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REVIEW ARTICLE

An Introduction to Needle-Free Injection Technology

A. S. Ligde[1], R. S. Wanare[2]*

[1]Sudhakarrao Naik Instutute of Pharmacy, Pusad 445-206, Maharashtra, India

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ABSTRACT

Needle free injection system are to introduce the various medicines into patients without piercing the skin with a conventional needle. Needle-free technology offers the many benefit of reducing patient concern about the use of needle. Needle free injection is the very effective injections a wide range of drugs and bioequivalent to syringe and needle. It results in less pain and is strongly preferred by patients. Additional benefits include very fast injection compared with conventional needles and no needle disposal issues. These systems are easy to use and does not require any skilled person. Not only benefit of the pharmaceutical industry to the increasing product sales, it has the added potential to increase compliance with dosage regimens and improved outcomes. Today, they are a steadily developing technology that promises to make the administration of medicine more efficient and less painful.

KEYWORDS

Needle free injection, Needle free devices, Needle free technology, Drug administration and drug delivery system

INTRODUCTION

Needle-free injection system or Needle-less injection technology or Needle-free injection technology was first introduced by Marshall Lockhart in 1936. Needle-free technology offers novel ways to introduce various medicines into patients without piercing the skin with a conventional needle.

*Address for Correspondence:
A. S. Ligde,
Sudhakarrao Naik Instutute of Pharmacy,
Pusad 445-206,
Maharashtra,
India

Needle-less system is based on the principle of electrophoresis to deliver the medicament through the skin. These devices are easy to use; it does not require any skilled person. This review is inclined on the needle-less injection system which gives detail information about the system. Today, they are a steadily developing technology that promises to make the administration of medicine more efficient and less painful. 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 company adopts needle-free technology and demonstrates its versatility, acceptance and value in major therapeutic area.

History

Though Syringes are pretty basic, standard items having fairly simple and straightforward design, it has a rich and varied history dating back thousands of years. It had quite the journey to get to where it is today. The word “syringe” is derived from the Greek word syrinx, meaning “tube”.

In Roman times during the 1st century AD, the first syringes were used. In a journal called De Medicina, they are mentioned as being used to treat medical complications. Then, an Egyptian surgeon, in the 9th century AD, created a syringe by using a hollow glass tube and suction.

In 1650, a syringe was invented by Blaise Pascal. In 1844, the hollow needle was invented by an Irish physician named Francis Rynd. He used it to make the first recorded subcutaneous injections. Then shortly thereafter in 1853, a medical hypodermic syringe with a needle fine enough to pierce the skin was developed by Charles Pravaz and Alexander Wood. In 1899, a patent was granted to Letitia Mumford Geer of New York for a syringe design that permitted the user to operate it one-handed. In 1946, in England, the first all-glass syringe with an interchangeable barrel and plunger was produced by Chance Brothers. Shortly thereafter, in 1949, the world's first plastic, disposable hypodermic syringe made from polyethylene was created by an Australian inventor Charles Rothauser, at his Adelaide factory. Then in 1956, patents were granted to a New Zealand pharmacist and inventor Colin Murdoch for a disposable plastic syringe. It was closely followed by the Plastipak – a plastic disposable syringe introduced by Becton Dickinson in 1961. In 1974 a US patent for a "Disposable Syringe" was received by an African American inventor Phil Brooks [8].

In 1936, Needle-free systems were first described by Marshall Lockhart in his patent jet injection. Then in the early 1940's, high pressure "guns" were developed by Higson and others using a fine jet of liquid to pierce the skin and deposit the drug in underlying tissue [2, 9].

Objective [3]

The main objective of needleless injection is:

1. To avoid the risks and complications involved in conventional needles
2. To be used in diseases like diabetes, skin disease, allergy, asthma, etc. as a drug delivery system.
3. To avoid the drawbacks of conventional injection such as anxiety, fear.

Advantages of Needle-Free Injection [3, 4, 10]

1. Prevent skin puncture hazards and its destruction; also, does not cause problem of bleeding or bruising and minimal skin response.
2. Imparts fast drug delivery and better reproducibility as compared to invasive drug delivery systems and hence enhance bioavailability when compared with invasive drug delivery systems.
3. Better drug stability during storage as it is delivered in dry powder form especially for water sensitive drugs.
4. Avoids problems of reconstitution and any effect of shearing.
5. Elimination of needle phobia.
6. Self-administration is feasible with needle free injections.
7. Improves immune response to vaccines. Immunization of influenza, tetanus, typhoid, diphtheria, pertussis, and hepatitis A vaccines can be delivered by needle free injections.
8. Bioequivalence has been demonstrated enabling the development of generic drug proteins.

A good dose response with increased drug doses.

Disadvantages of Needle-Free Injection [3, 4, 10]

1. Method is complex and expensive.
2. All systems are not fitted into one size.
3. Need for personnel training and maintenance.
4. It is not applicable for Intravenous route.

Classification of Needle-Free Injection Systems [5]

Needle-free injection technology systems are classified on various bases as follows:

1. On the basis of working

a) Spring systems.

b) Laser powered.
c) Energy propelled systems.
d) Lorentz force.
e) Gas propelled/air forced.
f) Shock waves.

2. On the basis of type of load [13]

a) Powder injections
b) Liquid injections
c) Depot or Projectile Injection.

3. On the basis of site of delivery

a) Intra dermal injectors.
b) Intramuscular injectors.
c) Subcutaneous injectors.

4. On the basis of the mechanism of drug delivery [2, 14, 15, 16]

a) Nano-patches.
b) Sandpaper assisted delivery.
c) Ionto-phoresis enabled.
d) Micro-needles.

Design And Components [2-4, 10, 17-22]

Needle-free injection devises consists of three main components as follows:

Component 1 - Injection device:

It has a drug chamber which is designed such that self-administration is possible. The device is made up of plastic. Sterility is maintained throughout the device. It has a sterilized needle-free syringe which is also made of plastic.

Component 2 - Nozzle:

The nozzle serves as passage for the drug and serves as the skin contacting surface. The nozzle has an orifice through which the drug enters skin when injected. The orifice has diameter of 100 μm. The nozzle fires drug particles at the speed of 100 m/s with a depth of 2 mm. The most common orifice size is 0.127mm, comparable to a 25-guage needle. Therefore, this injection is painless; the patient feels tap of gas on the skin which is like flicking your finger against your skin.

Component 3 - Pressure source:

It is important for delivering a drug forcefully into the systemic circulation via the skin. The pressure source can be a mechanical method which stores energy in a spring and is released by pushing a plunger to provide the necessary pressure. It can also be a pressure storage method that utilizes compressed gas in gas cartridge.

The most popular gases used in devices are carbon dioxide or nitrogen. Pressurized metal air cartridges are often provided for access in portable units.

The precision of drug delivery and stress imposed on the product is influence by device design. The device must assure the generation of sufficient high pressure to cause skin puncture as well as not harming the drug molecule. Fragile drug molecules are susceptible to damage due to high pressure like monoclonal antibodies. Hence, devices may vary in design depending upon the drug for which they are used.

Figure: Components of Needle-free injection devices

Principle

NFIT is based on the use of the energy which is stronger enough to propel a premeasured dose of medication, loaded in specific unique "cassettes" which can be rigged with the system [5, 7, 11]. These forces can be generated from any of the ways ranging from high-pressure fluids including gases, electro-magnetic forces, shock waves or any form of energy that is capable enough to impart a motion to the medicament [5, 7, 12].

Mechanism [4, 10]

It is based on the mechanism of generation of force by using compressed gas (such as carbon dioxide or nitrogen) for propelling the drug through an orifice at a very high speed. An ultra-fine stream of fluid penetrates through the skin layers while the administration of drug through the device. This helps in the delivery of the drug very quickly into the systemic circulation. The total time required for drug delivery is less than 1/3 of a second and occurs in three stages:

1. Peak pressure phase - optimal pressure requires penetrating the skin which last about < 0.025 sec.
2. Dispersion phase - which last about 0.2 sec.
3. The drop-off phase - which last about < 0.05 sec.

Raw Material

These devices must be fabricated from pharmacologically inert materials, as it directly comes in contact with the body. The materials for Outer shell which are synthetically produced and are easier to mold and light in weight, like as Polycarbonates including thermoplastics, are the most suitable raw material for making the outer compartment or the body of the device. Since the materials are heat sterilized, they must be capable to endure high temperatures. Colorants are added in most cases. Gas powered systems use helium or CO_2 as a source of propulsion. Some new designs also use butane for such operations. The body of the device must be made of material which does not react with the gas or the other adjutants including the colorants. In order to yield a final product, the raw materials are utilized through a step by step procedure as follows [7, 18].

The Manufacturing Process [3, 23]

For producing each needle-free injection system, numerous methods are available. The manufacturing of Needle-Free Injection System is given in the following steps:

1. Molding the pieces,
2. Assembling and labeling the pieces, and
3. Packaging

1. Molding the pieces

It involves production of the component plastic pieces from plastic pellets. This is done by a process called injection molding.

2. Assembling and labeling the pieces

Pieces are inserted into the main housing and buttons are attached. Machines apply markings that show dose levels and force measurements.

3. Packaging

Injection devices are first wrapped in sterile films and then put into cardboard or plastic boxes. These boxes are then stacked on pallets.

Quality Control:

Quality control checks are performed regularly during the manufacturing process. Line inspectors ensure that the plastic components match with the previously determined specifications. Dimensions such as size and thickness are checked by test methods such as visual inspections and measuring equipment dimensions. Laser micrometers, calipers and microscopes can be used to test the systems. Inspectors also confirm that the labeling and printing on the device is proper and complete and all parts are properly assembled in the device. Production of needle free devices is totally controlled by FDA due to the safety issues. Each manufacturer is expected to follow various production standards and specifications. Announced and unannounced inspections are regularly conducted to ensure that the companies are following good manufacturing practices (GMP). The manufacturers must also maintain a detailed record of production and design operations. [3, 17]

Applications [6]

(1) Hemophilia— It is a genetic disorder in which normal coagulation process is hindered resulting in bleeding problems. Recombinant antihemophilic factor is used to treat this disorder. ReFacto Antihemophilic Factor (Recombinant) R2 Kit, the first needle-less reconstitution device with a prefilled diluent syringe for hemophilia.

(2) Hyperhidrosis— It is a skin disorder in which excessive sweating takes place resulting in wet palm and other body parts. The chief problem encountered with the treatment of

hands and feet by Botox injections is the intense pain associated with the needle puncture into the densely innervated skin of these regions. The traditional technique is to perform a nerve block on the wrist or ankle before the injections to avoid the pain. The potential complications of a nerve block are nerve or vessel damage and temporary loss of hand dexterity. For this reason, many physicians who contentedly treat auxiliary hyperhidrosis refuse to treat palmar and plantar hyperhidrosis with Botox.

(3) Immunization through vaccination by delivering drug to the outer most layer of the skin where an individual response first takes place. This reduces the required dosage for vaccination consisting to this anatomical area saves money and material in long run.

(4) Heparin (an anticoagulant), erythropoietin, lidocaine hydrochloride (a local anesthetic) and various vaccines can be administered through needleless injection**.**

Limitations [6]

(1) Splashing- The critical velocity for penetration depends on the stiffness and thickness of as well as site of injection. Once the skin is punctured continued jet pressure increases the depth of the injection. If the delivered volume exceeds the size of puncture, some of the medicine may splash resulting in an incomplete or failed injection. Splashing is a major concern small amounts of blood on the tip of multi used nozzle jet injector were implicated in the transmission of hepatitis B.

(2) Affordability- Excessive prices relative to those of standard syringes is also a disadvantage. Widespread use and agency support will bring down the prices as it occurs with all the new technologies. Also in the long run it will be cheaper because it can be reused many times.

As there is no needle this system lacks the needle protection. The jet is exposed to atmosphere near the site of injection thus there are rare but possible chances of contamination during application.

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