the powderject technology. For powder injections, particle quality and size distribution are individually essential, not only traditional shelf life chemical stability but also physical stability is required. The powder must retain its size distribution during transport and storage and particles must be sufficiently robust to withstand the highly energetic gas jet within the device as well as ballistic impact with the skin. The dispersed particles must then dissolve and the payload diffuses to act locally or transported by the systemic circulation to the desired site of action in the body. The particles also must be strong because they hit the skin at high velocities. The particles have been clocked as fast as 900 meters per second, with 400 to 600 meters per second being the more typical range. For powders having particle densities around 1g/cc, mean diameters of greater than about 20 µm are required for skin penetration for typical velocities. For particle size ranges above 100 µm, local skin tolerability limits the delivery. In the powder injection system, process to make powder particles is powder compression, milling and sieving. Other more readily scalable methods include spray drying, spray freeze drying, fluid bed drying, spray coating of seed particles, solution filling and drying preformed hydrogel beads and

emulsion techniques to form erodible micro particles. By using the drug in powder form rather than dissolved in liquid, a much smaller volume of material is shot through the skin, so the injection becomes painless. Bio erodible carriers, slowly dissolving excipients or specific, less soluble salts or dissolution aids can provide sustained release or otherwise altered pharmacokinetics to improve drug performance. Protein drugs are very potent so it fits powderject systems perfectly.

2. Liquid injections

The basic principle of this injection is, if a high enough pressure is generated by a fluid in intimate contact with the skin, then the liquid will punch a hole into the skin and will be delivered into the tissues in and under the skin. Although the same principle is applied as in powder, there is difference in the actual design and operation of the powder injection devices.

3. Depot injections

Depot injections are given in the muscle, where they create a depot of a drug that is released continuously over a specified period of time.

DESIGN

The air forced needle free injection systems are usually made up of three components which include an injection device, a disposable needle free syringe and an air cartridge. The injection device is fabricated of a durable plastic. It is designed such that it is easy to hold for self administration of medicine. The needle free syringe is also fabricated of plastic. It must be sterilized and is the only piece of the device that must touch the skin. The syringe is made such that, it should be disposed after every use.

RAW MATERIALS

Since these devices directly come in contact with the body, they must be fabricated from materials that are pharmacologically inert. The materials also must be capable to endure high temperatures since they are heat sterilized. Air forced injection systems are available in different shapes and sizes. The external shell of the device is made from a high strength, lightweight thermoplastic such as polycarbonate. Polycarbonates are polymers that are formed synthetically through various chemical reactions. To make the polymer significant to mold, fillers are added. These fillers help to make plastics more durable, lightweight, and rigid. Colorants are also included into the plastic to modify the overall appearance.

THE MANUFACTURING PROCESS

There are various methods of producing needle free injection system. These systems are made through a step by step process which involves molding the pieces, assembling them, decorating and labeling the final product. The individual pieces are usually produced off site and arranged by the needle free injection system manufacturer. All of the manufacturing process is done under sterile conditions to avoid the spread of disease.

Making the pieces

a) The first step consists of production of the component plastic pieces from plastic pellets. This is done by injection molding process. Plastic pellets are put into large holding bin on an injection molding machine. They are then heated to make them flowable. b) The above material is then passed through a hydraulically controlled screw. As the screw rotates, the plastic is directed

all the way through a nozzle which then injects it into a mold. The mold is fabricated of two metal halves that form the shape of the part when brought together. When the plastic is in the mold, it is held under pressure for a specified period of time and then allowed to cool. The plastic inside hardens due to cooling. c) As the mold pieces are separated, the plastic part falls out on top of a conveyor. The mold closes again and the process is repeated. After the plastic parts are driven out from the mold, they are physically inspected to make sure that any kind of damaged parts are not used.

2. Assembling and labeling

The manufactured parts are then transported to an assembly line. In this fabrication phase various events occur. Machines apply markings on devices that give an idea about dose levels and force measurements. These machines are specially calibrated in order to make each printing exactly. Human workers or machines may assemble the devices, depending on the complexity of the device. This consists of inserting various pieces into the main housing and attaching any buttons.

3. Packaging

Following the assembly step, the injection devices are put into packaging. They are initially packed in sterile films and then put into cardboard or plastic boxes. Each part is packed so movement is negligible to avoid damage. These boxes are then stacked on pallets and shipped by means of truck to distributors.

4. Quality Control

Quality control checks are done during the manufacturing process. Line inspectors check the plastic components to ensure, that, they conform to predetermined specifications. Visual inspections are the first test method, but measuring equipment is also used to confirm the dimensions including size and thickness. Instruments used include laser micrometers, calipers and microscopes. Inspectors also check to ensure the printing and labeling is correct and that all the parts are included in the final packages. Since these devices can have a variety of safety issues, their production is strictly controlled by the Food and Drug Administration (FDA). Each manufacturer must conform to a range of production standards and specifications. Announced and unannounced inspections may occur to make sure that these companies are following good manufacturing practices. For the same reason detailed records must be kept related to production and design of the devices.

Mechanism of Working:

Needle free injection technology works by the mechanism in which liquid medication is forced at a high speed through a tiny orifice. The diameter of the orifice is lesser than the diameter of a human hair. An ultrafine stream of high pressure fluid is created that penetrates the skin without the use of a needle. The design of the device has a key impact on the correctness of subcutaneous delivery and the stresses forced on the product that is to be delivered. The design must ensure that a adequately high pressure is created to puncture the skin, while the following pressure is minimized to make sure that the molecule is deposited comfortably at a level that does

not reach the muscle tissue. High pressure delivery could potentially spoil fragile molecules, such as monoclonal antibodies. Successful delivery of such molecules, as a result, requires a device with carefully controlled power nuances.

Components of the Needle Free Injection Systems:

Nozzle:

The nozzle has two significant functions; it acts as the passage for the drug and as the surface which contacts the skin. The nozzle contains a flat surface and an orifice. The nozzle provides the surface which comes in contact with the skin and the orifice which the drug passes through when injected. The orifice controls the drug stream diameter and speed. A stream diameter of approximately 100 μm and traveling at 100 m/s can achieve the desired injection depth of 2 mm. Drug reservoir: The drug volume holds the injection fluid inside the device. Pressure source: The energy source provides the essential driving energy to the drug for injection. Many of the devices in the market use either mechanical or stored pressure as energy storage elements. The mechanical method stores energy in a spring which is released by pushing a plunger to provide the necessary pressure. The pressure storage method uses compressed gas in a vessel which is released at the time of injection.

DIFFERENT TECHNOLOGY

[1] Bioject’s needle free injection technology

Bioject has developed an extensive technology platform for delivering variety of medications and vaccines to the subcutaneous and intramuscular depths.

Dispersion Patterns

Bioject's needle free injection technology improves the dispersion of medication all over the tissue; it follows the path of least resistance, which results in a widely dispersed, spider web like distribution of the medication.

[A] Bioject's new Intradermal (ID) Pen spring powered needle free injector Intradermal (ID) Pen Injector

Bioject's ID Pen spring powered needle free injector is proposed to be used for intradermal injections for vaccinations and drug therapy. The system mainly consists of a hand held, user filled device that incorporates single use, and auto disable disposable syringes. The ID Pen is designed to deliver medications in doses such as 5 ml or 10 ml for each injection. The device is totally mechanical and is intended for administration by trained clinicians and properly trained users in home settings.

Iject® and Iject® R

Iject is a small, lightweight, gas powered injection system fabricated for home or professional use. This system has two versions, one is a pre-filled, single use disposable injector, and the other is a reusable injector that consists of prefilled medication cartridges.

Intradermal Syringe

Intradermal injections are shallow as compared to other injection types. They are very complicated to administer with a traditional needle because of the lack of skill and exactness required to deliver them properly.

Jupiter Jet

The Jupiter Jet is an exclusive hand held device that is capable of administering small volumes (0. 03 to 0. 2 ml) of drugs at SC, IM or ID depths.

Multi-Port Orifices

Bioject is also developing multi-port orifices for enhanced intradermal injections. This novel injector nozzle allows for a greater dispersion of injectable materials, improving the delivery and therapeutic effect of the drug. For many vaccines that require an intradermal injection, this new development could offer noteworthy benefits.

[B] The ZetaJet™

Bioject® ZetaJet™

The Bioject® ZetaJet™, is a Bioject's most recent advance in needle free delivery systems, it consists of two components, the portable injector and an auto disabling disposable syringe. It is anticipated to deliver vaccines and injectable medications either subcutaneously or intramuscularly and is indicated for both professional as well as home use for patients who self inject. The syringe assembly has a unique auto-disable characteristic that avoids reuse of the syringe. The device has FDA clearance for administering

subcutaneous or intramuscular injections of liquid medication, which includes vaccines and other injected medications.

Advantages

Capability to deliver to all three injection depths: Intramuscular, subcutaneous or intradermal. Injection volumes range from 0. 05ml to 0. 5ml. Leverages Bioject’s unique, patented pressure profile. Indicated for both professional and patient self injection. Polycarbonate syringe provides exceptional strength, clarity and heat resistance. Reliable stainless steel inner core enhances durability in rough environments.

[2] Biojector 2000

The Biojector 2000 is a tough, professional grade injection system designed especially for healthcare providers. The Biojector 2000 uses sterile, single use syringes for individual injections, which avoids the cross contamination that has been previously reported with fixed nozzle jet injection systems. Since there is no needle, the Biojector provides healthcare workers with an unmatched level of protection against accidental needle stick injuries. In high risk situations, such as delivering injections to patients suffering with HIV or hepatitis, the Biojector is an ultimate injection system.

[3] Vitajet 3

The Vitajet 3 is a user-friendly, economical needle free injection system for the delivery of insulin. With disposable nozzles that are replaced once a week, the Vitajet 3 offers the quality of a reusable medical product, with the ease and safety of a sterile disposable. The Vitajet 3 received the FDA

marketing clearance for the delivery of subcutaneous injections of insulin in 1996.

[4] Cool click

Bioject developed the cool click needle free injection system for the delivery of Saizen recombinant human growth hormone. The system includes modified dosage features to exactly deliver variable doses of Saizen and was designed with the use of bright colors to make the injector attractive and non-threatening to children.

[5] SeroJet

The SeroJet is a needle free injection system intended for the delivery of Serostim recombinant human growth hormone for treatment of HIV associated wasting in adults.

[6] Iject

The Iject is a pre-filled single use disposable injection device used to administer 0. 5 to 1. 0 ml subcutaneous or intramuscular injections. No additional parts or modifications are required for function. The Iject needle free injection system is a trial device, subject to the US Food and Drug Administration clearance for commercial distribution.

[7] Non-invasive DDS: unexploited potential

This is the only prefilled and disposable needle free device in late stage development, with commercial scale-up in process. The drug capsule is glass, a material that has proven excellent stability profiles for liquid protein formulations. The energy to drive the actuator forward to deliver the 0. 5 ml

formulation is provided by means of compressed nitrogen. The overall delivery process is completed in less than 60 milliseconds with less bruising and discomfort than that encountered with syringes, pens or other devices.

[8] Biovalve's Mini-Ject technology

The Mini-Ject can deliver a wide range of drugs, ranging from small molecules to large proteins, fragile antibodies, and vaccines. Delivery can be targeted to intradermal, subcutaneous or intramuscular depending on the clinical need. No other single use needle free delivery technology provides the same level of performance as the Mini-Ject technology with the ability to target specific tissue layers over such a broad range of drug volumes (0. 1 ml to 1. 3 ml) and viscosities.

[9] Antares' Medi-Jector Vision technology

Antares Pharma, one of the pioneers in the field of needle free injection technology has developed Medi-Jector Vision technology which is used to deliver insulin to diabetes sufferers. It is a newest marketed version of the reusable, variable dose, spring powered device for insulin delivery. This technology is also being used to deliver human growth hormone. Its plastic, disposable needle free syringe allows the patient to see the dose prior to injection. It is marketed in US and Europe for insulin administration since 1999.

[10] Implaject

Simple, hand held needle free injection device. It can be configured to be reusable with disposable cartridges.

[11] Crossject

Prefilled, single use disposable NFI. It uses chemical reaction to generate propellant at the time of administration.

[12]Powderject

It painlessly delivers DNA vaccines to the skin in a dry formulation.

[13] Zoma-jet 2 Vision

Customized version of Medi-Jector vision licensed to Ferring for administration of their human growth hormone, Zomacton for distribution in Europe.

[14] Valeo (MJ8)

Next generation pen style, spring-powered device. Designed for use with drugs in cartridge containers, rather than vials. Clinical Trials completed, available for licensing.

[15] Injex 30

Spring powered hand held device with disposable ampoules that delivers 0. 05-0. 3 ml. Focused on insulin delivery. Marketed in US.

[16] mhi-500

Spring-powered hand-held delivers volume in the range of 0. 02-0. 5 ml. Marketed in Europe as an insulin delivery device.

[17] Solid dose injector technology

Glide SDI (Solid Dose Injector) enables the injection of APIs in a solid dosage form without the need for a needle. The drug is mixed with selected

excipients and individual dosages are produced as tiny rods with a point at one end. A dosage is then pre-filled into a single use drug cassette. In use, the drug cassette is placed into a spring powered, handheld actuator. Pushing the end of the cassette against the skin target charges the spring in the actuator. At a preset spring force, the actuator automatically triggers, pushing the dosage from the drug cassette into the skin. The small, low cost drug cassette, which contains no sharps, can be safely thrown away and the actuator can be reused hundreds of times, resulting in low cost per administration. Because the drug is administered in a solid dosage form, the Glide SDI offers enhanced stability and potentially avoids the need for refrigeration, as well as providing the opportunity for controlled release formulations by using slower dissolving excipients rather than fast dissolving sugars. In the clinic in volunteer studies, the Glide SDI has been overwhelmingly preferred to an injection with a standard needle and syringe. A wide range of proteins, peptides and small molecules can be delivered using the technology. Preclinical studies with a range of antigens have also shown improved efficacy for vaccines in the Glide SDI when compared to a standard needle and syringe injection.

[18] SQ-PEN technology

The SQ-PEN was developed by Medical House Products Ltd and has been owned by Diabetes Management International since October 2007. The SQ-PEN uses pressure from a spring loaded piston to create a fine stream of insulin through a small bore nozzle. The pressure and speed of exit of the insulin stream causes it to penetrate the skin, delivering insulin to the subcutaneous layer. SQ-PEN uses a plunger which is activated when there is

sufficient depression of the nozzle tip into the skin. A recent randomized cross over study compared a needle free insulin delivery device to the Novopen 3. The Vitajet needle free insulin delivery system was fully evaluated in a randomized, controlled study reported by Katoulis et al. (1989). The authors concluded that Vitajet constitutes an efficient, safe and less painful needle less route than the conventional syringe for delivering insulin." The authors demonstrated that falls in blood glucose occurred earlier with Vitajet following injection with Actrapid insulin, with statistically lower levels of blood glucose for up to 2 hours post-injection. On the other hand however, short and long-term glycaemic control is reportedly improved by needle free insulin delivery. It should be noted that there are a wide range of factors that influence the absorption kinetics of insulin and the usage of the SQ-PEN needle free insulin injection device should be viewed within this context. As a direct consequence of changing to a needle free delivery device, the risks of hypoglycaemia are small. Indeed, less insulin overlap is seen with needle free insulin delivery as a result of the shortened duration of insulin. Therefore, on a twice-daily insulin regimen, less hypoglycaemia is more likely with a needle free delivery system, than with a needle based system.

Other needle less drug delivery systems

Patches

Patches are introduced as needle free delivery systems. These devices, which look like bandages, gradually transfer medicine through the skin. In a patch, thousands of tiny blades are imbedded on the patch surface. The patch is covered with medicine and placed on the skin. The blades create

microscopic cuts on the skin that opens a pathway for drugs to enter through when an electric current is applied; the medicine is then forced into the body. This process is known as iontophoresis and it does not hurt at all.

Nasal sprays, suppositories, and eye and nose drops

These forms of needle free systems deliver medications through the mucous membrane, where 90% of all infections occur. The mucous membrane is found throughout the body and includes the lining of the respiratory tract, digestive tract, and urinary and genital passages. These needle free systems prompt the body to produce both antibodies at the mucosal surfaces and system wide.

Nasal shot

The nasal shot is the first needle free flu shot. It is a syringe like device that has an aerosol sprayer, which is substituted for the needle. It delivers a weak flu virus directly to the nasal passages and creates immunity to the flu with negligible side effects.

Inhalers

In these systems, liquids or powders are inhaled and delivered into the lungs. These devices are excellent for delivering protein drugs because the lungs provide a quick absorption into the bloodstream.

Oral vaccines

These are the needle free systems that may prove as an alternative to vaccine injections. This technology has been complicated to perfect for many reasons. The basic problem with this type of delivery system is that the

milieu of the digestive system is harsh and typically destroys vaccines and other drugs. Also, vaccines do not work as well in aggravating antibody production in the digestive lining. One of the latest oral vaccines involves freeze drying the medicine and then mixing it with a salt buffer to protect it when it is in the stomach. Other edible forms of vaccines include a sugar solution of a vaccine against the bacterium that causes ulcers. For travelers, a typhoid vaccine capsule has been developed as an alternative to the two painful injection shots usually required.

Needle free insulin delivery

Insulin inhalers:

The basis behind developing a pulmonary drug delivery system is to make sure that insulin powder is delivered deep into the lungs, where it is effortlessly absorbed into the bloodstream, in a hand held inhalation device form. The device converts the insulin powder particles into an aerosol cloud, which the patient can inhale. Good glycemic control, as compared to modern subcutaneously administered insulin preparations, has been demonstrated, and no unexpected safety issues have been reported with inhaled insulin.

Insulin spray:

The buccal route is another promising alternative for the delivery of insulin. Since the buccal area has an abundant blood supply, it offers some advantages such as a means to deliver the acid labile insulin, and elimination of insulin destruction by first pass metabolism. The buccal spray formulation which is being developed by Generex Biotechnology, delivers insulin to the buccal cavity in the form of fine spray. The company's top

product is Oralin. It is currently in phase II B clinical trial. In Oralin, the patient actually does not inhale with the buccal spray device; instead, the drug is sprayed onto the buccal mucosa. The high speed of the spray allows the drug to be quickly absorbed into the blood stream.

Insulin pill:

Recently many biotech companies are conducting pilot trials in order to develop an insulin pill as a potential alternative to injected or pumped insulin. For example, Nobex Corporation has developed hexyl-insulin monoconjugate 2 (HIM- 2) in which single amphiphilic oligomer is covalently linked to the free amino group on the Lys-β 29 residues of recombinant human insulin by means of an amide bond. This alters the physicochemical characteristics, which leads to enhanced stability and resistance to intestinal degradation of ingested insulin. Oral HIM-2 is safe and reproduces the physiological pathway of insulin secreted by pancreas.

Insulin analogues:

Conventional insulin preparations such as NPH (Neutral Protamine Hagedom) insulin have 14 hours duration of action and plasma insulin peak level of 4-6 hours after administration. As a result, NPH insulin may need to be administered up to three times in a day in type 1 diabetic patients to provide sufficient insulin supply all over the day. Multiple dosing regimens are less optimal in terms of adherence, flexibility and choice for the patients to familiarize the treatment to their individual lifestyle. To satisfy the need for optimized basal insulin, recombinant human insulin analogues have been developed, like Glargine and Aspart. Glargine treated patients experienced

significantly less weight gain than those treated with NPH insulin, which had a lower risk of nocturnal hypoglycemia and was well tolerated, whether it is injected once daily before breakfast, dinner or at bedtime in Type 1 diabetic patients. Similarly, Aspart is also now well established as an effective and convenient means of providing glycemic control.

Insulin complement:

Apart from the new insulin, one new drug, Symylin, is ready to be launched by Amylin Pharma, San Diego. Symylin is a synthetic version of the human hormone amylin, which moderates the glucose lowering effect of insulin. Symylin has been designed to complement insulin action and has been shown to reduce blood glucose without causing an increase in hypoglycemic episodes. It could provide a potential adjunct to insulin therapy in both type 1 and type 2 diabetics.

Implantable insulin pumps:

Continuous improvements in microelectronics, as well as in the development of biomaterials and stable insulin solutions, have led to the availability of implantable pumps able to infuse insulin by the peritoneal route, in a continuous and programmable way, for several years. The Medtronic/Minimed 2007 system may offer treatment advantages for diabetic patients who have difficulty in maintaining consistent glycaemic control. This system delivers insulin into the peritoneal cavity in short, frequent burst or ''pulses'' similar to how pancreatic β cells secrete insulin. This system is placed external to the rectus muscle. Current model has eight

years battery life expectancy. The system's reservoir is refilled with fresh insulin every two or three months.

Transdermal patch:

Ozin and Landskron announced recently that they had created an unusual material using manmade molecules called dendrimers. It can store drugs and, when spread on the skin as a film, allow them to dissipate into a patient's bloodstream like a new type of patch. The problem with current drug delivery systems is that it is either injected in such a manner that acquires too high concentration to en-sure that it stays in the system but can be toxic, or it is injected too little into a person such that it is not effective. The new material, Periodic Mesophorus Dendrisil-licus (PMD) would let drugs seep through a person's skin in just the right amount and stay at that level.

APPLICATIONS OF NEEDLE FREE INJECTION TECHNOLOGY

1. Intraject (Weston medical) technology is used to deliver drugs including proteins, peptides, monoclonal antibodies, small molecules and vaccines. 2. Medi-Jector vision (Antares Pharma, lnc.) technology is used to create a micro thin stream of insulin that penetrates the skin. 3. Powderject (Powderject pharmaceuticals) technology is used to deliver inulin to hairless guinea pigs, delivery of large macromolecules across the skin, for intradermal DNA immunization against influenza virus in mice. 4. Jet injectors technology delivers proteins such as β-interferon as well as small organic conventional therapeutic agents such as lidocaine (lignocaine) for local anaesthesia. 5. The Disposable Syringe Jet Injector (DSJI) Project is

supporting clinical research on the delivery of vaccines with jet injectors. Current research work includes following applications

Inactivated polio vaccine

Inactivated polio vaccine has a long history of safety and effectiveness; additionally, it will be significant following the eradication of polio worldwide once oral polio vaccine is no longer used. Intradermal delivery at reduced doses could widen vaccine supplies and reduce costs to programs, improving access to this important vaccine in the developing countries. Jet injectors, which offer a simple approach to intradermal injection, could facilitate uptake of this vaccination strategy.

Influenza vaccine

Seasonal influenza vaccine is often omitted from national immunization programs. This study examined the safety and effectiveness of flu vaccine when given to toddlers in the Dominican Republic. This study tested whether a fractional dose given intradermally by jet injector works as well as a full dose given with a standard delivery method.

Intradermal delivery landscape

In conjunction with Project Optimize, the DSJI project supported a literature review to evaluate the landscape of intradermal vaccine research. The resulting report provided an overview of clinical research on intradermal vaccination and intradermal delivery devices and reviews the vaccines which are most suitable for future research on intradermal delivery for application in developing country immunization programs.

Measles-mumps-rubella vaccine

PATH is conducting a study to inspect the safety and effectiveness of this childhood vaccine when given by jet injector.

Yellow fever vaccine

This vaccine is given in endemic areas of South America and Africa, as well as to travelers from other countries; there are cyclic shortages of this vaccine. Reduced dose intradermal delivery by jet injector could alleviate shortages and increase access to yellow fever vaccine.

DTP-Hib-hep B vaccine

This is a type of combination vaccine, which protects against diphtheria, tetanus, pertussis, haemophilus influenzae type b (Hib) and hepatitis B. PATH's planned research will contrast delivery of this vaccine to delivery with a needle and syringe.

BCG vaccine

This vaccine is used in children for protection against tuberculosis. It is given intradermally, but there are challenges with the standard intradermal injection method. DSJIs may prove to be a safer and more reliable means of administering this vaccine.

Rabies vaccine

Intradermal delivery of decreased doses of rabies vaccine has been accepted by the WHO. Use of intradermal delivery devices could augment the ease of use of this life saving vaccine.

THE FUTURE

Many of these needle free alternative technologies are in the development stage. Companies are still working on producing devices that are safer and easier to use. They are also working on alternatives which can deliver even more types of medicines. Inhalers are being improved as are nasal sprays, forced air injectors and patches. In the future, other foods may be genetically enhanced to deliver vaccines and other drugs. These include foods like bananas and tomatoes. In fact, bananas are being looked at as carriers for a vaccine to protect against the Norwalk virus. Tomatoes that protect against hepatitis B are also being developed. In addition to new delivery systems, scientists are also investigating methods for producing longer lasting drugs that will reduce the number of needle injections.

CONCLUSION

Needle free technology offers the very obvious benefit of minimizing patients fear about the use of needle. Additional benefits include very fast injection as compared to conventional needles and there are no needle disposal issues. Not only it can benefit the pharmaceutical industry in rising product sales, but also it has the added potential to increase compliance with dosage regimens and improved outcomes. In the developing world, there are major challenges of disease transmission due to reuse of needles. Organizations such as WHO and CDC (Centre for Disease Control) and groups like Gates Foundation have supported the development of needle free alternatives for drug delivery. The biotech revolution is bringing in a range of protein based therapeutics into the market place at rapid pace, more than 300 products in active development. This protein based therapeutics especially monoclonal

antibodies (MAbs), which are anticipated to represent 30 percent of pharmaceutical sales by 2007 and which are otherwise challenging to deliver non-invasively, will continue to be formulated as injectables. There appears to be tremendous opportunity for needle free technology to have major impact in the industry. It is obvious that spectacular change may occur only when a large pharmaceutical or biotechnology company adopts needle free technology and demonstrates its flexibility, acceptance and value in major therapeutic areas.