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NEEDLE FREE INJECTION TECHNOLOGY: A REVIEW

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ABSTRACT
Needle-free injection systems are novel ways to introduce various medicines into patients without piercing the skin with a conventional needle. They can take the form of power sprays, edible products, inhalers, and skin patches. Needle-free systems are designed to solve these problems making them safer, less expensive, and more convenient. It is anticipated 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. Today, they are a steadily developing technology that promises to make the administration of medicine more efficient and less painful. 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.

Keywords: Needle, Free injection, drug delivery

INTRODUCTION

Hypodermic needles were first introduced during the 1800s; needle-free systems are relatively recent inventions. Needle Free Injection Technology (NFIT) discovered in 19th century in France. Needle-free injection systems are novel ways to introduce various medicines into patients without piercing the skin with a conventional needle. They can take the form of power sprays, edible products, inhalers, and skin patches. While hypodermic needles were first introduced during the 1800s, needle-free systems are relatively recent inventions. Today, they are a steadily developing technology that promises to make the administration of medicine more efficient and less painful [1].

People are given injections to protect them from 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 because the vaccine gets into the bloodstream and provokes the body to create antibodies that are carried throughout the entire body. Unfortunately, there are a variety of problems associated 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 these problems making them safer, less expensive, and more convenient. It is anticipated 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. One company offers an injection system where the drug is dispersed through the skin as a fine mist or powder. In this system, a tube-shaped device is held against the skin and a burst of air forces the molecules of medicine into the body. The device is designed to force the medicine far enough through the skin so it enters the bloodstream. An application for which this system is particularly useful is for patients who need daily doses of growth hormone. Patches have been introduced as needle-free delivery systems.

These devices, which look like bandages, slowly transfer medicine through the skin. In one type of patch, thousands of tiny blades are imbedded on its surface. The patch is covered with medicine and then placed on the skin. The blades make microscopic cuts in the skin that opens a path for drugs to enter through. When an electric current is applied, the medicine is forced into the body.

This process, called iontophoresis, does not hurt. 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.

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

In one system there is a pump unit that atomizes a powdered medication. This allows the patient to inhale the proper amount of medicine without it getting trapped in the back of the throat. For diabetics who require daily injections of insulin, an aerosol inhaler has also been introduced. Oral vaccines are needle-free systems that may replace vaccine injections. This technology has been difficult to perfect for many reasons. The primary problem with this type of delivery system is that the environment of the digestive system is harsh and typically destroys vaccines and other drugs. Also, vaccines do not work as well in provoking antibody production in the digestive lining.

One of the latest oral vaccines involves freeze drying the medicine and mixing it with a salt buffer to protect it when it is in the stomach. Other edible forms 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 shots typically required. Genetic engineering has enabled the production of oral vaccines in food. In 1998, potatoes were produced that contained genes from the virus that causes cholera.

These potatoes showed efficacy in protecting people from this disease. This is particularly useful for developing countries where potatoes are a dietary staple and the refrigeration that is typically required for transporting vaccines is not readily available.

History: As long as drugs have been known to cure diseases, people have searched for better methods of delivering them. During the early nineteenth century researchers made a series of discoveries that eventually led to the development of the hypodermic needle by Alexander Wood in 1853. This device was used to give morphine to patients suffering from sleeping disorders.

In subsequent years, the hypodermic needle underwent significant changes which made them more efficient to use, safer, and more reliable. However, needles still have significant drawbacks which prompted researchers to find needle-free alternatives.

The first air-powered needle-free injection systems were developed during the 1940s and 1950s. These devices were gun-shaped and used propellant gases to force fluid medicines through the skin. Over the years, the devices have been modified to improve the amount and types of medicines delivered, and the efficiency 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 underneath the skin. Human skin is generally made of two layers i.e., epidermis and dermis.

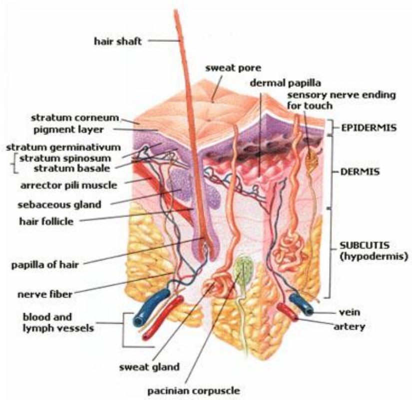

Fig 1: Human skin

Epidermis: It is the outmost layer of the skin. It forms the waterproof, protective wrap over the body's surface and is made up of stratified squamous epithelium with an underlying basal lamina. The epidermis contains no blood vessels, and cells in the deepest layers are nourished by diffusion from blood capillaries extending to the upper layers of the dermis. The main type of cells which make up the epidermis are Merkel cells, keratinocytes, melanocytes and Langerhans cells also present. The epidermis can be further subdivided into the following strata (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 beneath the epidermis that consists of connective tissue and cushions 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 contains the hair follicles, sweat glands, sebaceous glands, apocrine glands, lymphatic vessels and blood vessels. The blood vessels in the dermis provide nourishment and waste removal from its own cells as well as from the Stratum basale of the epidermis.

Hypodermis: The hypodermis is not part of the skin, and lies below the dermis. Its purpose is to attach the skin to underlying bone and muscle as well as supplying it with blood vessels and nerves. It consists of loose connective tissue and elastin.

The main cell types are fibroblasts, macro phages and adipocytes (the hypodermis contains 50% of body fat). Fat serves as padding and insulation for the body. Another name for the hypodermis is the subcutaneous tissue.

Advantages:

1. It is trouble free, simple, self-administered
2. Avoids needle stick hazard
3. Speeds the injection cycle
4. Low sensation and safety
5. Solid dosage forms can be administered
6. Elimination of needle phobia
7. Minimal skin response and no bleeding or bruising
8. Easy and safe disposal
9. Easy to transport and store without refrigeration
10. Excellent dose response is observed with increased drug doses
11. Rapid delivery of the drug to the systematic circulation
12. Bio-equivalence has been demonstrated enabling the development of 'generic'drug proteins.

Disadvantages:

1. High start-up cost
2. No one size-fits all system
3. Greater complexity
4. Cannot be used for Intravenous route

Types of Needle Free Injection Systems[2]:

Needle free technologies are of three types:

1. Powder injections
2. Liquid injections
3. Depot or projectile injection.

All these technologies have the same basic principle of delivering medication by pressurized contact of fluids with the skin. In powder injection systems, a pre measured powdered medication is put in a drug cassette which is opened by the compressed gas and thus the medication is delivered to tissue.

The powders used in these systems require specific properties and specific size to ensure their stability and proper dispersion into the tissue. These type have certain advantages over the others like the therapeutic agent will be more stable and may not require cold storage. In addition, for vaccines, a solid formulation presents the opportunity to combine fast acting and delayed-release forms of the vaccine so that the prime and boost shots can be given together in a single administration. Depot injections are given in the muscle where they create a store of a drug which is released continuously over a specified period of time.

Mechanism of Working: Needle-free injection technology works by forcing liquid medication at high speed through a tiny orifice that is held against the skin. The diameter of the orifice is smaller than the diameter of a human hair. This creates an ultra-fine stream of high-pressure fluid that penetrates the skin without using a needle. The design of the device has a major influence on the accuracy of subcutaneous delivery and the stresses imposed on the product to be delivered. The design must ensure that a sufficiently high pressure is generated to puncture the skin, while the subsequent pressure is reduced to ensure that the molecule is deposited comfortably at a level that does not reach the muscle tissue. High-pressure delivery could potentially damage fragile molecules, such as monoclonal antibodies. Successful delivery of such molecules, therefore, requires a device with carefully controlled power nuances. Several companies are involved in development of this technology, which includes, Antares Pharma Inc, Aradigm Corporation, Bioject Medical Technolo-gies Inc and Biovalve Technologies Inc.

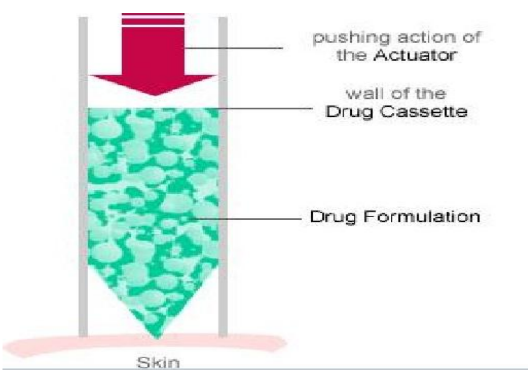

Fig 2: Mechanism of Working

Raw Materials: Since these devices directly contact the body, they must be made from materials that are pharmacologically inert. The materials also must be able to withstand high temperatures because they are heat-sterilized. Airforced injection systems are available in different shapes as sizes. The outer shell of the device is made from a high strength, lightweight thermoplastic such as polycarbonate. Polycarbonates are polymers produced synthetically through various chemical reactions. To make the polymer easier to mold, fillers are added. These fillers make plastics more durable, lightweight, and rigid. Colorants are also incorporated into the plastic to modify the appearance. Prior to manufacture, the plastics are typically supplied in pellet form with the colorants and fillers already incorporated. Air-forced systems typically use carbon dioxide or helium gas to propel the medicine into the body.

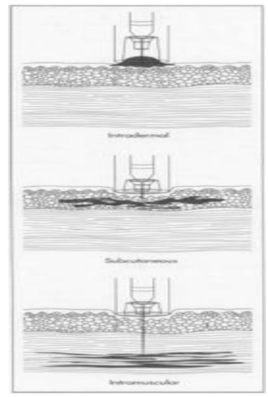

Fig 3: Different types of injections

Certain types of medicines work better with needle-free injection systems than other. Insulin, which must be administered daily to diabetics, can be incorporated into an inhaler system. Lidocaine hydrochloride, a local anesthetic is suitable to be delivered needle free. Other medicines suitable for needle free systems include Fentanyl (an opioid analgesic), Heparin (an anticoagulant) and a variety of vaccines. Various adjunct ingredients included in these medicines include cyclodextrins, lactose, liposomes, amino acids and water.

Design: The air-forced needle-free injection systems are typically made up of three components including an injection device, a disposable needle free syringe and an air cartridge. The injection device is made of a durable plastic.

It is designed to be easy to hold for self-administration of medicine. The needle-free syringe is also plastic. It is sterilized and is the only piece of the device that must touch the skin. The syringe is made to be disposed after every use. For portable units, pressurized metal air cartridges are included. Less mobile devices have air hook-ups that attach to larger containers of compressed air. Some air-forced systems use a re-usable **spring** to generate the pushing force instead of pressurized air cartridges.

The Manufacturing Process[3,8]**:** There are numerous methods of producing each needle-free injection system. The following process focuses on the production of an air-forced system. These systems are made through a step by step procedure which involves molding the pieces, assembling them, and decorating and labeling the final product. The individual pieces are typically produced off-site and assembled by the needle free injection system manufacturer. All of the manufacturing is done under sterile conditions to prevent the spread of disease.

Making pieces: The first step requires the production of the component plastic pieces from plastic pellets. This is done by a process called injection molding. Pellets of plastic are put into a large holding been on an injection molding machine. They are heated to make them flow able. The material is then passed through a hydraulically controlled screw. As the screw rotates, the plastic is directed through a nozzle which then injects it into a mold. The mold is made up 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 amount of time and then allowed to cool. As it cools, the plastic inside hardens. The mold pieces are separated and the plastic part falls out onto a conveyor. The mold then closes again and the process is repeated. After the plastic parts are ejected from the mold, they are manually inspected to ensure that no significantly damaged parts are used.

Assembling and labeling: The parts are next transported to an assembly line. In this production phase various events occur.

Machines apply markings that show dose levels and force measurements. These machines are specially calibrated so each printing is made precisely. Depending on the complexity of the device, human workers or machines may assemble the devices. This involves inserting the various pieces into the main housing and attaching any buttons.

Packaging: After the assembly step, the injection devices are put into packaging. They are first wrapped in sterile films and then put into cardboard or plastic boxes. Each part is packaged so movement is minimal to prevent damage.

For consumer products, an instruction manual is included along with safety information. These boxes are then stacked on pallets and shipped via truck to distributors.

Applications:

1. Intramuscular ,subcutaneous and intradermal administration of Vaccines e.g.., smallpox, polio, measles
2. Intradermal administration of hormones e.g..; growth hormone
3. Intradermal administration of anesthetics e.g.., lidocaine
4. Subcutaneous administration of insulin
5. Used in the treatment of migraine e.g.., sumatriptin

KEY NEEDLE FREE INJECTION SYSTEM MANUFACTURERS [4, 7, 8, 11]

Mhi-500: Mhi-500 is the novel needle frees insulin delivery system which offers benefits for all those involved in diabetes care and also for those involved in the management of clinical waste. It is a real alternative to needle-based delivery systems. Compared with a needle injection system, the mhi-500's needle-free insulin delivery technology improves the dispersion of the insulin throughout the tissue. This technology achieved the Food and Drug Administration (FDA) approval in 1996 for the subcutaneous delivery of insulin and is CE marked for sale throughout the Europe. This system has been used to give thousands of successful injections without the use of a needle. The mhi-500 injects insulin by using a fine, high pressure jet of insulin. This jet then penetrates the tissue, depositing the insulin in the subcutaneous layer. The jet is created by forcing the insulin through a precisely designed nozzle that is held in contact with the tissue during the injection.

Recojet: Shreya Life Sciences has recently launched its recombinant human insulin under the brand name Recosulin and a needle-free insulin delivery device, Recojet. According to the company sources, Recojet is India's first needle-free insulin delivery device and poised to revolutionise the insulin therapy.

The new device is expected to give a boost to the therapy, as needle phobia was one of the reasons preventing insulin use on a wider scale. In general, needle-free injection technology works by forcing liquid medication at high speed through a tiny orifice that is held against the skin. This creates an ultra-fine stream of high-pressure fluid that penetrates the skin without the use of a needle.

Bioject's needle free injection technology: Bioject's needle-free injection technology works by forcing liquid medication at high speed through a tiny orifice that is held against the skin. The diameter of the orifice is smaller than the diameter of a human hair. This creates an ultra-fine stream of high-pressure fluid that penetrates the skin without using a needle. Bioject's technology is unique because it delivers injections to a number of injection depths and supports a wide range of injection volumes. For instance, the Biojector 2000 can deliver intramuscular or subcutaneous injections up to one ml in volume. In addition, Bioject is developing a syringe for the Biojector 2000 that delivers intradermal injections that is currently in clinical trials. Bioject has a portfolio of needle-free injection products to meet the varied needs of today's healthcare environment. Each product is unique in its power source.

Biojectorr 2000: The Biojector 2000 is a durable, professional-grade injection system designed for healthcare providers. The Biojector 2000 is the only needle-free system in the world cleared by the FDA to deliver intramuscular injections. The system can also deliver subcutaneous injections, and is being used for intradermal injections in clinical trials.

Fig 4: Biojector 2000

The Biojector 2000 uses sterile, single-use syringes for individual injections, which prevent the cross-contamination that has been reported with fixed-nozzle jet injection systems. More than 10 million injections have been administered successfully using the Biojector 2000, with no reports of major complications. Because there is no needle, the Biojector provides healthcare workers with an unparalleled level of protection against accidental needlestick injuries. In high-risk situations, such as delivering injections to patients known to be infected with HIV or hepatitis, the Biojector is an ideal injection system.

Vitajet 3: The Vitajet 3 is an easy-to-use, economical needle-free injection system for delivering insulin. The system requires no maintenance or re-assembly. With disposable nozzles that are replaced once-a-week, the Vitajet 3 offers the quality of a reusable medical product, with the convenience and safety of a sterile disposable. The exclusive, easy-to-read Crystal Check disposable transparent nozzle allows inspecting the dosage prior to injection and visually confirming loading and full discharge of your insulin after each use. The Vitajet 3 received the FDA marketing clearance for delivering subcutaneous injections of insulin in 1996. Since then, the system has been used to deliver hundreds of thousands of injections, safely, economically, and without the use of a needle.

Cool.click: Bioject developed the cool.click needle-free injection system for delivering Saizen recombinant human growth hormone. In some children, naturally occurring growth hormone is absent or is produced in inadequate amounts. In these cases, Saizen or growth hormone replacement must be injected to maintain normal growth.

Fig 5: cool.click needle-free injection system

Cool.click is a customised version of Bioject's Vitajet 3 needle-free injection system. The system includes customized dosage features to accurately deliver variable doses of Saizen and was designed with bright colors to make the injector attractive and non-threatening to children. The cool.click received FDA market clearance for delivering subcutaneous injections of Saizen in June, 2000.

SeroJet: The SeroJet is a needle-free injection system for delivering Serostim recombinant human growth hormone for treatment of HIV-associated wasting in adults. HIV-associated wasting is a metabolic condition in which people infected with HIV lose body weight. If not treated, this could result in increased morbidity and mortality.

Fig 6: SeroJet

Serono developed Serostim to treat this condition by utilizing the natural properties of growth hormone in increasing lean body mass. SeroJet is a customised version of Bioject's Vitajet needle-free injection system. The system includes customised dosage features to accurately deliver variable doses of Serostim. The SeroJet received FDA market clearance for delivering subcutaneous injections of Serostim in March 2001.

Iject: Bioject has developed a second-generation gas-powered injector known as the Iject, which is based on the design and performance of the B2000 and is intended to serve as a single-use pre-filled device. The pressure profile of the Iject has been documented by in vitro testing to be virtually the same as that of the B2000, and injection performance of the two devices is therefore predicted to be equivalent. The Iject is a pre-filled single-use disposable injection device (Figure 1) configured to administer 0.5 to 1.00 ml subcutaneous (Figure 2) or intramuscular injections. The device is distributed "ready to use." Thus, it requires no additional parts or modifications for function.

The device is primed by rotating the trigger sleeve 180 degrees, and an injection is administered by advancing the trigger sleeve while the nozzle is held against the injection site (Figure 3) The Iject needle-free injection system is an investigational device, subject to the US Food and Drug Administration clearance for commercial distribution.

Non-invasive DDS: Untapped potential: Aradigm Corporation has recently acquired the Intraject technology, initially developed in the UK by Weston Medical. It is the only pre-filled and disposable needle-free device in late-stage development, with commercial scale-up in process. Aradigm's Intraject collaborators include Roche for the delivery of pegylated interferon alpha (Pegasys) and GlaxoSmithKline for Imitrex. The Intraject device is about the size of a fountain pen. The drug capsule is glass, a material that has demonstrated excellent stability profiles for liquid protein formulations. The energy to drive the actuator forward to deliver the 0.5-ml formulation is provided by compressed nitrogen. The delivery process is completed in less than 60 milliseconds with less bruising and discomfort than may be encountered with syringes, pens or other devices.

Biovalve's Mini-Ject technology: The Mini-Ject represents the next generation in needle-free injection systems by combining the features of accuracy reliability, a variety of pre-filled options, comfortable administration, and full disposability, all within a patient friendly easy-to-use design. 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.

Quality control[6,7]: It checks are done throughout the manufacturing process. Line inspectors check the plastic components to assure they conform to predetermined specifications. Visual inspections are the first test method, but measuring equipment is also used to check the dimensions including size and thickness. Instruments that can be used include laser micrometers, calipers and microscopes.

Inspectors also check to make sure the printing and labeling is correct and that all the parts are included in the final packages. Since these devices can have various safety issues, their production is strictly controlled by the Food and Drug Administration (FDA). Each manufacturer must conform to various production standards and specifications. Announced and unannounced inspections may occur to ensure that these companies are following good manufacturing practices. For this reason detailed records must be kept related to production and design.

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 reducing patient concern about the use of needle. Additional benefits include very fast injection compared with conventional needles and no needle disposal issues. Not only it can benefit the pharmaceutical industry in increasing product sales, 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 through re-use of needles. Organisations 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 marketplace at rapid pace-more than 300 products in active development. These protein-based therapeutics especially monoclonal antibodies (MAbs), which are anticipated to represent 30 per cent 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 likely that dramatic change may occur only when a large pharmaceutical or biotechnology company adopts needle-free technology and demonstrates its versatility, acceptance and value in major therapeutic area.

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