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Comparative Studies of Needle Free Injection Systems and Hypodermic Needle Injection: A Global Perspective

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ABSTRACT

Needle-free injection (NFI) is a novel transdermal either intramuscularly or subcutaneously drug delivery system, where innovative ways to introduce a variety of medicines like as antibiotics, iron, or vaccines comfortably, accurately, easily and rapidly without piercing the skin compared to traditional needle. While hypodermic needle is inject substances into body by intradermal, intramuscular, subcutaneous, intravenous, etc or extract fluids from the body, for example taking blood from a vein in venipuncture successfully but creates pain, needle phobia, inflammation, scars, and contagious diseases. Even after so many advantages of needle, the needle phobia, pain and needle stick injuries from the injection is not gone. It is expected that NFIs will augment the rate of vaccination and reduce the amount of oral medicines prescribed. Moreover, NFIs decrease the occurrence of needle stick accidents that have been seen in some health care workers. NFIs are successfully being used for various dosage forms including liquid dosage, solid dosage forms etc. Various types of NFIs are available in the market like as Ojector, Vita jet, Iject, Cool click etc. Manufacturers are not only working on developing technologies that are safer and easier to use but also an alternatives which can deliver more types of medicines(American Nurses Association,2008.Vivek Ranjan Sinha, 2005) .

Keywords: Needle Free Injection**,** Hypodermic needle, Types of NFIs

INTRODUCTION

In Bangladesh, children may get many vaccine injections by the age of 16. 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 and phobia of the needles. The drawbacks results in a lower vaccination rate, especially for children in developing countries (including Bangladesh). 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. 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. 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; these drawbacks have led to the development of alternative delivery systems to needle injections.

Needle-free systems are solves 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, reduce the number of needle stick accidents that have resulted in some health care workers contracting diseases. NFI that is 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 by a tube-shaped device is held against the skin and a burst of air forces the molecules of medicine so it enters into the bloodstream.NFIs was first described in the 19th century in France, when the French company-H Galante-manufactured an apparatus for aquapuncture but first air-powered needle-free injection systems were developed during the 1940s and 1950s. Since then, the demand had increased considerably. It was first commercialized in the US in 1960s; which 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 ease of use. Needle free injection products are safe to use and also safe to dispose of which makes them environmentally friendly and easily accessible. Scientists have also been exploring new ways of delivering drugs by producing more potent or longer lasting medications, which will reduce the number of injections a patient will receive. The pitfalls of needle-based injections are well known. Psychological resistances to self-injection or needle-phobia have been documented across large demographic groups, such as diabetics. The result of this phobia is that many outpatient injectable are dosed sub-optimally. Furthermore, awareness of serious problems has caused physicians and their patients to either delay therapy initiation or seek out less-invasive alternatives, even at some cost to clinical effectiveness. To overcome the problems related to needle based injections, considerable attention during the past few years to (Vivek Ranjan Sinha, 2005). The growing number of biotech drugs particularly protein-based, gene- based, vaccine-based that cannot be delivered by the oral route for example insulin, growth hormones and other similar biologics that have to be injected, the development of self-injection and the need for differentiation are now causing pharmaceutical and biotech companies to look for more and more convenient ways of administrating their products; in this context needle free, single use and disposable devices are becoming increasingly relevant as an attractive alternative to needle. Innovators in needle-free injection technologies aim to achieve this by improving the patient experience and removing the barriers to self-injection, such as the fear of needles, lack of confidence to self-inject, and dealing with the complexity of needle-based injections. The vaccine delivery is one of the areas where a lot of research has been done to replace needle use because of concerns about pandemic diseases. In Bangladesh Needle Free Injection Technology (NFIT) iHealthNet a US registered company, launched the first commercially available Needle Free Injection Technology system for the citizen of Bangladesh. This is comprised to different medical device and their accessories, the bio-injector B-2000 and the Zeta jet. Both of these devices have FDA clearance and have been in use since 1987 in various part of the world including the USA, France, Malaysia, Philippines, Africa, Maldives, Sri Lanka, and Australia (Tawfiq Hassan, 2013).

Hypodermic Needle:

Is commonly used with a syringe to inject substances into body by intradermal, intramuscular, subcutaneous, intravenous, etc or extract fluids from it. They may also be used to take liquid samples from the body, for example taking blood from a vein in venipuncture. It creates pain, needle phobia, inflammation, scars, and contagious diseases.

The advantages of the Hypodermic Method: It creates pain, needle phobia, inflammation, scars, and contagious diseases. But have many potential advantages; 1st, certainty of effect, and 2nd, rapidity of action. As absorption of a drug takes place so much more rapidly from the subcutaneous cellular tissue than from the stomach, a less quantity is excreted during the process of absorption, and consequently a smaller quantity of the drug is required. But absorption does not take place with equal rapidity from all parts of the intercellular tissue.

The present research works discuss the development of a UV estimation method for febuxostat. Simple, fast, accurate and cost efficient and reproducible. Spectrophotometric method has been developed for the estimation of febuxost at in bulk and tablet formulations. The wave length (λ max) selected for the febuxost at was 315 nm. The linearity for this drug at the selected wavelength is lies between 0.2 to 1µg/ml.Beer's law obeyed in this concentration range with correlation coefficient of 0.9999. The limit of detection and limit of quantification was found to be 1.0585 & 3.2077 µg/ml respectively. The validity of the described procedure was assessed.

Picture1: Syringe for hypodermic injection

Objections to Hypodermic Injections: The chief objections are, (1) the pain caused at the time by the introduction of the needle, or by the drug itself after its injection, (2) the inflammation which either the needle or the drug may give rise to subsequently, (3) the scars which may be left by the frequent repetition of the injection, (4) the danger of communicating a specific or contagious disease, (5) the danger of injecting the drug directly into a vein, and thus producing a dangerous or fatal effect from the too rapid entrance of the drug into the circulation. With a little care these untoward results may be almost entirely avoided.

Factors Affecting Pain from Needle Insertion:

Hypodermic needles are in widespread use, but patients are unhappy with the pain, anxiety, and difficulty of using them. To increase patient acceptance, smaller needle diameters and lower insertion forces have been shown to reduce the frequency of painful injections. The mechanics of needle insertion has been found to significantly affect pain. Both the force and the mechanical workload (i.e., area under the force-displacement curve) of hypodermic

needle insertion have been found to positively correlate with the frequency of pain. Thus, needle tip sharpness and other factors, such as lubrication, which can reduce the force of insertion and mechanical workload, are important parameters that can be optimized to reduce pain from needle insertions. Fine needles and micro needles have been developed to minimize pain and have found the greatest utility for delivery of vaccines and biopharmaceuticals such as insulin. However, pain reduction must be balanced against limitations of injection depth, volume, and formulations introduced by reduced needle dimensions. In some cases, needle-free delivery methods provide useful alternatives(Reis EC, Jacobson RM, 1998. T. Lauder Brunton).

Other Problem with the Hypodermic Injections:

i. Needle phobia
ii. Needle stick injuries
iii. Disposal problems
iv. Training required
v. Infections
vi. Difficult to insert the needle to correct depth.
vii. Necessity of aspirating a needle to ensure not hitting a blood vessel.

Needle Phobia, Needle-stick injuries and contamination, Patient Care, Self-administered injectable and Emergency situations are important public health issues where needle free devices can bring significant improvements (American Nurses Association, 2008, World Health Organization; (GIVS) Global Immunization Vision and Strategy 2006-2015).

Delivery System of Needle Free Injection:

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

Liquid Dosage Injections Method:

Needle-free injection technologies have been developed for injecting liquid formulations, the basic principle of this injection is high enough pressure is generated by a fluid (Chandan Mohanty, Oct 2011). Several liquid jet injection technologies are available on the market including Ferring's Zomajet 2 Vision, Merck Serono's Saizen Cool click and Teva's Tev-Tropin Tjet, which are all human growth hormone products. One of the main attributes of the liquid jet injectors is that used drug in a liquid form which does not typically require re-formulation from standard needle and syringe formats. The jet injectors have been developed as both single-use devices and multi-use systems. All require a power source that provides a very high peak pressure behind the liquid in order that it can drill a hole in the skin, without the use of a needle, followed by a reduced pressure profile to force the rest of the liquid into the skin. This requires careful control over the power source to ensure accurate and reliable delivery of the drug to different skin locations on the same person (Rapolu Bharath Kumar, 2012.M. Sunitha Reddy, 2011).

Solid Dosage Injections Method:

The technology of Glide SDI (Solid Dose Injector) enables the injection of APIs (Active pharmaceutical ingredients) in a solid dosage form without 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, preset spring force, the actuator automatically triggers, pushing the dosage from the drug cassette into the skin. Because the drug is administered in a solid dosage form, the Glide SDI offers enhanced stability and potentially avoids the need for refrigeration or may not require cold chain storage, as well as providing the opportunity for controlled release formulations by using slower dissolving excipients rather than fast dissolving sugars. 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 (Dr.C.Potter; Glide Pharmaceutical Technologies Ltd)

Depot Injections Method:

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 (Rapolu Bharath Kumar, 2012.M. Sunitha Reddy, 2011).

Different Popular Medical Devices or Injectors Presents Nationally and Internationally:

A needle-free delivery system that can deliver the drug either actively or passively is a rational alternative. In the case of delivering the drug actively, a driving force is necessary for the transport of drug across the skin, which may be accomplished using jet injectors, electroporation, iontophoresis, ultrasound, powder injection, and tape stripping. So different delivery systems have been developed to deliver vaccine to the epidermal layer of skin (Gopalan J, 2011)

The Air-forced Needle-Free Injection System:

Air-forced needle-free injection systems are typically made up of three components including Injection device, disposable needle free syringe and air cartridge. The injection device is made of a durable plastic. It is designed to

be easy to hold for self-administration of medicine. 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. Some air-forced systems use a reusable spring to generate the pushing force instead of pressurized air cartridges. (Henry, C.,1998).

Picture 2: Air-forced needle-free injection systems

Biojector B2000: The Biojector 2000 (commonly known as B2000, figure 4) is a Needle free injection Technology (NFIT) System designed to deliver vaccines and other pharmaceutical injectables. Intramuscularly (IM). Subcutaneously (SC) and Intradermally (ID) by pressurizing and liquid dose in a chamber from which it is ejected through a small orifice of a syringe with sufficient force to penetrate human tissues. It is intended for clinical use by medical personnel on humans, as well as for self-use by patients when prescribed by their healthcare provider. The Bijector B2000 shots respectively before the manufacturer's warranty recommend recalibration. To date, there has never been any instance, known or reported of device failure on field even when the device was used for 350,000 shots before recalibration.

The system is comprised of three major components:

1. Biojector 2000 injector device;
2. Sterile, single use disposables syringe, vial adapter and syringe safety cap;
3. Carbon dioxide [CO_2] power source in portable cartridge or tank.

Picture 3: BiojectorB2000 **needle-free injection systems**

Vitajet:

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 insulin after each use. The Vita jet 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.

Picture 4: Vita jet **needle-free injection systems**

Coolclick:

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.

Picture 5: Cool click **needle-free injection systems**

In these cases, Saizen or growth hormone replacement must be injected to maintain normal growth. Cool Click is a customized 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.

Sero Jet: The Sero Jet is a needle-free injection system for delivering Serostim recombinant human growth hormone for treatment of HIV-associated wasting in adults.

Picture 6: Sero Jet **needle-free injection systems**

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.Serono developed Serostim to treat this condition by utilizing the natural properties of growth hormone in increasing lean body mass. Sero Jet is a customized version of Bioject's Vitajet needle-free injection system. The system includes customized 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.

Picture 7: Iject **needle-free injection systems**

The Iject is a pre-filled single-use disposable injection device configured to administer 0.5 to 1.00 ml subcutaneous 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. The Iject needle-free injection system is an investigational device, subject to the US Food and Drug Administration clearance for commercial distribution.

Intraject:

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 (Vivek Ranjan Sinha, 2005)

Zeta jet:

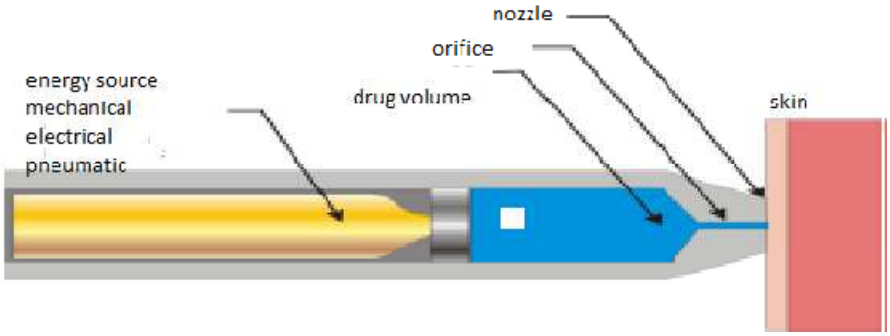
This is the world's first auto-disable and dose adjustable combination of Needle free Injection delivery System that has received FDA clearance, defining safety to the next level. The device is used for Subcutaneous and Intramuscular injections capable of delivering up to 0.5 ml. The Spring Powered Technology allows for lower operating cost and eliminates the need for any external power source thus making it highly portable to remote areas. Zetajet is very simple to use and requires winding the device, filling the syringe (pre-fitted with a vial adapter) with medicine, and pushing a button to deliver the medicine through the skin (Karine Talbot)

Methodology of Released Medicines from NFIs:

Needle-free injection devices, first called "jet injectors," were developed in the 1930s and used extensively for over 50 years in mass human vaccination programs for smallpox, polio, and measles (Dr. Charles potter, Henry, C).However, only recently they are being promoted as devices for the self-administration of parenteral drugs. When administered vaccine through the skin mechanical compression to force fluid through a small orifice (force generated by a compressed gas typically air, CO2 or nitrogen), an ultrafine stream of fluid penetrates the skin, delivering the vaccine in a fraction of a second to the skin, (these devices produced a high-pressure stream 76 to 360 μm in diameter, compared to 810 μm for a 21-gauge needle) Injection event requires less than 0.5 seconds. All require a power source that provides a very high peak pressure behind the liquid in order that it can drill a hole in the skin, without the use of a needle, followed by a reduced pressure profile to force the rest of the liquid into the skin. This requires careful control over the power source to ensure accurate and reliable delivery of the drug to different skin locations on the same person (Needle free insulin devices, 2004).

Components for Needle less Injection Shown in the Picture Below:

Components for needle less injection shown in the picture



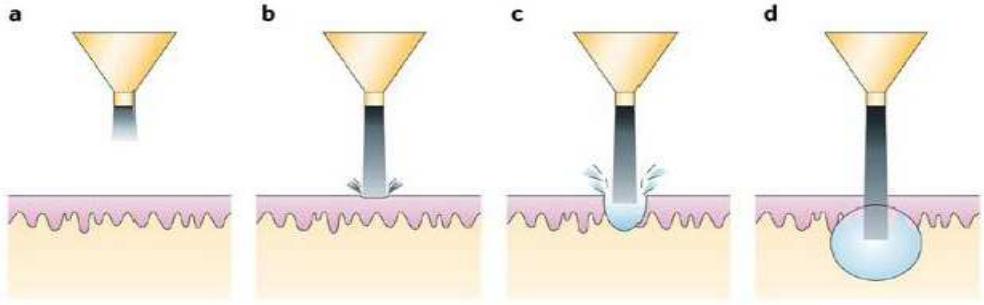
Picture 8: Components for Needle less Injection

Nozzle: The nozzle has two critical 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.

Drug reservoir: The drug volume holds the injection fluid inside the device.

Pressure source: The energy source provides the necessary driving energy to the drug for injection. Many of the devices on the market use either mechanical or stored pressure as energy storage elements. The mechanical method stores energy in a spring which is released pushing a plunger to provide the necessary pressure. The pressure storage method uses com-pressed gas in a vessel which is released at the time of injection (Reddy M. S, 2011)

Mechanism of Working:



Picture 9: Visualizing the Process of Transdermal Injection

a. Impact of a piston on a liquid reservoir in the nozzle increases the pressure, which shoots the jet out of the nozzle at high velocity (velocity > 100 m/s).
b. Impact of the jet on the skin surface initiates formation of a hole in the skin through erosion, fracture, or other skin failure modes.
c. Continued impingement of the jet increases the depth of the hole in the skin. If the volumetric rate of hole formation is less than the volumetric rate of jet impinging the skin, then some of the liquid splashes back towards the injector.
d. As the hole in the skin becomes deeper, the liquid that has accumulated in the hole slows down the incoming jet, and the progression of the hole in to the skin is stopped. The dimensions of the hole are established very early in the process (a few tens of microseconds) from the time of impact. Stagnation of the jet at the end of the hole disperses the liquid into the skin in a near-spherical shape (highplainsdairy.org)

Stages of Needle free drug delivery (Dr. Bruce G., August 2005): There are three stages in the needle free drug delivery:
1. The peak pressure phase-optimal pressure used to penetrate the skin (<0.025 sec)
2. Delivery or dispersion phase (up to 0.2 sec)
3. Drop off phase (<0.05 sec)
The total amount of time required to deliver the vaccine is up to 0.5 seconds
Types of Medicines Used in as Alternative Delivery System to Needle Injection:
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. Many of the needle free technologies are in the growth stage. Companies are working on producing devices that are harmless, easier to use & can deliver more types of medicines. Inhalers, nasal sprays, forced air injectors and patches are being developed. In the near future, genetically enhanced foods may prove as an alternative for the delivery of vaccines and other drugs are described shortly below:
1. For Growth hormone 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.
2. 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.
3. 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.
4. 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.
5. 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 (Seppa, N., 2000).
6. 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 (Henry, C., 1998).

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 (Henry. C., 2000).

Advantages of Needle Free Drug Delivery (Potera, C., October, 1998. Adam Levy)

1. Safety: Employees are less likely to be pricked with contaminated needles. Furthermore, this system will eliminate the high number of tissue damage that results when a needle breaks upon insertion into a patient.
2. Sterility: Needle-free injections eliminate the possibly of reusing needles from one patient to another by eliminating the needle all together. According to the World Health Organization, it is estimated that 40-70% of needle are reused, leading to cross-transmission with hepatitis, HIV, and other diseases. This technology will significantly decrease the spread of diseases and cross contamination.
3. Convenience :For patients who need daily injections of medications, they no longer need to inject themselves with painful needles, but rather a simple and efficient needle-free injection that can be self-administered, require no prior training, and take less than 0.5 seconds.
4. Reduces costs
5. Promotes patient compliance: It is estimated that 10% of Americans have aichmophobia, belonephobia, or enetophobia, a fear of sharp things, such as needles. Patients may be more compliant on their medications and treatment plans when using needle-free injection systems.
6. Greater medication dispersion: When using a traditional needle-based delivery system, the medication is delivered from the syringe as a spherical pool with the needle doing the penetration. However, the medication itself is responsible for penetrating the skin using needle-free injection systems and thus follows the path of least resistance. This results in a wider dispersion of the medication. This can provide greater efficacy.

Disadvantages of Needle-Free injection System:

There are numerous advantages of the needle-free injection systems; however, it is typically not widely used as a drug-delivery system. This may be attributed to the fact that there are also some disadvantages as well. These include:

1. Unreliable penetration of the skin due to the shape of the diffusive jets used with these devices.
2. Unreliable injection amount when using small volumes.
3. Often painful for patients.

The World Health Organization does not endorse jet injection due to the risks of disease transmission. One notable case was in a weight loss clinic in Brazil that resulted in an outbreak of hepatitis B. 24% of those receiving treatment via jet injector experienced acute hepatitis B infection while none of those receiving the treatment by needle had a hepatitis B infection. Another case in a podiatry clinic led to eight Mycobacterium chelonae infections (Yang, S.Y. et al., 2013).

Newest Needle Free Injection System:

1. The Needles Free injection system represents the latest alternative to injection on the market and it can deliver transdermally ionic drug solution into the body for medical purposes (Mattioli engineering)
2. Capability of transdermal delivery of ionic solution of drugs.
3. Capability of transdermal delivery for the first time ever of ionic drug solution of either micro or macromolecules (greater than 800.000Dalton).
4. No electrolysis of ionic drug solutions nor variation in the ionic drug solution pH
5. Both positive and negative ions of the drug are transdermally delivered at the same time.
6. Promotes transdermal delivery rate by means of prior microdermabrasion and pulses delivery reproducibility of dose delivered control on the transdermal delivery of ionic drug solutions.
7. Patient's perception of electrical pulses significantly decreased due to vibration feature.
8. Non-Invasive action and no trauma from injections.

Control of Newest Needles Free Injection System (Mattioli engineering-Needles Free Injection System).

The Needles free injection system can control all the parameters concerning

1. Reproducibility on any skin condition
2. Optimizing absorption characteristics.
3. Amount of drug to be delivered.
4. Time of delivery
5. Digitally controlled exfoliation accuracy.

Comparison of Needle Free Injection v/s Needle Free Injection:

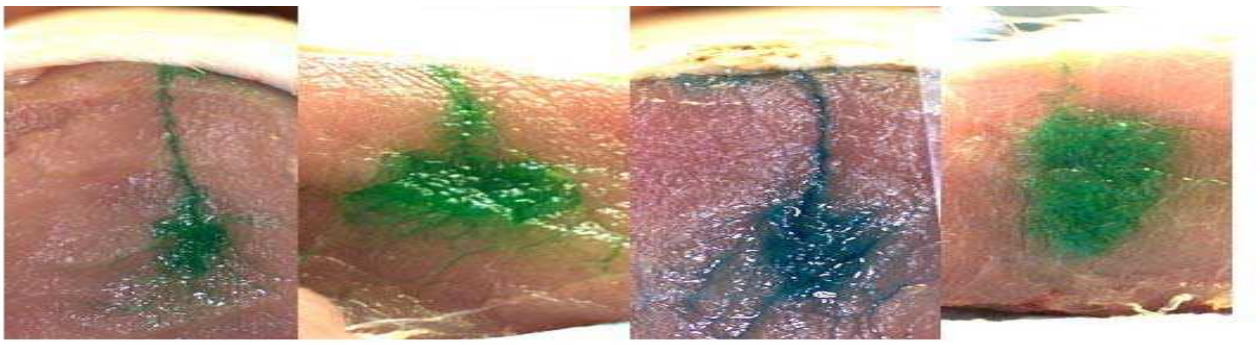
For the purpose of delivery via skin, the needles must pierce the outermost barrier of the skin i.e. the stratum corneum. So, the delivered drug reaches the circulatory system at a faster rate. The Needle free injection system is

also intended to deliver various medications and vaccine intramuscularly or subcutaneously by means of a narrow, high velocity fluid jet, which penetrates the skin and delivers the medicine or vaccine to the body at same rate but without pierce the outermost barrier of the skin. The principle of all the devices is the same; i.e. the energy generated by a NFIs is used to accelerate a premeasured dose of particulate drug formulation and have demonstrated consistent delivery through the epidermis, the dermis, the subcutaneous and intramuscular space(Chandan Mohanty,Oct 2011.Patwekar S.Lgattani, S, G., 2013). Jet Injectors (is an effective method of delivery has been enhanced since the introduction of Disposable Syringe Jet Injectors, its developed, tested and validated in accordance with FDA regulations and requirements set by the International Organization for Standardization) eliminate the necessity of using an invasive needle and remove the human variability associated with syringe filling and injection by employing innovative design in a needle-free syringe mechanism. This is accomplished while still utilizing the identical route of administration, depth, dose and mechanism of action as needle and syringe, maintaining a robust safety profile. Jet Injectors have delivered millions of doses of vaccines intended for the intramuscular and subcutaneous tissue depths to prevent diphtheria, hepatitis A, hepatitis B, influenza, meningococcal disease, pertussis, polio, tetanus, yellow fever, anthrax, cholera, DTP, typhoid, and influenza, and other diseases. This is accomplished by processing of the antigens by the immune system following intramuscular/subcutaneous deposition by needle free devices (Dr. Bruce G., August 2005).

Intramuscular Injection with Jet Injector v/s Needle and Syringe:

Depicts 0.5ml intramuscular injections of dye performed by both the device and a needle/syringe. Both systems utilize matching routes of administration and mechanism of action.

Jet Injector **Needle and Syringe** **Injector** **Needle and Syringe**



Picture 10: Dye performed by both the device and a needle/syringe

Table Below Compares a Needle Free Device v/s Needle-Based Syringe Delivery

	DSJI - PharmaJet	**Needle/Syringe**
Route of Administration	Intramuscular/Subcutaneous	Intramuscular/Subcutaneous
Volume	0.5ml	0.5ml
Orifice Inner Diameter	0.010"	0.0095" for 25 gauge (0.0035" for 33 gauge)
Barrel Inner Diameter	~.25”	~.25” - .5”
Stroke	~1”	~ 0.5” - 1”
Speed of Injection	~.3-.5 sec	~.3 - 1 sec

To ensure that from above picture and table, devices maintain their delivery performance; tests are conducted across a wide range of viscosities. Needle free device provides the same route of administration, depth and dose as a needle/syringe injection, without the drawbacks of using needles Both Jet Injectors and needle and syringe have been proven to inject the prescribed depth and dose and do so in an analogous way. Needle-free injectors, depth of penetration (DOP) and delivery volume accuracy are tested throughout the development cycle to ensure the devices meet or exceed standards and also describes the development, verification and validation activities performed to ensure the 0.5ml Needle free injection system meets established performance criteria (Dr. Bruce G.,August 2005)

Forth Coming Technology for NFIs:

Many of the needle free technologies are in the growth stage. Companies are working on producing devices that are harmless, easier to use & can deliver more types of medicines. Inhalers, nasal sprays, forced air injectors and patches are being developed. In the near future, genetically enhanced foods may prove as an alternative for the

delivery of vaccines and other drugs. These include foods like bananas and tomatoes. Actually, bananas are looked as carriers for vaccines to defend against the Norwalk virus and tomatoes for protection against hepatitis B. Besides these novel delivery systems, scientists are also investigating methods for producing long lasting drugs that will minimize the number of needle injections. Recently these issues have been addressed in a trial to increase the reliability of the needle-free injection system. They made a micro jet system that uses a laser pulse to vaporize a liquid, this creates a shock wave that curves the interface, and eventually ends up releasing the medication by a high-speed micro jet. The jet, and therefore the penetration and drug release, can be controlled through the manipulation of the laser, the contact angle between the glass tube and liquid, as well as the diameter of the tube. This injection system decreases the amount of pain experienced by patients as well as allows for controlled drug delivery (M. Sunitha Reddy, 2011.World pharmaceutical frontiers).

Limitation:

Like all technologies too has its share of draw backs. Though it is not aplenty but one major drawback which is a clinical concern is that the high pressure delivery of drugs by the jet pressure needle free injection can damage fragile molecules beneath our skin surface, specially Monoclonal antibodies but this can be resolved if a specialized device is employed to control the exact pressure of drug delivery (Karine Talbot, Hytek La Broquerie).

Literature review:

A comprehensive and thorough literature review was done about hypodermic injection, needle free injections technologies, needle free injection devices currently available on the market and the information regarding it was clearly placed in this article.

Recommendation:

The future of needle-free injection systems looks bright, with a steady growth due to increasing demand for prevention of needle stick injuries and painless delivery of medication and this fact is further strengthened by the strong clinical trial data available above.

CONCLUSION

Needle Free Injectors are more reliable, easier to use, more efficient, much safer and have no disposal problems. Acceptance by patients, continuing developments and lowering costs, all make needle free systems the best method for vaccinations, insulin self treatments. NF technology offers the very apparent benefit of minimizing patients fear and other problems regarding the use of needle. Other benefits comprise very fast injection as compared to traditional needles. Not only it can assist the pharmaceutical industry in rising product sales, but also it has the extra potential to increase conformity with dosage regimens and enhanced outcomes. Needle free devices have demonstrated consistent delivery to the epidermis, the dermis, the subcutaneous and the intramuscular space. The biotech revolution is bringing a series of protein based therapeutics into the market place at rapid speed, more than 300 products in active development. Today, Needle-free devices have come a long way to the present state and are expected to play an increasingly important role in the novel drug delivery technologies markets in the coming years. While, instead of steadily developing of needle injection that promises to make the administration of medicine more efficiently but pain, needle stick injuries, contamination, resist self administration and needle phobia could not solve yet (Katrina Megget, July 2007.Dr. J K Patel, 2006.Bhagyashri Chavan, 2013),for that in some cases, needle-free delivery methods provide useful alternatives.

REFERENCES

1. American Nurses Association; "2008 Study of Nurses' Views on Workplace Safety and Needle stick Injuries"; summer 2008.
2. Adam Levy., Advances in disposable needle-free injector technology, Weston Medical Ltd, Drug Delivery, Innovations in Pharmaceutical Technology, Page no. 100-109.
3. A future free from needles, world pharmaceutical frontiers, www.worldpharmaceuticals.net, Page no. 20-22.
4. Bhagyashri Chavan, Abha Doshi, Yashwant Malode, Balu Misal, Needle Free Drug Delivery Systems; International Journal of Pharma Research & Review, Sept 2013; 2(9):30-36
5. Chandan Mohanty, Needle free drug delivery systems, International Journal of Pharmaceutical Research and Development, Oct 2011; 3(7): 7-15.
6. Dr. Bruce G. Weniger Needle-Free Injection Technology, August 2005
7. Dr Charles Potter, Needle-Free Injection; Pharmaceutical Technology Europe, Volume 23, Issue 2: Feb 11, 2011
8. Dr. J K Patel Painless and needle free supersonic injection technologies, pharmainfo.net, 10/04/2006.
9. Gopalan J, Divya G, Chakravorty D. Needleless Vaccine Delivery Using Micro-Shock Waves. Clinical and Vaccine Immunology: CVI, journal of American Society for Microbiology. April 2011; 18(4): 539–545.
10. Henry, C. "Special Delivery." Chemical & Engineering News September 18, 2000: 49-65.

11. Karine Talbot, Hytek La Broquerie. Life beyond needles La Broquerie MB ROA 0W0 Canada
12. Hingson RA, Davis HS, Rosen M. The historical development of jet injection and envisioned uses in mass immunization and mass therapy based upon two decades experience. *Mil Med.* 1963; 128:516–524.
13. Katrina Megget. Needle free injection device a winner, 16 July 2007,
14. Mattioli Engineering, Needles Free Injection; Systemwww.matteng.com/needles.html
15. M. Sunitha Reddy, M. Ranjith Kumar, K.Sanjay Kumar, Anil Goli, P.Santhosh Kumar, Needle free drug delivery systems, J. Rev. Life. SCI, 2011; 1 (2): 76-82.
16. Needle free insulin devices- how does it work, British Journal of Diabetes and Vascular Disease. 2004; 4 (2), 2004, Sherborne Gibbs Ltd.
17. Patwekar S.Lgattani, S, G.Needle free injection system, IJPPS; 2013: Vol 5, (4)
18. Potera, C. "Making Needles Needless." Technology Review (September/October 1998): 67-70.
19. Peter Crocker, Dr. Kevin Maynard and Mervyn Little, Pain-free, blunt-needle injection technology Imprint Pharmaceuticals Ltd, Drug Delivery, Innovations in Pharmaceutical Technology, Page No. 111-115
20. Priya KJ, Deepthi T, Varsa B, Varsa MJ, Vilasrao K. Needle Free Injections: The Renaissance and technique. IJPRD 2013; 5(6): 46-55.
21. Potera, C. "No-Needle Vaccine Techniques." Genetic Engineering News (August 1998)
22. Patwerar S.L., Gattin.S.G, Needle free injection system; International Journal of Pharmacy and Pharmaceutical Sciences Vol 5, Issue 4, 2013
23. Rapolu Bharath Kumar; Needle free injection systems, the Pharma Innovations Journal, 2012; 1(9).
24. Reis EC, Jacobson RM, Tarbell S, Wenige BG. Taking the sting out of shots: control of vaccination-associated pain and adverse reactions. *Pediatr Ann.* 1998; 27:375–386.
25. Ranjan Sinha, Aman Trehan, Pramil Tiwari:"Needle Free Injection Technology": Express Healthcare Management (1st-15th July 2005) expresshealthcaremgmt.com/20050715/pharma01.shtml
26. Reddy M. S, Kumar M, Kumar K.S, Goli A, Kumar P.S. Review on Needle free drug delivery systems. International Journal of Review in Life Sciences. 2011; 1(2):76-82.
27. Seppa, N. "Edible Vaccine Spawns Antibodies to Virus." Science News (July 22, 2000)
28. T. Lauder Brunton "A Text-Book of Pharmacology, Therapeutics and Materia Medica
29. Tawfiq Hassan.CEO, iHealthNet; Free Injection Technology; The world Pharma, August, 2013:51 Vivek
30. Yang, S.Y. et al. A bio-inspired swellable micro needle adhesive for mechanical interlocking with tissue. Nat. Commun. 4:1702 doi: 10.1038/ncomms2715 (2013).
31. World Health Organization; "(GIVS) Global Immunization Vision and Strategy 2006-2015"; October 2005
32. www.bioject.com/ Biojectorr 2000 technology overview
33. www.bioject.com/ Coolclick technology overview
34. www.zetajet.com/ Bioject-zetaget technology-system overview.
35. www.pharmajet.com/ pharmajet needle free injection system-general information.
36. www.crossject.com/ crossject needle free devices- benefits and uses.
37. www.penjet.com/ needle free pen injectors
38. www.medijector.com/zomajet devices information
39. www.highplainsdairy.org