JAPR

Vol. 02, Issue, 04, pp. 6-12, 29 December, 2025

REVIEWARTICLE

Prefilled Syringes: A Comprehensive Review of Design, Manufacturing, Clinical Benefits, and Future Trends

Aisha Siddiqua * [a], **Tariq Khalil** [b], **Humaira Siddiqua** [b]

[a] *Gomal Center of Biochemistry & Biotechnology, Gomal University, Dera Ismail Khan, 29171, Khyber Pakhtunkhwa, Pakistan.*
[b] *Faculty of Pharmacy, Gomal University, Dera Ismail Khan, 29171, Khyber Pakhtunkhwa, Pakistan.*

ARTICLE INFO

Article History:
Received 9 September, 2025
Received in revised form 23 September, 2025
Accepted 28 September, 2025
Published online 29 *December*, 2025

Keywords:
Biologics
Drug device combination products
Injectables
Prefilled syringes
Parenteral drug delivery
Pharmaceutical packaging

ABSTRACT

Prefilled syringes (PFSs) are increasingly used as primary packaging systems for parenteral drug delivery due to their ability to enhance medication safety, dosing accuracy, and operational efficiency. As drug–device combination products, PFSs integrate the pharmaceutical formulation with a delivery system that is ready for administration, minimizing preparation steps at the point of care. Their adoption has been particularly prominent for biologics, vaccines, and emergency medicines. Despite these advantages, prefilled syringes present unique challenges related to material compatibility, extractables and leachables, injectability performance, and regulatory compliance. This review provides a comprehensive overview of prefilled syringe technology, including design and components, manufacturing processes, clinical and operational benefits, formulation considerations, challenges and limitations, regulatory aspects, and future trends.

Corresponding authors: Aisha Siddiqua
Email**:** *draisha@gu.edu.pk*

1. Introduction

Parenteral drug delivery remains a cornerstone of modern medical therapy, particularly for biologics, vaccines, and critical care medications [1]. Conventional vial-and-syringe systems, although widely used, are associated with several limitations, including dosing inaccuracies, contamination risks, medication errors, and increased preparation time. These challenges have driven the development of alternative delivery systems that improve safety and efficiency at the point of care [2].

Prefilled syringes are single-dose delivery systems in which the drug product is filled, assembled, and sealed by the manufacturer under controlled aseptic conditions [3]. By eliminating the need for drug preparation prior to administration, PFSs reduce handling steps and associated risks. Their use has expanded rapidly across hospital, outpatient, and home-care settings, supported by the growing demand for ready-to-administer products and patient self-injection therapies [4].

The increasing complexity of injectable formulations, particularly high-concentration biologics, has further accelerated the adoption of prefilled syringes [1]. At the same time, these developments have introduced new challenges related to drug–container interactions, material selection, injectability, and regulatory oversight. This review aims to provide a structured and comprehensive overview of prefilled syringe technology, highlighting both its benefits and limitations, and discussing emerging trends shaping its future [1-3].

2. Design and Components of Prefilled Syringes

Prefilled syringes are complex drug–device combination products in which each component plays a critical role in ensuring drug stability, sterility, functionality, and user safety. The design of a prefilled syringe must account for compatibility with the drug formulation, manufacturability, regulatory requirements, and ease of use by healthcare professionals or patients (Table 1) [3].

2.1 Syringe Barrel

The syringe barrel serves as the primary container for the drug product and must provide chemical compatibility, mechanical strength, and transparency for visual inspection. Traditionally, Type I borosilicate glass has been the material of choice due to its high chemical resistance and low extractables profile. However, glass barrels are prone to breakage and delamination, particularly when exposed to certain formulations or processing conditions [5].

In recent years, polymer-based materials such as cyclic olefin polymer (COP) and cyclic olefin copolymer (COC) have gained acceptance. These materials offer improved break resistance, reduced risk of delamination, and lower levels of particulate generation. Nevertheless, polymer syringes require careful evaluation of oxygen and moisture permeability, as well as potential extractables [6].

2.2 Elastomeric Plungers and Stoppers

Elastomeric components, including plungers and tip stoppers, are essential for maintaining container closure integrity and enabling accurate dose delivery. These components are typically made from synthetic rubber formulations and may be coated or laminated to minimize interaction with the drug product [7].

To ensure smooth plunger movement, silicone oil is commonly applied as a lubricant. While silicone reduces break-loose and glide forces, it can pose challenges for protein-based drugs by inducing aggregation or particle formation. As a result, low-silicone and silicone-free technologies are increasingly being explored [9].

2.3 Needle Systems

Prefilled syringes may be designed with either staked-in needles or luer-lock adapters that allow attachment of separate needles. Staked-in needles reduce dead space and simplify use, making them suitable for vaccines and emergency medicines. Luer-lock systems provide greater flexibility but introduce additional assembly steps and potential leakage risks [3].

Needle characteristics such as gauge, length, and bevel geometry significantly influence injection force, patient comfort, and tissue penetration. Safety needle designs are often incorporated to reduce the risk of needlestick injuries [3,5].

2.4 Tip Caps and Needle Shields

Tip caps and needle shields protect the sterile pathway of the syringe prior to use and prevent leakage during storage and transport. These components are typically made from elastomeric materials and must maintain a secure seal throughout the product shelf life. Proper design is critical to avoid issues such as cap loosening, leakage, or difficulty during removal [9].

2.5 Lubrication and Surface Treatments

Surface treatments are applied to syringe barrels and plungers to optimize injectability performance. Siliconization remains the most common approach; however, alternative coatings and surface modification techniques are under development to reduce silicone-related risks while maintaining acceptable injection forces [10].

Table 1. Key Components of Prefilled Syringes and Their Functions

Component	Common Materials	Primary Function
Barrel	Glass, COP, COC	Drug containment and visibility
Plunger/Stopper	Elastomers	Sealing, dose delivery
Lubricant	Silicone oil	Reduce friction and glide force
Needle	Stainless steel	Drug administration

3. Manufacturing and Filling Processes

The manufacturing of prefilled syringes is a highly specialized process that integrates pharmaceutical aseptic processing with medical device assembly. Due to their classification as drug–device combination products, prefilled syringes require stringent control of materials, environments, and process parameters to ensure sterility, quality, and functional performance (Table 2) [11].

3.1 Component Preparation and Cleaning

Prior to filling, syringe components such as barrels, plungers, needles, and tip caps undergo thorough cleaning and preparation. Glass barrels are typically washed using multi-stage washing processes involving purified water and, in some cases, water for injection (WFI). Polymer barrels are manufactured under controlled conditions and may require less intensive washing but still undergo particulate and contamination control steps [10,11]. Elastomeric components are commonly washed, siliconized, and sterilized before use. The level of siliconization is carefully controlled, as excessive silicone oil can adversely affect drug stability, particularly for protein-based formulations [3,10].

3.2 Sterilization of Components

Sterilization is a critical step to ensure aseptic conditions throughout the filling process. Common sterilization methods include steam sterilization for glass components, gamma irradiation for polymer parts, and ethylene oxide sterilization for elastomeric closures. The choice of sterilization method depends on material compatibility and potential impact on component performance. Sterilization processes must be validated to demonstrate effectiveness

without compromising material integrity or generating unacceptable levels of extractables [12].

3.3 Aseptic Filling Operations

Prefilled syringes are filled under aseptic conditions using automated filling lines housed within isolators or restricted access barrier systems (RABS) [10]. Filling technologies may involve vacuum filling, time-pressure filling, or peristaltic pumping, depending on formulation characteristics such as viscosity and sensitivity to shear.
Accurate fill volume control is essential to ensure dose accuracy while minimizing overfill. Immediately following filling, syringes are stoppered to maintain sterility and prevent contamination [3,11].

3.4 Stoppering, Plunger Insertion, and Needle Assembly

Following filling, plungers are inserted into the syringe barrels under controlled conditions. For syringes with staked-in needles, needle assembly is performed prior to filling, whereas luer-lock systems may be assembled post-filling. The stoppering process must ensure proper placement and sealing to maintain container closure integrity throughout the product shelf life [13].

3.5 Inspection and Quality Control

Each prefilled syringe undergoes multiple inspection steps, including visual inspection for particulates, cracks, and cosmetic defects. Automated inspection systems are increasingly used to enhance detection accuracy and consistency. In-process and finished product testing includes sterility testing, endotoxin testing, container closure integrity testing, and functional tests such as break-loose force and glide force measurements [14].

3.6 Packaging and Labeling

Filled and inspected syringes are typically packaged in nests or tubs designed to protect them during handling, transport, and storage. Secondary packaging includes labeling and carton assembly, which must comply with regulatory requirements for traceability and patient information. Packaging systems are designed to maintain sterility and mechanical protection while enabling efficient handling in healthcare settings [11,12,14].

Table 2. Key Manufacturing Steps in Prefilled Syringe Production

Manufacturing Step	Purpose	Key Considerations
Component washing	Remove particulates and residues	Water quality, validation
Sterilization	Ensure aseptic components	Material compatibility
Aseptic filling	Accurate dose delivery	Fill accuracy, sterility
Stoppering/assembly	Maintain closure integrity	Seal quality, alignment
Inspection	Detect defects	Sensitivity, consistency
Packaging	Protect product	Sterility maintenance

4. Clinical and Operational Benefits

The use of prefilled syringes offers several advantages over conventional vial-based systems (Table 3).

4.1 Improved Medication Safety

By reducing preparation steps, PFSs minimize the risk of dosing errors, incorrect drug selection, and contamination.

4.2 Enhanced Efficiency

Prefilled syringes significantly reduce preparation time for healthcare professionals, enabling faster drug administration and improved workflow efficiency.

4.3 Reduced Drug Wastage

Single-dose prefilled formats minimize overfill losses and reduce waste associated with partially used vials.

Table 3. Comparison of Prefilled Syringes and Conventional Vial-and-Syringe Systems

Parameter	**Prefilled Syringes**	**Vial-and-Syringe**
Preparation time	Minimal	High
Dosing accuracy	High	Variable
Contamination risk	Low	Higher
Drug wastage	Low	Moderate to high
User convenience	High	Moderate

5. Drug Formulation and Compatibility Considerations

The successful development of prefilled syringe products requires careful consideration of the interactions between the drug formulation and the syringe components. Unlike traditional vial systems, prefilled syringes maintain prolonged and direct contact between the drug product and

multiple materials, increasing the potential for physical and chemical incompatibilities. Early integration of formulation science and device design is therefore critical (Table 4) [15].

5.1 Drug Container Interactions

Drug container interactions can significantly affect the quality, safety, and efficacy of injectable products. Components such as glass barrels, polymer materials, elastomeric stoppers, lubricants, and adhesives may interact with the formulation through adsorption, absorption, or chemical reaction [15]. These interactions may lead to potency loss, changes in pH, or formation of visible and subvisible particles. For protein and peptide formulations, adsorption to container surfaces is a particular concern, as it may induce aggregation or denaturation. Surface chemistry, formulation pH, ionic strength, and the presence of surfactants all influence the extent of these interactions [16].

5.2 Extractables and Leachables

Extractables and leachables (E&L) are chemical species that can migrate from syringe components into the drug product over time. Extractables are compounds that can be extracted under exaggerated conditions, while leachables are those that actually migrate during normal storage [17]. Regulatory agencies require comprehensive E&L assessments to identify, quantify, and evaluate the toxicological risk of these substances. Common sources include elastomeric closures, silicone oil, tungsten residues from needle manufacturing, and polymer additives. Risk-based approaches are typically employed to establish acceptable safety thresholds 15, 16].

5.3 Impact of Silicone Oil

Silicone oil is widely used as a lubricant in prefilled syringes to ensure smooth plunger movement and acceptable injectability performance. However, silicone droplets can act as nucleation sites for protein aggregation, particularly in monoclonal antibody formulations [17]. This phenomenon may result in increased particulate counts and potential immunogenicity concerns. To address these issues, alternative approaches such as reduced-silicone, baked-on silicone, and silicone-free coating technologies are being developed and evaluated [18].

5.4 Formulation Strategies for Compatibility

Formulation strategies play a key role in mitigating compatibility issues in prefilled syringes. The use of stabilizing excipients, such as surfactants (e.g., polysorbates), buffering agents, and chelating agents, can help reduce surface adsorption and chemical degradation [19]. Optimization of formulation parameters, including pH, ionic strength, and protein concentration, is essential to maintain stability throughout the product shelf life [17, 18]. Compatibility studies are typically conducted early in development using representative syringe components [19].

5.5 Injectability and Rheological Considerations

Injectability performance is influenced by formulation viscosity, syringe geometry, needle dimensions, and lubrication [20]. High-viscosity formulations, commonly associated with high-concentration biologics, require higher injection forces, which may affect patient comfort and usability [19]. Rheological characterization and injectability testing, including break-loose force, glide force, and total injection force measurements, are therefore essential during product development, particularly for self-administered therapies [20].

Table 4. Key Drug Formulation and Compatibility Considerations for Prefilled Syringes

Consideration	Potential Impact	Mitigation Strategies
Drug–surface interaction	Adsorption, aggregation	Surfactants, surface treatments
Extractables/leachables	Toxicological risk	Material selection, E&L studies
Silicone oil	Protein aggregation	Low- or silicone-free systems
High viscosity	Increased injection force	Needle optimization, formulation adjustment
Long-term contact	Stability loss	Early compatibility testing

6. Challenges and Limitations

Despite the numerous advantages of prefilled syringes, several technical, operational, and regulatory challenges limit their universal adoption. These challenges must be carefully addressed during product development to ensure safety, efficacy, and commercial viability (Table 5) [21].

6.1 Manufacturing Complexity and Cost

The production of prefilled syringes involves sophisticated aseptic filling operations, specialized equipment, and stringent environmental controls. Compared with conventional vial-based systems, PFS manufacturing requires higher capital investment and operational costs [20]. In addition, lower production flexibility and longer

changeover times may limit manufacturing efficiency, particularly for products with multiple dose strengths [21].

6.2 Material-Related Issues

Material selection remains a critical challenge in prefilled syringe development. Glass syringes may be prone to breakage and delamination, leading to particulate contamination and potential recalls [22]. Polymer-based syringes mitigate some of these risks but introduce concerns related to gas permeability, moisture transmission, and extractables [20]. Elastomeric components may also interact with drug formulations through adsorption or leaching of chemical substances, necessitating extensive compatibility testing [21].

6.3 Extractables, Leachables, and Particulates

The presence of extractables and leachables from syringe components poses potential toxicological and regulatory risks [12]. In addition, subvisible particles originating from silicone oil, glass, or elastomeric materials are of particular concern for injectable products, especially biologics. Regulatory agencies increasingly scrutinize particulate matter levels, requiring robust analytical methods and control strategies [21].

6.4 Formulation and Stability Constraints

Not all drug formulations are suitable for presentation in prefilled syringes. High-viscosity formulations may result in unacceptable injection forces, while sensitive biologics may be destabilized by prolonged contact with syringe materials. These constraints may limit formulation options or require additional development efforts to achieve acceptable stability and injectability [20,21].

6.5 Regulatory and Compliance Challenges

Prefilled syringes are regulated as drug–device combination products, subjecting them to complex regulatory pathways [3]. Developers must comply with both pharmaceutical and medical device regulations, including good manufacturing practices, risk management, and human factors engineering requirements. Navigating these regulatory expectations can be resource-intensive and time-consuming [20].

6.6 Supply Chain and Scalability Limitations

The availability of specialized components and filling capacity can constrain the scalability of prefilled syringe products. Dependence on a limited number of qualified suppliers for barrels, elastomers, or filling services may increase supply chain risk. Technology transfer between development and commercial manufacturing sites also presents significant challenges [21].

Table 5. Major Challenges and Limitations of Prefilled Syringes

Challenge Category	Description	Impact
Manufacturing	Complex aseptic processing	Increased cost
Materials	Glass delamination, polymer extractables	Quality risk
E&L and particulates	Chemical and particulate contamination	Safety concern
Formulation	Viscosity and stability limitations	Reduced flexibility
Regulatory	Combination-product requirements	Longer development timelines
Supply chain	Limited suppliers and capacity	Scalability risk

7. Future Trends and Developments

The landscape of prefilled syringe technology is rapidly evolving, driven by advances in materials science, device design, digital integration, and changing therapeutic needs. These trends reflect broader shifts in healthcare toward patient-centric care, biologic therapies, and smart medical devices [11].

7.1 Expansion of Polymer and Advanced Materials

Traditionally dominated by glass syringes, the field is witnessing a shift toward polymer-based systems such as cyclic olefin polymer (COP) and cyclic olefin copolymer (COC) [11]. These materials offer reduced breakage risk, lower potential for delamination and extractables, and improved compatibility with sensitive biologics. Ongoing innovations aim to expand polymer use while addressing concerns about permeability and long-term stability [20].

7.2 Dual-Chamber and Complex Delivery Systems

Dual-chamber prefilled syringes, which allow on-demand mixing of components (e.g., lyophilized drugs and diluents), are gaining importance for complex biologic therapies that require reconstitution at the point of use. These systems reduce preparation error and expand the applicability of PFS formats to a broader range of drug classes [11,20].

7.3 Digital and Smart Connectivity Integration

A major emerging area is the integration of digital features and connectivity technologies into prefilled syringes. For example, RFID-based traceability systems are being piloted to improve fill-and-finish tracking and supply chain visibility, enhancing safety and inventory management. Smart syringes with embedded sensors or connectivity

modules for dose tracking and adherence monitoring are also being explored, particularly for chronic disease management [11].

7.4 Self-Administration and Patient-Centric Design

Patient demand for greater autonomy in healthcare delivery is driving innovations in ease-of-use and comfort. Syringe designs are increasingly focused on ergonomic features, safety needle systems that reduce needlestick injuries, and compatibility with self-injection devices such as autoinjectors [21]. These developments facilitate home-based therapy administration, especially for chronic conditions like diabetes and autoimmune diseases [20].

7.5 Smart Manufacturing and Supply Chain Integration

Future developments also include enhanced manufacturing automation and digitalization to improve consistency, quality control, and production scalability [10,11]. Real-time performance monitoring and supply chain digitization systems are anticipated to become more prevalent, enabling proactive quality assurance and faster response to production challenges [20].

7.6 Sustainability and Regulatory Alignment

Environmental and regulatory pressures are encouraging innovations in sustainable materials and packaging. Efforts are underway to develop recyclable polymers and reduce waste associated with syringe systems [18]. Regulatory bodies continue to refine guidelines for extractables, leachables, and device safety, shaping future device design and testing protocols [11-20].

8. Conclusion

Prefilled syringes represent a significant advancement in parenteral drug delivery, offering clear benefits in terms of safety, accuracy, and efficiency. Their growing adoption reflects broader trends toward patient-centric care and the increasing complexity of injectable therapies. However, successful implementation requires careful consideration of material compatibility, manufacturing processes, and regulatory requirements. Continued innovation and interdisciplinary collaboration will be essential to fully realize the potential of prefilled syringes in modern healthcare.

References

[1]. Muralidhara, B.K. and Wong, M., 2020. Critical considerations in the formulation development of parenteral biologic drugs. *Drug Discovery Today*, *25*(3), pp.574-581.

[2]. Heidt, B., Siqueira, W.F., Eersels, K., Diliën, H., van Grinsven, B., Fujiwara, R.T. and Cleij, T.J., 2020. Point of care diagnostics in resource-limited settings: A review of the present and future of PoC in its most needed environment. *Biosensors*, *10*(10), p.133.

[3]. Ingle, R.G. and Agarwal, A.S., 2014. Pre-filled syringe–a ready-to-use drug delivery system: a review. *Expert Opinion on Drug Delivery*, *11*(9), pp.1391-1399.

[4]. Zehrung, D. and Free, M.J., 2025. Advances in Drug and Vaccine Delivery for Low-and Middle-Income Healthcare Programs—The Case for Replacing Multi-Dose Vials with Prefilled Single-Dose Delivery Systems. *Pharmacy*, *13*(6), p.180.

[5]. Parenky, A.C., Wadhwa, S., Chen, H.H., Bhalla, A.S., Graham, K.S. and Shameem, M., 2021. Container closure and delivery considerations for intravitreal drug administration. *AAPS PharmSciTech*, *22*(3), p.100.

[6]. Nunes, P.S., Ohlsson, P.D., Ordeig, O. and Kutter, J.P., 2010. Cyclic olefin polymers: emerging materials for lab-on-a-chip applications. *Microfluidics and nanofluidics*, *9*(2), pp.145-161.

[7]. Parenky, A.C., Wadhwa, S., Chen, H.H., Bhalla, A.S., Graham, K.S. and Shameem, M., 2021. Container closure and delivery considerations for intravitreal drug administration. *AAPS PharmSciTech*, *22*(3), p.100.

[8]. Cui, J., Yang, J.X., Li, Y.G. and Li, Y.S., 2015. Synthesis of high performance cyclic olefin polymers (COPs) with ester group via ring-opening metathesis polymerization. *Polymers*, *7*(8), pp.1389-1409.

[9]. Chandra, T., Zebrowski, J.P. and Lenertz, L.Y., 2022. Safe handling of cannulas and needles in chemistry laboratories. *ACS Chemical Health & Safety*, *29*(2), pp.175-183.

[10]. Wang, Y., Li, H., Wu, L., Zhao, Z., Chen, Q. and Guo, J., 2025. Improving prefilled syringe injectability: influences of critical component attributes and human factors. *European Journal of Pharmaceutics and Biopharmaceutics*, p.114901.

[11]. Sacha, G., Rogers, J.A. and Miller, R.L., 2015. Pre-filled syringes: a review of the history, manufacturing and challenges. *Pharmaceutical development and technology*, *20*(1), pp.1-11.

[12]. Jildeh, Z.B., Kirchner, P., Oberlaender, J., Vahidpour, F., Wagner, P.H. and Schöning, M.J., 2020. Development of a package-sterilization process for aseptic filling machines: A numerical approach and validation for surface treatment with hydrogen peroxide. *Sensors and Actuators A: Physical*, *303*, p.111691.

[13]. De Bardi, M., Müller, R., Grünzweig, C., Mannes, D., Boillat, P., Rigollet, M., Bamberg, F., Jung, T.A. and Yang, K., 2018. On the needle clogging of staked-in-needle pre-filled syringes: Mechanism of liquid entering the needle and solidification process. *European Journal of Pharmaceutics and Biopharmaceutics*, *128*, pp.272-281.

[14]. Levine, C., 2021. Validation of Primary Packaging, Inspection and Secondary Packaging Processes. In *Handbook of Validation in Pharmaceutical Processes, Fourth Edition* (pp. 549-566). CRC Press.

[15]. Badkar, A., Wolf, A., Bohack, L. and Kolhe, P., 2011. Development of biotechnology products in pre-filled syringes: technical considerations and approaches. *Aaps Pharmscitech*, *12*(2), pp.564-572.