Review Article

Needle free injection technology: A complete insight

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Abstract

Needle free injection technology (NFIT)is an extremely broad concept which include a wide range of drug delivery systems that drive drugs through the skin using any of the forces as Lorentz, Shock waves, pressure by gas or electrophoresis which propels the drug through the skin, virtually nullifying the use of hypodermic needle. This technology is not only touted to be beneficial for the pharma industry but developing world too find it highly useful in mass immunization programmes, bypassing the chances of needle stick injuries and avoiding other complications including those arising due to multiple use of single needle. The NFIT devices can be classified based on their working, type of load, mechanism of drug delivery and site of delivery. To administer a stable, safe and an effective dose through NFIT, the sterility, shelf life and viscosity of drug are the main components which should be taken care of. Technically superior needle-free injection systems are able to administer highly viscous drug products which cannot be administered by traditional needle and syringe systems, further adding to the usefulness of the technology. NFIT devices can be manufactured in a variety of ways; however the widely employed procedure to manufacture it is by injection molding technique. There are many variants of this technology which are being marketed, such as Bioject® ZetaJetTM , Vitajet 3, Tev-Tropin® and so on. Larger investment has been made in developing this technology with several devices already being available in the market post FDA clearance and a great market worldwide.

Key words: Immunization, syringe systems, needle stick injuries, propel, sterility

INTRODUCTION

Needle free injection technology (NFIT) encompasses a wide range of drug delivery systems that drive drugs through the skin using any of the forces as Lorentz, shock waves, pressure by gas or electrophoresis which propels the drug through the skin, virtually nullifying the use of hypodermic needle.[1] The devices as such are available in reusable forms. In contrast to the traditional syringes, NFIT not only gives the user freedom from unnecessary pain but drugs in the form of solid pallets can also be administered. The future of this technology is promising ensuring virtually painless and highly efficient drug delivery. The major drawback associated with this technology is postadministration "wetness" of the skin which may, if not taken care of, harbor dust and other untoward impurities.[2] This technology is being backed by organizations as World Health Organization, Centers for Disease Control and Prevention and various groups including Bill and Melinda Gates Foundation. This technology is not only touted to be beneficial for the pharma industry but developing world too find it highly useful in mass immunization programs, bypassing the chances of needle stick injuries and avoiding other complications including those arising due to multiple uses of single needle.[3] Better patient compliance has been observed.

PURPOSE

This review article endows the drugs suitable to be formulated as NFIT, manufacturing, and quality control of NFIT dosage

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form. It also discusses the mode of action, present scenario, and limitation associated with NFIT.

BACKGROUND

Syringes and hypodermic needles have been used to administer the drug to the body for more than 150 years. It was in 1844; hollow needles were devized and the first injection was administered soon. However, only those drugs could be given which possessed a specific combination of physiochemical properties.[4] Primitive syringes were one-piece metal systems attached to rubber plunger used to inject the drug. These syringes were reused and were difficult to sterilize. The evolution of modern day syringe systems has led to the involvement of medical-grade stainless-steel as hypodermic needles while the body is made of plastic, developing the syringes as a two-part disposable system.[5] However, the technical advancements and bioengineering capabilities have led to the emergence of various "newer" active enhancements, designed so as to circumvent the barrier function of the stratum corneum.

Since the invention of drugs was capable of curing ailments, newer and better method of delivering them has been sort after.[6] Use of syringes as a medium of drug delivery has been very common and widely accepted in spite of having been associated with the following drawbacks as depicted in Figure 1.

NFIT are novel ways of direct transfer of medicine through the skin, without breaching the integrity of the skin or even piercing it. These devices can be used to drive medicaments into the muscle too.[7] NFIT has shown promising results in mass immunization and vaccination programs. These systems are virtually painless as they avoid the use of conventional needles.

Principle

NFIT harnesses energy stronger enough to propel a premeasured dose of a particular drug formulation, loaded in specific unique "cassettes" which can be rigged with the system.[8] These forces may be generated from any of the ways ranging from high-pressure fluids including gases, electro-magnetic forces, shock waves or any form of energy capable enough to impart motion to the medicament.[9]

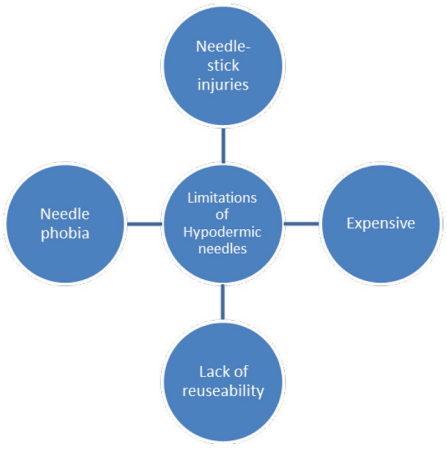

Figure 1: Limitations of hypodermic needles

CLASSIFICATION OF NEEDLE FREE INJECTION TECHNOLOGY

1. On the basis of working.
   - Spring systems.
   - Laser powered.
   - Energy propelled systems.
     - Lorentz force.
     - Gas propelled/air forced.
     - Shock waves.
2. On the basis of type of load.
   - Liquid.
   - Powder.
   - Projectile.
3. On the basis of mechanism of drug delivery.
   - Nano-patches.
     - Sandpaper assisted delivery.
     - Iontophoresis enabled.
     - Micro-needles.
4. On the basis of site of delivery.
   - Intra dermal injectors.
   - Intramuscular injectors.
   - Subcutaneous injectors.

MODE OF ACTION OF NEEDLE FREE INJECTION TECHNOLOGY

On the basis of working

Spring system

Springs have been used to harbor energy and have been proven to be quite effective in powering NFIT devices. For NFITs, energy storage and further transmittance via spring is one of the easiest and simplest. However, the design of the spring must follow the standard protocols and the storage conditions must be simple or the spring will take a "set" over time deteriorating the performance of the device.

The basic issue with respect to the design of the spring is that the force provided by the spring will reduce in proportion to the distance over which the load has been applied as according to the Hook's law.[10] In simple words, in spring assisted NFIT, the pressure shall gradually decreases throughout the injection.

Laser powered

A newer dimension of NFIT developed by Prof Jack Yoh and his team (Department of Mechanical and Aerospace Engineering, Seol National University, South Korea) uses laser based system that blasts microscopic jets of drugs into the skin.

The technology uses an erbium-doped yttrium garnet laser (the one used in the care of laser resurfacing of the skin) to drive a

very fine and precise stream of drug or medicament with the right amount of force.

The laser is integrated with an adapter which holds the drug to be administered. The device also contains a chamber for water which is used to drive the medicine; however, the arrangement is so done that the drug is separated from the driving fluid (water) with the help of a membrane.

Working

The laser pulse of a wavelength of about 2940 nm is emitted, which has a life span of about 250 millionth of a second. It attacks the driving fluid generating a vapor inside the fluid.[11] The bubble formed impacts on the membrane, applying a pressure to it causing a strain on it leading the drug to be forcefully ejected from a minute nozzle of about 150 millionth of a meter in diameter with very great impact on the skin, sufficient enough to smoothly penetrate into the skin, without any damage to the tissues and no drug splash back happen.

The research team in association with a major company is still working on the technology to develop better and more advanced variants of this technology.

Energy propelled system

Commercial spring powered jet injectors offer little to no control over the pressure applied to the drug during the time of the injection; also these devices are often loud and sometimes painful. The force required to propel the drug so as to have a penetrating effect can also be generated by energy in various forms.

Lorentz force

Researchers at MIT have engineered an NFIT device which uses Lorentz force to push a piston forward ejecting the drug at very high pressure and velocity (almost equal to that of sound in air). The main component of the device is the Lorentz force actuator which facilitates the entire process.[12]

Working

The design of the device is built around a Lorentz force actuator which consists of a small and powerful magnet which is surrounded by a wire coil that remains attached to a piston which is inside a drug ampoule. When current is applied, it interacts with the magnetic field so as to produce a force, which pushes the attached piston forward, while the stream of the formulation from the device is forced out as thin as the mosquito's proboscis.

The amount of current supplied can be very well regulated enabling the speed of the coil to come under our regulation. This would finally control the velocity with which the drug is ejected. The research team has even demonstrated the device to act in a high pressure phase when the drug penetrates deeper into the skin at desired strength and in a low pressure phase where the drug is delivered in a lower stream so as to be absorbed by the surrounding tissues. This capability of the device has made it be a versatile NFIT system suitable for corneal drug application and also fit for pediatric use.

Gas propelled/air forced

Gas, as a power source will be less suitable for reusable devices unless special arrangement and design alterations or component modifications may be made such that the pressure is not lost, and the spring is reset for each injection, still, gas powered NFITs have greater scope since compressed gas offer higher energy density than a metal spring. Gas powered devices tend to be either single use or need a periodic replacement of the gas cartridge. Some devices employs gas as a simple spring where the stored gas accelerates the piston there are portable and compact, however, developing a gas spring which retain a specific proportion of the gas to work at the lapse of its shelf life is a major challenge.[10]

To overcome such challenges, an alternate method has been developed which uses carbon dioxide liquefied at the storage temperature and pressure. This approach has been proven beneficial as a minimal loss of gas from the container inflicts virtually "no" or "zero" reduction in pressure. However, the pressure in such containers is highly sensitive to temperature with the pressure doubling between 0° and 40°. This may affect the performance of the device if a broader operating temperature range is desired. This problem can be sorted out by using a pressure regulator.

Further research has led to the evolution of reusable, sophisticated and comparatively more portable gas powered NFITs as in such systems (one developed by Team Consulting Ltd., Cambridge, UK) simple Butane combustion engine is used to power the device. The complete efficacy of this system is yet to be established, and data published.[13]

Major industries (Cross-Ject and BioValve) working for the development of NFIT systems have employed a technique of gas generation chemically in which the gas is produced at a reproducible and predictable rate to power the device. The reaction is initiated either mechanically or electrically, where the chemical "burns" generating gas.

The major drawbacks associated with this technology include:

1. Complicated validation protocols.
2. Foul odor due to combustion of reactants.
3. Large volume manufacture of reactants.

Shock waves

Shock waves are generated by any sudden release of energy. These disturbances carry energy and can be propagated through a medium. Researcher at the "Indian Institute of Science" (IISc) Bengaluru have developed a needless noninvasive drug delivery system employing this energy at supersonic levels.

The prototype of this device consists of following major parts:

a. Ignition system to ignite the "charge."
b. Polymer tube which contains the explosive material which is suitably coated.

c. Drug holding chamber to load the drug.
d. The system also contains the cavity holder and metal foils.

A micro-blast is induced through a tiny "controlled" explosion which is propagated at supersonic speeds, yielding high pressure and temperature. The pressure generated via this "explosion" technique is strong and potent enough to eject the drug (a vaccine as in the case of system developed by IISc) filled in a miniature model device. The drug is forced into the skin while the integrity of the skin remains intact.

If the technology developed by IISc proves to be successful, the institute will offer cheaper, noninvasive technologies which will not only arrest the incandescence needle stick injuries but would also limit infections at healthcare centers.[14]

ON THE BASIS OF TYPE OF LOAD

Liquid

Liquid NFIT is the first variant of the NFIT systems and still, major players in the pharma industry are working on it.[15] The entire mechanism of achieving a successful injection with a needle free system depends upon the ability of a liquid jet, stronger enough to penetrate the skin and the underlying fat layer without harming the skin or the integrity of the drug molecule. The mechanics involved in liquid NFITs is so complex that the recent studies have been carried out to understand the complete procedure of it.[16]

Delivering fluid from NFIT involves a thorough application of fluid mechanics. The steps involved are:[17]

- "Registration": The orifice of the device is placed exactly over the pores of the skin.
- Exact pressure: The fluid must be forced at an optimum pressure, stronger enough that it keeps the holes in the skin open and consistent enough that it avoids the resealing of the holes.
- Channel drilling: The initial pulse of the fluid drill a channel into the fat layer deep enough that the dose is drifted from the hole into the skin.
- Quicker pressure fall: The pressure drops quickly and sufficiently so that the fluid may not penetrate the muscles underlying the skin.

Powder

Powder needle free injection depends on being able to formulate the particles of sufficient density and accelerating them to sufficient velocity strong enough to penetrate the skin and in a quantity sufficient enough to reach the therapeutic dose levels.[18] This was made successful by using helium as a power source assisted by modifications in the ways of formulation of the drug as:[19]

- Conversion of the drug either pure or along with excipients into hard particles of 10-50 nm in diameter, with a density approximately the same as a crystalline drug.
- Coating the drug onto gold spheres which may act as a vector of few micrometers in diameter, this method is mostly applicable to DNA vaccines.

Working

The drug is stored in a "cassette" designed so as to house the drug in the center, while the cassette is capped with a polymeric lid, upon activation a gust of helium gas ruptures the lid, forcing the drug forward due to specially designed convergent-divergent type nozzles the drug particles attain the speed near about to that of sound, hence penetrating the skin.

Drug delivery through this system is limited only to those candidates with an effective dose of about 1 mg max. Since in powder drug delivery through NFIT systems, it is difficult to predict the proportion of dose that is difficult to determine the proportion of dose that is to be delivered to the epidermis, also the maximum payload for a 20 mm diameter target area of skin is about 2-3 mg.

This technology is highly suitable for DNA vaccines and the delivery of local anesthetic to the skin and oral mucosa.[20]

Projectile/depot

Highly advanced compared to the prior developed into this variants of the NFITs, the drug is processed into a long thin depot having sufficient mechanical strength strong enough to transmit a driving force to a pointed tip which may be formed either of an inert material or medicament itself.

Generally, a depot is in the form of the cylinder measuring around 1mm in diameter and few millimeters in length. This dimension may be small enough to limit the payload, but the quantity of the payload is sufficient enough for many new therapeutic proteins, antibodies, and other smaller molecules. The depot is strong enough to puncture the skin when punched with the sharp tipped punch by applying a pressure of the order of 3-8 mega Pascal (MPa). For a depot preparation of around 1 mm, only a few Newton's of force are required. The delivery device, therefore, would employ the transfer of energy from a suitable "spring" upon the depot.[21]

ON THE BASIS OF MECHANISM OF DRUG DELIVERY

Nano-patches

The working of nano-patch or micro-projection depends on the use of an applicator to deliver the drug through the skin. Nano-patch projections are invisible to the naked eye and thereof are not anticipated to inflict fear into the people. Drug delivery using nano-patches have been highly efficient with respect to vaccines. Nano-patches enable the vaccine to reach the key immune cells located below the skin surface while the entire process is pain free.

Sandpaper assisted delivery

Mostly, a 220 grit "sandpaper" kind of agent is rubbed onto the skin the skin so as to result in micro-derma abrasion a phenomena where the superficial layer of the skin is removed, thereby facilitating the entire drug delivery process.[22] Microdermabrasion has been widely accepted for cosmetic purposes. Sandpaper aided drug delivery has been successful in increasing the skin permeability, for several vaccines and other methods of Microdermabrasion have been used to facilitate the movement of drugs such as lidocaine, 5-flurouracil.[23] Till now, vaccinations for traveler's diarrhea and influenza have been developed using this technique (Clinical trials in progress).[24]

Iontophoresis enabled

The lipophilic nature of skin debars several salts and other molecules from entering the skin. By iontophoresis, a small electric current of about 0.5 mA/cm^2 is used to force several drug molecules across the skin.[25] The working of this method involve the use of two electrodes as patches, where one acts as a drug reservoir, which can either be positively or negatively charged depending upon the nature of the drug, another patch is placed somewhere else on the body to complete the circuit.

For successful drug delivery by iontophoresis, both the quantum of charge (positive and negative) and type of the drug must be compatible with the process. Excipients in the drug and condition of the skin need to be considered too.[26] Iontophoresis have shown excellent results as means of drug delivery system for peptides, therapeutic proteins or vaccines, and oligonucleotides.[27]

Iontophoresis has also been modified so as to remove molecules from the blood circulation. GlucoWatch, a needless procedure involves a reverse iontophoresis technique to monitor blood glucose level.[28]

Micro-needle

Micro-needle patches, as the name suggest, employs the use of thousands of tiny spikes all around 750 μ long. These patches are pressed onto a person's skin while the spikes pierce the outer most layer of the skin so as to deliver the drug, while the piercing is not deep enough to hit the blood vessels or even the pain receptors so as to cause pain. Different types of micro-needles have been developed from the sophisticated metallic to plastic ones. While some are just "coated" with the drug, others are hollow having a liquid vaccine or the formulation filled inside.[29]

In some cases, the spikes are made of the formulation itself, in many cases, dissolvable patches are used which are made of cellulose and/or sugar molecules.

Researchers have revealed the drug delivery (mainly vaccines) have been more efficient when administered via micro-needle patch than the traditional intra-muscular injection, since larger number of dendritic cells (which are more susceptible to vaccines) are located in the skin.

Even micrograms level of drugs can be delivered using micro-needle based drug delivery system. This makes it the most suitable choice for highly potent and small molecules or peptides.

Micro-needle patches have not only proven to be highly effective but have even shown better patient compliance. However, certain limitations are associated with the use of micro-needle patches.[30]

- Larger doses require bigger patch size.
- The formulation must be able to "coat" or "stick" on to the spikes on needle surface.
- In cases, if the needle itself is made of the drug, the formulation must have required physico-chemical property to maintain a sharp tip for adequate skin penetration.
- The depth of penetration of the micro-needle may differ from person to person, based on thickness, toughness of the skin and reproducibility of the application.
- Movements of the body or the body part upon which the patch is applied may lead to dislodging of the needle.

ON THE BASIS OF SITE OF DELIVERY

Intradermal injector

These systems have been employed to deliver comparatively newer, DNA-based vaccines to the intradermal layer.[31] The system delivers the drug at a very shallow depth that is, between the layer of the skin.

Intramuscular injector

One of the most developed NFIT systems employed for intramuscular drug administration. Drug delivery via this system is the deepest among all. Drug delivery through NFIT devices has been most successful for vaccination.[32]

Subcutaneous injector

Certain therapeutic proteins including the human growth hormones have been administered by this system. The medicament is delivered to the adipose layer just below the skin.[32]

NEEDLE FREE INJECTION TECHNOLOGY: DRUG PREQUISTS

Shelf life

Nonprefilled devices need to have a longer shelf life which can be attained by the stable power source. The mechanics of the device must be so as to enable it being trigged even after 2-3 years of storage in varied storage conditions.

When talking about the prefilled NFIT system, the following points need to be considered over the entirely intended shelf life:[33]

a. The product must remain sterile throughout.
b. Endotoxins and foreign particulates must not exceed the predetermined limit.

c. The leachable profile into the formulation from the contact component of the device must not be excessive, rather acceptable.
d. The purity composition and concentration shall not be compromised throughout the intended shelf life at any case.
e. The entire device must be made of a material which remains stable, offer good mechanical strength, cost effective, and inert in nature.

Viscosity

Newer pharmaceutical preparations are being formulated because the molecule is often larger and needs to be concentrated enough to lie in a range of volume that can be injected comfortably.

When we see the case of traditional needle syringe system, the hypodermic needle act as a pipe decreasing the pressure along the length of the pipe (here, needle) making difficult to deliver the various preparations, or in simple words, the user has to apply more pressure on the plunger, while injecting a viscous fluid than during a nonviscous one. And as the viscosity increases the further force required rises too.[34]

Needle free devices don't have to suffer such events and are proven efficient in delivering a wide range of formulations of varying viscosities, as the devices don't employ the use of any hollow needle.

MANUFACTURING OF NEEDLE FREE INJECTION TECHNOLOGY

There are a number of ways for manufacturing the NFIT devices; however, the following discussion gives an insight over the production of an air forced system as shown in Figure 2.

Raw material

As the device is in direct contact with the skin, so it needs to be made from materials that are pharmacologically inert in nature. Polycarbonates including thermoplastics, those which are synthetically produced and are easier to mold and light in weight are the most suitable raw material for making the outer compartment or the body of the device. If needed, and in most cases, colorants are added. Gas powered systems use helium or CO_2 as a source of propulsion, even newer designs use butane for such operations. The body of the device must be made of material like such that, it does not react with the gas or the other adjutants including the colorants.[35]

The raw materials are utilized through a step by step procedure so as to yield a final product. Pieces are produced off site, and the manufacture assembles them while all the assembling process is alone under sterile conditions.

Making the pieces

An extremely versatile process used in the plastic manufacturing industry is used for manufacturing of the devices, called, injection

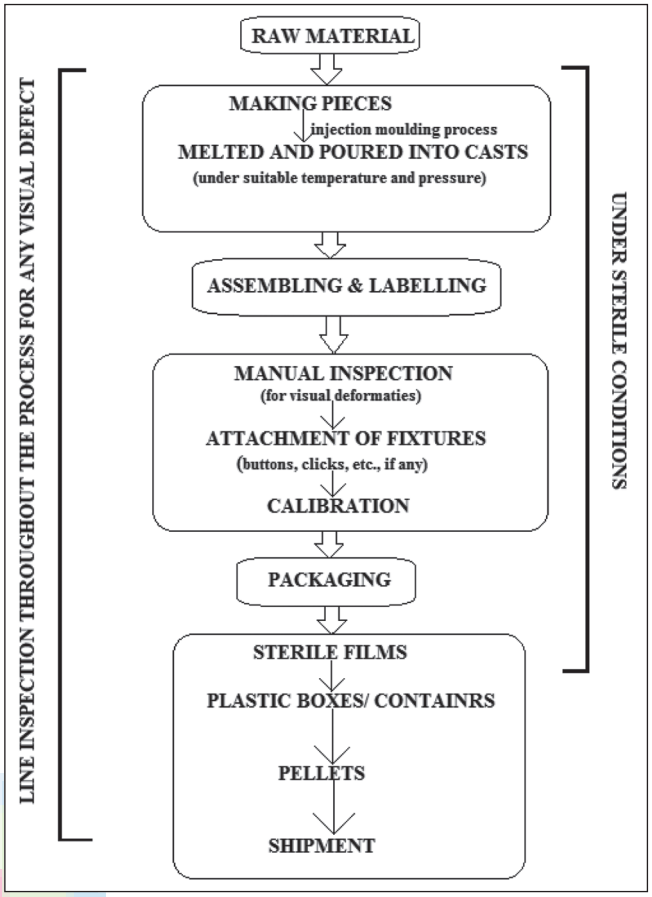

Figure 2: Needle free injection technology manufacturing process

molding process. In this process, the suitable raw materials in the form of pellets are fed into the hopper either manually or mechanically.

The hopper directs the pellets into the cylindrical body of the machine with the help of a rotating screw.[36] The rotating screw pushes the pellets to its nozzle, while the dimension of the screw decreases, causing the pellets to melt due to the frictional forces generated due to gliding of the pellets one over the other also, the tube may be heated externally to increase the temperature which may aid in melting the pellets and increasing the flowability.

The melt is injected into the mold through the nozzle by the help of screw. When the plastic enters into the mold, it is kept for some time under increased pressure, allowed to cool and harden.

The mold parts are opened or separated to eject the formed "design." The design formed, or the device made is inspected manually to ensure that no defects or structural deformity and the process repeat.

Assembling and labeling

The formed design is then transported to an assembly line where sophisticated and highly precise machines apply markings on the design or on the parts. Their markings may be for dose levels etc.,

Table 1: Needle free injection technology devices available in market

Device name	Energy source	Maximum volume (in ml)	Comments
Biojector 2000	Gas propelled (CO_2)	Up to 1	Able to deliver intra-muscular, subcutaneous and intra-dermal injection
Vitajet 3	Spring powered	0.5	For subcutaneous administration only
Tev-Tropin®	Spring powered	Variable (as directed by physician)	For subcutaneous administration only
Sumavel®DosePro™	Gas propelled (compressed nitrogen gas)	0.5	For subcutaneous administration only, prefilled single unit
Bioject®ZetaJet™	Spring powered	0.05-0.5	Highly efficient for mass immunization, self-medication, can deliver intra-muscular, subcutaneous or intra-dermal
PharmaJet Stratis®	Spring powered	0.5	Penetrate skin in about one tenth of second. No external power required
Jupiter Jet™	Gas propelled (CO_2) (either by gas cartridge or an external CO_2 tank)	0.03-0.2 ml, prefilled variants of 3, 5, 10 available	Deliver intra-muscular, subcutaneous or intra-dermal. Efficient in delivering extremely low doses
ChemLock™	Gas generated	Variable (as directed by physician)	First needle free closed system transfer device to receive FDA 510 (K) clearance

Source:bioject.com; pharmajet.com/product/. FDA: Food and drug administrations

during this stage, workers are employed to insert various separate compartments so as to form a complete device. Any attachment if needed such as buttons etc., are fixed at this stage.

Packaging

After the device is completely assembled, and attachments fixed, the next step includes packaging. The device is first wrapped in sterile films and then put into cardboard or plastic boxes. All the required manuals or insects are put into those boxes. The boxes are then stacked on pallets and shipped.

Quality control

The entire process is thoroughly supervised for any visual defects or structural deformity by line inspectors throughout the manufacturing process. The equipment are also checked for accuracy and precession along with the dimensions and thickness of the device. Inspectors also go through the labeling and calibration.[37]

These devices can have various safety issues, so they are manufactured under strict control of Food and Drug Administrations (FDA). FDA conducts an inspection of the manufacturing units at regular intervals.

CONCLUSION

The evolution of drug delivery system aiming to penetrate the skin has been dependent on the simple engineering concepts. One of the major drawbacks of such devices includes the associated pain. The use of the hypodermal needle in the traditional two-piece syringes has added to the woes. Needle phobia and accidental needle-stick injuries have not only worsen patient compliance, but even unnecessary problems have surfaced.

Needle free technology are capable of delivering a wide spectrum of medicinal formulations into the body with the same bioequivalence as that which could have been achieved by drug administration by a two-piece syringe system, without inflating unnecessary pain to the patients. These devices are very easy to be used, don't require any expert supervision or handling, easy to store, and dispose.

These devices are suitable for delivery of drugs to some of the most sensitive parts of the body like cornea. They are efficient to administer intra-muscular, subcutaneous and intra-dermal injections. These systems require a power source which may be obtained either physically or by the application of some force. The drug is forced and is ejected through a superfine nozzle at speeds near about to that of sound.

A great deal of investment has been made in developing this technology with several devices already being available in the market post FDA clearance [Table 1].

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Nil.

Conflicts of interest

There are no conflicts of interest.

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