

Prefilled Syringes: A Comprehensive Overview



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Introduction

Over the last two years, the COVID-19 pandemic has urged healthcare industries to look into major advancements in the field of vaccines and parenteral drug administration routes, thus spurring up new innovations in the pre-filled syringe and fill/finish product operations. Traditionally, prefilled or prefillable syringes were used for vaccine and anticoagulant administrations, however, they have now garnered importance in anti-thrombotic and biotechnology drugs too. (1) A steep rise is expected in the prefilled syringes sector over the upcoming few years, such that the compound annual growth rates (CAGR) range around 10-11%. It has also been estimated by a report that by 2028, the market value could scale up to \$11.4 billion. (2)

The History of Prefilled Syringes

The thought of intravenous drug delivery arose from snakebites and the discovery of the circulatory system by William Harvey. Earlier, crude instrumentation techniques were used to inject humans and animals (dogs specifically) which might have been harmful due to the lack of knowledge of particulate formation and pathogenic infections. Thus, a deeper study into parenteral administration began. The next surge in development occurred during World War II when efficient parenteral packaging was demanded to be sent into the battlegrounds. The Syrette was made of a needle and flexible metal tub that punctured the skin to inject the medication into the body. The Ampin followed a similar mechanism, however, it had a glass ampule attached to a needle for administration. Further, the Tubex system consisted of a glass cartridge and a needle which was introduced into a plunger to eject the medication. It was only by the 1980s that prefilled syringes gained popularity due to the launch of prefilled heparin syringes by Sanofi and Rhone Poulenc-Rhorer, which was an extremely successful approach. Prefilled syringes were then known to replace liquid and lyophilised vials due to their usefulness. (3)



Figure 1: Syrette (4)

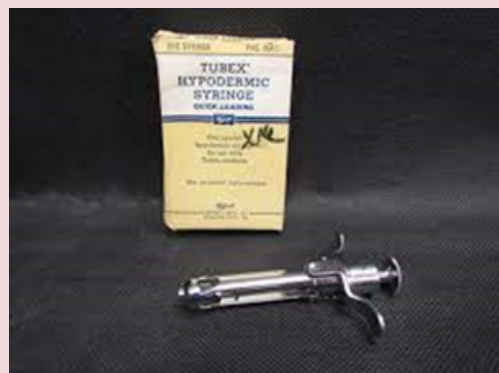


Figure 2: Tubex System (5)

The Rise of Prefilled Syringes

USD 6.6 billion was the market size of prefilled syringes globally in 2021. A projection to 7.51 billion in 2022 and further is expected within the upcoming decade. (6) The trends in the market share were seen as follows:



Figure 4: Trends in Market Share
Author compiled; Adapted from (6) (7) (8) (9)

Europe took over the market by generating a revenue of USD 2.66 billion, followed by North America. Due to the prevalence of chronic diseases, Asia Pacific was likely to witness steep growth while Latin America and Middle-East & Africa were to have a slow growth due to decreased exposure to innovations and slow market insight. (6)

The Growing Demand for Prefilled Syringes

The demand for prefilled syringes accelerated due to their convenient usage, sterility and accuracy. These can boost the drug market share due to their low drug waste production and increased product lifespan. The simplicity of administration along with dose precision makes these syringes user-friendly and reduces their dependence on hospitals. Prefilled syringes have proven to be advantageous to healthcare professionals by reducing the hazards of pathogenic contamination and dose inaccuracy, thus administering precise and pre-measured doses quickly to patients. The overfill required in prefilled syringes is substantially lower compared to the USP recommended overfill needed for parenteral delivery, thus producing more doses with the same resources. Other benefits of using prefilled syringes include the removal of the use of preservatives (for single-dose syringes) and better moderation in the dispensing of narcotic substances. (1)

What are Prefilled Syringes made of?

The components of prefilled syringes include a plunger rod, plunger, barrel, pre-staked needle and needle cover. The barrel is usually made of glass or plastic, where the former dominates the manufacturing market. Glass, despite being stable on storage and generally inert, is brittle. The manufacture of barrels is done by hydrolytic class 1 borosilicate glass. These syringes are siliconized in the parts where there exists direct contact between the rubber and glass surfaces else it could lead to a breakout which could contaminate the drug. Thus, the silicone layer keeps the chances of breakout at bay. Borosilicate glass has a transformation temperature of 565° C, thus subjecting it to a wide temperature range during manufacture which can lead to leaching. Sodium ions leach out into the product on storage, thus increasing the hydroxyl ion concentration. Thus, the pH of the formulation is altered. To cope with these drawbacks, plastic or polymer was introduced as an alternative for manufacturing barrels. Plastic barrels have a lightweight and reduced breakability. Additionally, the plastic syringe cartridges available are less expensive in comparison to the bulky glass rods and barrels. They can be classified based as- cyclo olefin polymer (COP) and cyclo olefin copolymer (COC). COCs are clear amorphous resins that are preferred over COPs due to properties like high transparency, good moisture blocking capacity, low density and resistance to organic media. (1)

Sterilization of Prefilled Syringes

Post manufacture, prefilled syringes are filled under aseptic conditions. These syringes can be bulk or ready-to-use syringes. The bulk syringes are sterilised and silicone is applied to their parts by pharmaceutical companies while the ready-to-use syringes are pre-sterilised and siliconized. The ready-to-use syringes are sealed in tubs and covered with polymeric bags that are progressively removed as the tubs are transferred to more controlled manufacturing areas. The syringes are then filled in rows using the automated syringe filling machine followed by the addition of the stoppers. (3) This traditional method can cause the entry of bubbles into the

syringe. Thus, online vacuum filling and stoppering (called bubble-free filling) are carried out. The sterilization techniques used for these syringes are autoclaving and ionising radiations i.e., gamma radiations exclusively (as they have a high penetrating power that can sterilise packaged syringes too). (1)

Types of Prefilled Syringes

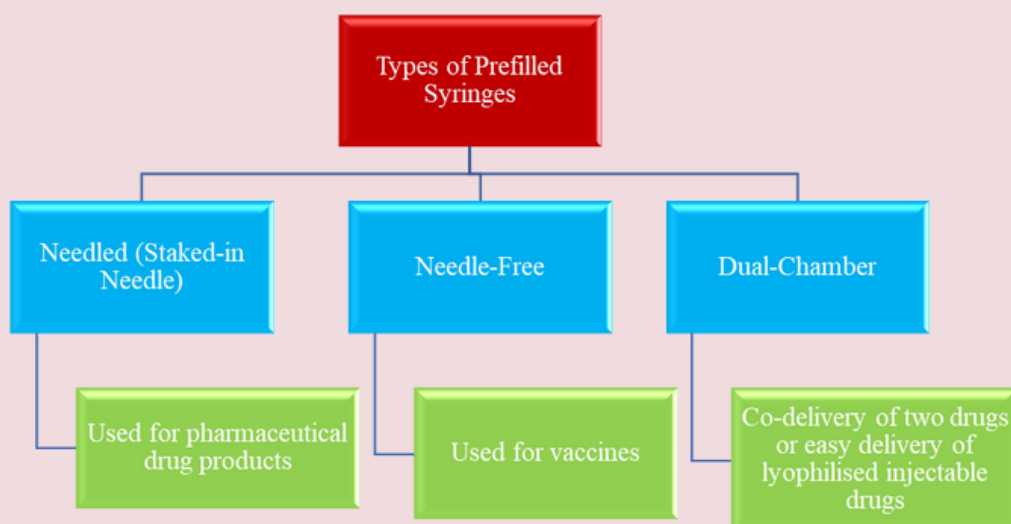


Figure 5: Types of Prefilled Syringes along with Uses (10)

Needle-free prefilled syringes are composed of a Luer Lock attachment and a barrier cap. The syringe nozzle has a circular fitting which ensures that it is well secured in the plastic Luer Lock attachment. To maintain sterility, an elastomeric plug is introduced onto the nozzle. The barrier cap is pressurised which holds the nozzle in place, without permitting it to open up. (10)

The dual-chamber prefilled syringes consist of a partition between the two chambers. (10) The two chambers can either contain the two drugs set for delivery or the first chamber is filled with the lyophilised, freeze-dried drug while the second chamber is filled with its diluent. (11) A lock is placed between the two chambers so that when the plunger is pushed, the contents of the back chamber flow into that of the front chamber, without causing a backflow of the solution, so that they are co-administered well. (10) The efficiency of such co-administered drugs is proven to be greater (e.g.: pralidoxime chloride and atropine combination for treating CNS poisoning). (11) Given below is a list of drugs marketed in dual chamber syringes:

Brand Name	Active Pharmaceutical Ingredient	Disease	Manufacturer	Approval Year
Abilify Maintena	Aripiprazole	Schizophrenia	Otsuka	2020
Lupron Depot	Leuprolide acetate	Hormonal Therapy	Abbott Laboratories	2019
PegIntron	Pegylated interferon alpha 2	Hepatitis C	Schering	2018
Caverject	Alprostadil	Erectile Dysfunction	Pfizer	2017
Genotropin	Recombinant Human Growth Hormone	Growth hormone deficiency	Pfizer	2016

Table 1: List of Marketed Drugs in Dual Chamber Syringes
Author compiled; Adapted from (12)

Manufacturers of Prefilled Syringes

As the prefilled syringes sector is broadening its horizons, the leading manufacturers i.e., Becton Dickinson (BD)-USA, Nipro-Japan, SCHOTT-Germany, Ompi-Italy, Oval Medical Technologies-UK, Weigao Group-China, Gerresheimer-Germany etc. are introducing innovations in their types of equipment and techniques to combat the odds of prefilled syringes, especially post the pandemic era. SCHOTT's syriQ BioPure prefilled syringes claim to be silicone-free, thus eliminating aggregate formation by depending on having a powerful hydrolytic resistance and tight dimensional requirements. (13) Gerresheimer offers a flat shoulder glass syringe which holds accurate doses, eliminating the overfill volume, which can be extremely beneficial in the procurement of expensive drugs. (13) BD is on the road to launching a prefilled glass syringe for mRNA vaccines, stored at ultra-low temperatures, against COVID-19. For the storage of mRNA vaccines, sub-zero temperatures of around -20 to -40 °C are required. Thus, testing of several prefilled glass syringes was done with different barrel coatings and volumes to analyse any of the factors that could witness a change at ultra-low temperatures. However, it was noticed that all product functions and container closure were maintained unaltered, thus promoting BD into its next league of vaccine study. (14) Owen Mumford, in January 2022, was known to launch the UniSafe 1ml safety device for pre-fillable syringes in Asia. The device has a spring-free mechanism with reduced complexity and expense to be used as a combination drug product for treating rheumatoid arthritis. (14)

Applications of Prefilled Syringes

Based on their medical uses, prefilled syringes can be used for the treatment of:

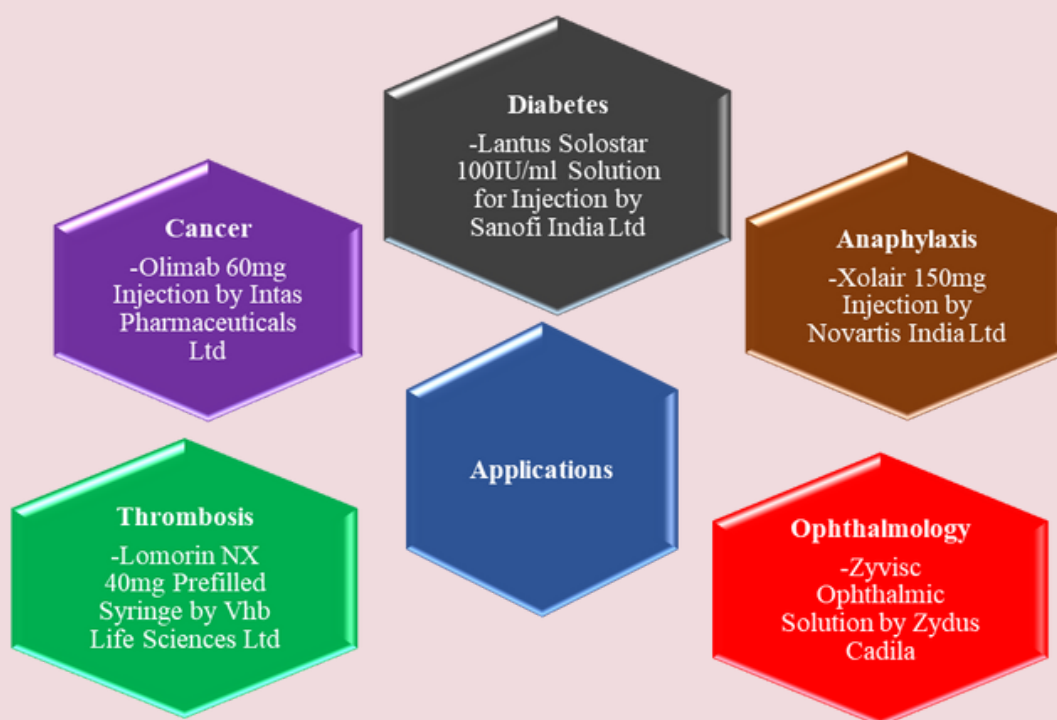


Figure 3: Applications of Prefilled Syringes with selective examples
Author compiled; Adapted from (15)

Pitfalls of Prefilled Syringes

Despite having several positive outcomes, prefilled syringes have some disadvantages too. The cost of these syringes is higher than that of the regular vials used for parenteral delivery. The filling and sealing procedures of prefilled syringes are cumbersome and require engineering and expertise. These expenses may impact their use in comparison to low-cost medicines. The silicone layer used to prevent friction can interact with contents (like proteins) in the formulation and cause coagulation. Further, these aggregates formed can be a source of false rejections during particle testing. (3) Another drawback is the lack of integrated safety devices for prefilled syringes due to which needle-stick injuries can occur. (1) Lastly, the disposal of these syringes can pose a threat as they require a biological hazard container for disposal which may not be available to patients consistently. (3)

Conclusion

The invention of prefilled syringes has been a boon to the pharmaceutical market due to their significant benefits. However, there does exist scope for improvement wherein such promising opportunities can be instrumental in making monumental innovations in the field of healthcare.

References

1. Makwana S, Basu B, Makasana Y, Dharamsi A. Prefilled syringes: An innovation in parenteral packaging. *Int J Pharm Investig* [Internet]. 2011 [cited 2022 Jul 20];1(4):200. Available from: [/pmc/articles/PMC3465144/](https://www.pharmaceutical-technology.com/sponsored/prefilled-syringes-benefits-performance-siliconization/)
2. Prefilled syringes: benefits, performance, and why siliconization matters - Pharmaceutical Technology [Internet]. [cited 2022 Jul 20]. Available from: <https://www.pharmaceutical-technology.com/sponsored/prefilled-syringes-benefits-performance-siliconization/>
3. Sacha G, Rogers JA, Miller RL. Pre-filled syringes: a review of the history, manufacturing and challenges. *Pharm Dev Technol* [Internet]. 2015 Jan 1 [cited 2022 Jul 20];20(1):1–11. Available from: <https://pubmed.ncbi.nlm.nih.gov/25589433/>
4. Sold Price: WWII US ARMY / MARINE CORPS MORPHINE SYRETTE LOT 2 - October 6, 0120 10:00 AM EDT [Internet]. [cited 2022 Jul 25]. Available from: <https://www.invaluable.com/auction-lot/wwii-us-army-marine-corps-morphine-syrette-lot-2-614-c-d174e21a08>
5. "Tubex Syringe" by Normadeane Armstrong Ph.D, A.N.P. [Internet]. [cited 2022 Jul 25]. Available from: https://digitalcommons.molloy.edu/nur_hagan/628/
6. Prefilled Syringes Market Size & Share | Growth Report [2029] [Internet]. [cited 2022 Jul 20]. Available from: <https://www.fortunebusinessinsights.com/industry-reports/prefilled-syringes-market-101946>
7. Prefilled Syringes Market Size & Share | Global Industry Report, 2027 [Internet]. [cited 2022 Jul 20]. Available from: <https://www.polarismarketresearch.com/industry-analysis/prefilled-syringes-market>
8. North America Prefilled Syringes Market Report – Industry Trends and Forecast to 2028 | Data Bridge Market Research [Internet]. [cited 2022 Jul 20]. Available from: <https://www.databridgemarketresearch.com/reports/north-america-prefilled-syringes-market>
9. Asia-Pacific Prefilled Syringes Market Report - Industry Trends and Forecast to 2028 | Data Bridge Market Research [Internet]. [cited 2022 Jul 20]. Available from: <https://www.databridgemarketresearch.com/reports/asia-pacific-prefilled-syringes-market>
10. An Introduction To Prefilled Syringe Selection — Needle-Free And Dual-Chamber Devices [Internet]. [cited 2022 Jul 20]. Available from: <https://www.pharmaceuticalonline.com/doc/an-introduction-to-prefilled-syringe-selection-needle-free-and-dual-chamber-devices-0001>
11. (PDF) Prefilled Dual Chamber Devices (DCDs) – Promising High-quality and Convenient Drug Delivery System [Internet]. [cited 2022 Jul 20]. Available from: https://www.researchgate.net/publication/348996207_Prefilled_Dual_Chamber_Devices_DCDs_-_Promising_High-quality_and_Convenient_Drug_Delivery_System
12. Ingle RG, Fang WJ. Prefilled dual chamber devices (DCDs) – Promising high-quality and convenient drug delivery system. *Int J Pharm*. 2021 Mar 15;597:120314.
13. Pre-filled Syringes Show Strong Growth [Internet]. [cited 2022 Jul 20]. Available from: <https://www.pharmtech.com/view/pre-filled-syringes-show-strong-growth>
14. India's most comprehensive portal on pharmaceutical News, Tenders, Patents, Notifications, Projects, Stocks, Drugs & Medicines [Internet]. [cited 2022 Jul 20]. Available from: <http://pharmabiz.com/>
15. Prefilled Syringes Market - Global Forecast to 2025 | MarketsandMarkets [Internet]. [cited 2022 Jul 20]. Available from: <https://www.marketsandmarkets.com/Market-Reports/prefilled-syringes-market-16618331.amp>