INTRODUCTION

Prefilled syringes for packaging and administrations of parenteral product have been increased significantly because of various advantages. Prefilled syringes are those syringes which are filled at the time of manufacturing and packaging instead of drug administration. Most of the time products come in glass ampoule or vial and when administration is required; it is withdrawn into syringe and then injected in patient. This may lead to lack of convenience, affordability, accuracy, sterility, safety etc. To avoid this, prefilled syringes are now a day used. Prefilled syringes are manufactured by over 20 pharmaceutical companies mainly for delivery of nearly 50 injectable drugs and vaccines with estimated annual sales of 6-7 billion by 2021. This sale is probable to accelerate in future because of advantages of prefilled syringe for manufacturer and patient. Prefilled syringes provide advantage of contamination free packaging and delivery of single dosed drug which helps pharmaceutical companies to check cost and microbial growth.

History of prefilled Syringe

William Harvey in early 1600 put forth the theory of administration of drugs through on the parenteral route based on his observations of snake bite and knowledge of circulatory system. Later on knowledge on parenteral medicines advanced slowly on the account of life of several animals and humans. Later on as Word war II started, need was generated for the development of portable packaging of medications which can easily carried on the battle ground for the treatment of pain. Initially Syrette, Ampin and Tubex systems were developed. Syrette has a disposable injection unit having a collapsible tube which is attached to hypodermic needle and a single dose morphine for treatment of strong pain. Ampin consists of glass ampoule with attached needle. Tubex system developed by Wyeth can be said as pioneer of prefilled syringe. Tubex consists of needle with glass cartridge attached to stainless steel holder with metal plunger which is used to apply pressure for injecting solution. In 1867 British pharmacopoeia introduced first official injection of Morphine. Later on in 1980s prefilled syringe of heparin by Sanofi and Rhone Poulenc was introduced, which made this method of drug delivery popular within short period of time. From there on prefilled syringes are used for administration of different classes of therapeutics like vaccines, anticoagulants and others. Recent development in prefilled syringe is two chambered syringe for lyophilized drugs.

**Review Article**

**REVIEW ON PREFILLED SYRINGE AS A MODERN TECHNIQUE FOR PACKAGING AND DELIVERY OF PARENTERAL**

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**ABSTRACT**

Administration of drug via parenteral route is advantageous for fast onset of action and 100 % bioavailability. There are number of requirement for parenteral dosage form. Prefilled syringe fulfill requirements of parenteral dosage form such as convenient means for delivery of parenteral medication, maintenance of sterility of product, dosage accuracy, increased patient compliance, improved cost efficiency, reduced product contamination and safety. Prefilled syringe contain single dose of parenteral drug with a needle fixed. This review aims to provide insight of history, manufacturing of prefilled syringe, advantages and disadvantages, directions for use, challenges and regulatory requirements related to prefilled syringes.

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Advantages of Prefilled Syringe

Prefilled syringes provide various advantages for the manufacturer, physician and patient over conventional method of parenteral drug delivery. Some of these advantages can be listed as accuracy, sterility, convenience, affordability and safety.\(^{(7,8,9,10)}\)

Accuracy

During conventional administration of drug through parenteral route, physician has to take dose from the vial or ampoule into the syringe through needle. This can lead to inaccuracy in dosing by overfilling or underfilling. Also some patients require self medication without proper medical training. Prefilled syringe contains the exact dose. Hence accuracy in dosing is one of the main advantage of prefilled syringe.

Sterility

Sterility is the foremost important requirement for parenteral product. There are chances of contamination of parenteral product while breaking ampoule or while withdrawing product from vial. Prefilled syringe avoid this risk as packed sterile product directly goes into patients circulatory system.

Convenience

Prefilled syringes provide convenience to medical practitioner as it reduces additional step of breaking of ampoule and sample withdrawal. It is very useful in case of emergency patient as breaking of ampoule and filling of regular syringe can be time consuming.

Affordability

Regular syringes have cylindrical glass barrels and glass rod tightly fitted in it. These conventional syringes are more expensive than plastic based prefilled syringes. Also prefilled syringes provide advantage of less cracking and breaking as compared to glass syringe.

Safety

Because of accuracy in dosing, prefilled syringes are safer for use. Some prefilled syringes are fitted with self aspirating syringes which deliver drug to the perfect depth of skin making it safer.

Advantages to manufacturers

Regular filling of vials and ampoules require overfill. As per USP, for 0.5 ml vial, 20 to 25% overfill is required. But prefilled syringes require very less overfill which is less than 2% or not required at all. Hence company can reduce costs by reducing overfill.

Medical advantages

Medical practitioners have lots of benefits like they get premeasured and accurate dosing, reduction in dosing error and convenient in emergency condition. According to recent studies nine out of ten practitioners preferred prefilled syringes.

Disadvantages

In case of vials and ampoules drug comes in contact with glass and rubber only which makes it easy to establish extractables and leachables profile and there is no adverse effect of primary packaging material on drug molecule. But in case of prefilled syringe multiple material come in contact with parenteral which makes it difficult to establish extractables and leachables profile. Pharmaceutical companies must ensure safety of patient by confirming extractables and leachables profile of material and components and ensure that primary packaging has no adverse effect on drug molecules.\(^{(11,12)}\)

Material used for manufacturing of prefilled syringe

Glass

Glass is main component used in production of prefilled syringe. Main advantage of glass is that it is non-reactive and stable. Type I borosilicate glass used in manufacturing of prefilled syringe. Borosilicate glass has several advantages like it is easy to sterile, has good visibility, low reactivity with product and nature and content of this glass is well known.\(^{(13,14)}\)

Along with advantages glass has several disadvantages like it is easily breakable and require care while handling. Also glass components can leak into product. Some products like proteins and peptides get adsorbed on glass surface due to which potency of proteins and peptides may decrease.

Plastic

Plastic can be used instead of glass in manufacturing of prefilled syringe as plastic provides several advantages over glass. Cyclo olefin polymer and cyclo olefin copolymer based plastic is used for manufacturing of prefilled syringe. This type of plastic is unbreakable with elevated heat resistance, less permeable to water, less leachables, lightweight, shatter resistant, can be used for wide range of pH from 2 to 12, brilliant low temperature characteristics, solvent resistance, excellent drain ability and autoclavable.\(^{(15)}\)

Material used in production of prefilled syringe must be tested for biocompatibility in order to avoid adverse effects in patients. All material should be studied for release of impurities, extractables and degradation product. Biocompatibility tests include acute and chronic toxicity studies, carcinogenicity, reproductive effects and irritation of skin, eyes and mucosal membrane.\(^{(16)}\)

Components of prefilled syringe

Prefilled syringe has following components

<table>
<thead>
<tr>
<th>Component</th>
<th>Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrel</td>
<td>Plastic</td>
</tr>
<tr>
<td>Piston</td>
<td>Plastic</td>
</tr>
<tr>
<td>Tip cap</td>
<td>Elastomer</td>
</tr>
<tr>
<td>Plunger rod</td>
<td>Plastic</td>
</tr>
<tr>
<td>Needle</td>
<td>Stainless steel</td>
</tr>
<tr>
<td>Needle cover</td>
<td>Plastic</td>
</tr>
<tr>
<td>Lock Adapter</td>
<td>Plastic</td>
</tr>
<tr>
<td>Tamper evident</td>
<td>Plastic</td>
</tr>
<tr>
<td>Finger grip extender</td>
<td>Plastic</td>
</tr>
</tbody>
</table>

A barrel having an opening at opposite ends and an inward projection of annular wall at front end.

A plunger fluid-tightly fitted in the end of the barrel so that it can slide inside the wall of barrel.

A needle-connecting member, joined to the annular wall to fluid-tightly close the opening of the annular wall.
A elastic plastic film tube within the barrel hermetically attached to the needle-connecting member and the plunger at each end. Needle-connecting member having at its back end a skirt segment of an outer diameter equal to an inner diameter of barrel skirt segment being fitted in the far end of the barrel, film tube being attached to the outer wall of the rear side of the skirt segment.(17)

Manufacturing of prefilled syringe

Manufacturing of prefilled syringe can be divided into parts such as syringe components manufacturing, filling and closing of syringe and final sterilization of syringe.

Manufacturing of syringe components

Manufacturing of glass syringe is carried out from glass tubing. Glass mixture is heated at 1500°C. Molten glass is pulled out continuously along with hollow spindle. Air is blown inside the rotating hollow spindle to form hollow glass tubes under strict processing conditions in order to avoid any failure of glass. (18) During forming of glass tubing it may be cut in desired size or after formation of whole glass tubing, it is heated and then cut into desired size of syringe. (19) All the process is carried out under particulate and pyrogen free condition in class 100 environment. The plunger cover and tip seal are molded from elastomeric material by any suitable molding method like compression molding. After molding inner wall of syringe, plunger cover and seal tip are lubricated with silicone oil and baked to avoid chattering. Chattering is process when plunger stop in middle of barrel of syringe when pushing due to lack of silicone. Plastic syringes are also formed from polymeric granule. Polymeric granule is melted and injection molded. The formed syringes are then removed from mold and silicone is applied on inner surface of syringe. (19)

Filling and assembling the syringe

Four principal methods are used for filling of syringes. Among these methods high-speed equipment filling, Online high-speed filling followed by Offline vacuum stoppering & Online vacuum filling followed by online vacuum stoppering method can create bubble in the syringe. This bubble may cause instability in protein and peptides and oxygen sensitive products and loss of product. The fourth and latest method overcomes this disadvantage. The latest method of vacuum filling and vacuum stoppering of syringes can produce bubble free syringes. This method provides advantages like enhanced dosing frequency, improved product sterility and stability and more safety. (20, 21) Also stability of oxygen sensitive product is increased. One more advantage of this method is that it is compatible with coated stoppers. After filling of syringe by using vacuum stopper is placed instead of pushing with rod which may cause damage to stopper. (22)

Sterilization of prefilled syringe

Sterilization of prefilled syringe is majorly done by using methods like steam sterilization like autoclave and ionization radiation. However steam sterilization may cause packaging degradation. Also steam sterilization can be time consuming and cumbersome. (22) Following points are considered for sterilization like drug stability, packaging stability, temperature sensitivity and regulatory compliances from various regulatory authorities. (23) Along with autoclave, gamma radiation can also be used for terminal sterilization of prefilled syringes. This method has unique advantage that sterilization of prefilled syringe can be carried out when it in package which reduces possible contamination. The ionizing dose can be easily recorded. (24, 25) Radiation also has disadvantages in case of plastic syringes like increased gas permeability and yellowing of container. (26)
collar torque resistance testing, Luer lock rigid tip cap unscrewing torque testing. Retention volume and deliverable volume are also tested for prefilled syringes. All of these tests give only information about the quality and performance of the container.

**Functionality testing**

Functionality testing (e.g., gliding force, mechanical resistance, opening force, etc.) involves examination of the force required to initiate movement of the plunger and the pressure required to maintain the movement; the test is usually destructive. As a result, it is only performed with a reduced inspection plan and limited sample population.

**Container closure integrity testing (CCI)**

Container closure integrity (CCI) testing is one of key tests to be performed to ensure the combination product passes all the requirements. CCI testing evaluates the adequacy of container closure systems to maintain a sterile barrier against potential contaminants. Deterministic methods are non-destructive and can be used to test every unit from the batch. These methods include vacuum/pressure decay testing, high-voltage leak detection, and analysis of the head space within the syringe.

**Automated inspection for prefilled syringes**

Automatic inspection equipment is used to check the product for particles, for aesthetic defects, and for proper placement of the plunger.

**Types of prefilled syringe**

There are two main types of prefilled syringes based on material from which it is made, glass based system and plastic based system.

**Glass based system**

Conventionally, barrel of these prefilled syringes is made up from glass tubing. Main disadvantage of these syringes is that it is easily breakable and hence requires more caution while handling. Also glass may leak alkali in product causing change in pH. Glass syringes are further classified as oil siliconised syringes and baked on silicone syringes.

**Oil siliconised syringe**

In this type of syringe there is direct contact of rubber plunger to the inner surface of glass. When such syringe ages there are chances of higher breakout force during movement of plunger.\(^{(21)}\)

**Baked on silicone syringe**

In this type inner surface of syringe is coated with layer of silicone. Silicone is applied on the glass by spraying or by coating glass with silicone emulsion. The syringes are then baked at about 300\(^\circ\)C after application of silicone emulsion. This causes layer of silicone to chemically bind with glass which is around 300-1000 nm thick.\(^{(18)}\) This layer of silicone makes plunger easy to glide on glass surface. Breakout forces are low during ageing of this type of syringe.

**Plastic syringe**

Syringes made from plastic have several advantages over glass. It is easy to handle and robust in nature. Also gas permeability of plastic is low. These syringes are available in the size range of 1 to 50 ml. There are two types of polymers that are often used for plastic syringes and those are cyclic polyolefin and cyclic olefin copolymer (COC). Plunger rods are white in color and are made up of polypropylene.\(^{(18)}\)

**Prefilled syringes in market**\(^{(27)}\)

**Dual Chambered syringes**

Vetter Pharma Fertigung formulated Vetter Lyo-Ject dual chambered syringe. This system has two chambers separated by stopper in the middle. One chamber contains lyophilized drug and other chamber contains solvent. Drug is lyophilized in the syringe itself and chamber is sealed while the syringe is still in the lyophilizer. Then solvent is added in another chamber and again sealed with stopper. On the distal portion is a screw-taper plunger rod that goes through the finger rest. As plunger is pushed, it puts pressure on the solvent. The solvent then moves the center stopper into a bypass in the side of the glass.

**Prefilled Diluent Syringe**

West currently offers Clip’n’Ject reconstitution system containing prefilled diluent syringe packaged along with the drug vial, containing the lyophilized or dry powder drug.

**UniJect Pre-filled Syringe**

UniJect is a disposable injection device made up of plastic. It pre-filled with a single dose of medication. When needle cap is pushed towards the body, it gets activated and opens the fluid path between the needle and the blister. Needle is then inserted into patient by opening the cap and the dose is delivered by squeezing the blister until it collapses.
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BD Readyfill™

BD Readyfill™ is an innovative formulation. It has some unique features like rigid needle shield which makes it safer, needle is isolated from product so that drugs sensitive to needle material is not affected, has baked silicone surface, oversized finger grip make it more easy to handle. (28)

Steps for use of prefilled syringe

Step 1: Verification of label is carried out to avoid further serious issues.
Step 2: Syringe cap and needle cap is removed carefully to avoid contamination.
Step 3: If needle is dual chamber type, then carefully push the plunger to mix diluents and lyophilized product. Shake well for uniform distribution.
Step 4: Insert the needle carefully to avoid any to avoid any type of injury. Auto injector might be useful in this situation in self medication.
Step 5: Once injection is completed, syringe is disposed carefully. (10)

Regulatory aspects

Regulatory accepts of prefilled syringe can be fairly complex because of issues of sterility and stability. Going from regular injectable to the prefilled syringe, companies must establish and evaluate changes which can occur in manufacturing, packaging and shipping process. The US Food and Drug Administration requires that any change in the manufacture of a drug product, whether major or minor, be put into place only after the license holder assesses the effect of the change on the identity, strength, quality, purity, and potency of the molecule, because these factors will influence the safety and effectiveness of the pharmaceutical. (29) FDA gives vary rigid requirements for changes which can affect stability and sterility of parenteral product. Any change in any process of product must be documented and validated. Such changes are change in container–closure system, silicone treatments in the closure systems such as in elastomeric closures or the syringe barrels, and changes in the size or shape of a container that holds a sterile drug product. (30, 31) FDA will require three months of relative accelerated data and long-term data on three batches of drug product. The stability tests will need to focus on appearance, color, clarity, sterility, pyrogens, syringe functionality, container– closure integrity, impurities, and particulates. The company also will need to commit to placing the first three production batches and annual batches on long-term stability tests. (32)

Challenges

The world of prefilled syringe may seem fascinating but there are some major challenge faced in prefilled syringes like interaction of product with different syringe components. Challenges during manufacturing prefilled syringes include drug stability, shelf life, leachables, extractables, and rising costs. The silicone used for lubrication purpose may react with biological product causing degradation of product. Tungsten is used for fluid path from syringe barrel to needle. This tungsten can react with protein product to cause aggregation. (33) The staked syringes are held in place with adhesive. This adhesive may be extracted into product. (34) Another challenge is faced during terminal sterilization and transportation. The changes in pressure during sterilization may cause plunger to move from its position and compromise sterility of product. (35)

Future of prefilled syringe

There is lot of potential for prefilled syringes in future if proper profile of relationship between interaction between syringe components and product is established. Prefilled syringes are gaining approval in market as a drug delivery system for injectable. Putting new drugs inside prefilled syringe will defiantly increase uptake by end users. There are lots of advantages of prefilled syringes over conventional system but manufacturing cost is increasing because of adaptation of safety measures and stringent guidelines by regulatory authorities. In future more range of container closure system will give more option to manufacturer. Also growing preference to self medication will be boost prefilled syringe market. Another dimension of prefilled syringe can be explored with autoinjectors and peninjectors. In short if properly explored by taking need of market into consideration of market, prefilled syringe sell can see a huge growth in future.

CONCLUSION

From this review it can be concluded that prefilled syringes have great potential as drug delivery system. Prefilled syringe has number of advantages like accuracy, sterility, convenience, affordability and safety. Different type of prefilled syringes exists in market. Compliance with regulatory authorities and proper safety profile of product with syringe components will prove as a key in growth of prefilled syringe market.

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