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Advancements in sterilization packaging systems: Ensuring patient safety

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Abstract
Sterilization packaging systems are pivotal in preserving the integrity of medical instruments and devices, crucial for ensuring patient safety in healthcare settings. This paper explores recent advancements in sterilization packaging technologies, emphasizing their critical role amid the persistent threat of healthcare-associated infections. As the healthcare landscape evolves, the demand for reliable and innovative sterilization packaging solutions becomes increasingly urgent.
The paper reviews traditional sterilization methods such as steam and ethylene oxide, examining their impact on packaging materials. It further explores emerging techniques like hydrogen peroxide plasma and gamma irradiation, highlighting their compatibility with modern packaging materials and their potential to reduce environmental impact.
In-depth discussions cover advancements in barrier materials, including high-performance polymers, breathable films, and microbial-resistant coatings. These materials enhance protective properties, preventing contamination and maintaining sterility until use.
The integration of data-driven technologies, such as RFID tracking and smart sensors, is explored for traceability and monitoring throughout the sterilization and transportation process. These innovations promote accountability, transparency, and regulatory compliance, reducing the risk of human error.
Addressing sustainability concerns, the paper investigates eco-friendly sterilization packaging materials and reusable options, aligning with the global focus on reducing medical waste.
In conclusion, this paper showcases the latest sterilization packaging advancements, underlining their crucial role in patient safety. These innovations not only enhance sterilization processes' reliability but also contribute to healthcare sustainability and efficiency. The abstract provides insights into ongoing efforts to elevate sterilization practices, benefiting healthcare professionals and patients alike.

Keywords: Sterilization packaging systems, patient safety, healthcare-associated infections advancements, packaging technologies, barrier materials, data-driven technologies, traceability

Introduction
This comprehensive review focuses on the critical role of packaging in pharmaceutical products to ensure their safe delivery to patients. Quality assurance in pharmaceutical manufacturing is essential, defined as the arrangements made to guarantee that products meet the required standards for their intended use [1].
Packaging is often underestimated by the public, but it serves crucial functions in preserving the stability and quality of medicinal products, protecting them from spoilage and tampering. The complexity of packaging materials and the advanced technology involved in pharmaceuticals present challenges for manufacturers [2]. The interaction between various container components and active ingredients underscores the importance of packaging in maintaining product quality.
Pharmaceutical packaging must protect against external influences like moisture, light, oxygen, and temperature variations, as well as biological contamination and physical damage. Additionally, it should provide accurate information and identification of the product. The chosen packaging materials must not adversely affect the product or vice versa throughout the intended shelf-life [3].
The system of quality assurance for pharmaceutical packaging aligns with WHO guidelines for Good Manufacturing Practices (GMP). Requirements outlined in compendia and standards, such as those from ISO, are considered general, and detailed packaging and stability studies are necessary for specific products.

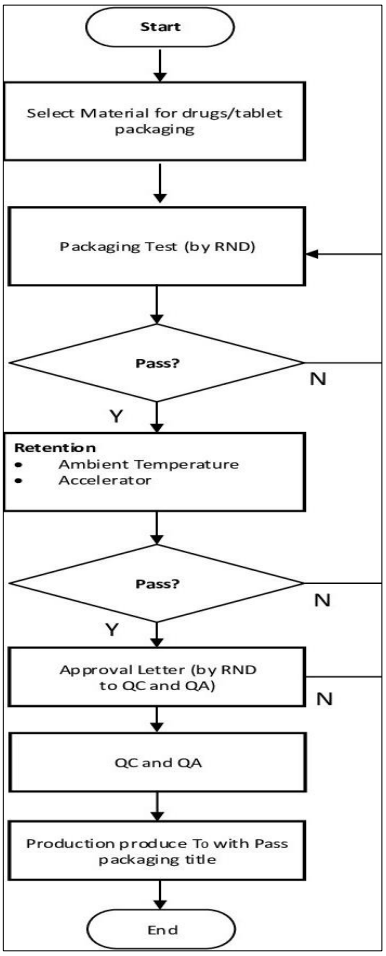
Containers for pharmaceutical use must not interact with the substance in a way that alters its quality. Different types of closures are defined, each with specific requirements for protecting the contents under normal handling, shipment, or storage conditions [4]. Light-sensitive substances require packaging in light-resistant containers or appropriate coverings.

Labels play a crucial role in identifying finished drug products, providing information on active ingredients, batch numbers, expiry dates, storage conditions, directions for use, warnings, and manufacturer details [5]. Marketing authorization, issued by drug regulatory authorities, includes detailed information on product composition, formulation, specifications, packaging, labeling, and shelf-life.

Materials in pharmaceutical production encompass starting materials, process aids, intermediates, active pharmaceutical ingredients, and packaging and labeling materials. Packaging processes involve operations like filling and labeling to transform bulk products into finished ones [6].

The production of pharmaceuticals includes all operations from receiving starting materials to completing the finished product. Quarantine status applies to materials or products isolated while awaiting a decision on release, rejection, or reprocessing [7].

In conclusion, this review emphasizes the integral role of pharmaceutical packaging in maintaining product quality and ensuring the safety and efficacy of medicines throughout their lifecycle. Manufacturers must adhere to stringent quality assurance standards and consider the specific requirements of each product in their packaging design and material selection.



Flowchart: Packaging approval process

Aspects of packaging

The packaging of pharmaceutical products is a critical aspect encompassing various components from production to end-use. Primary and secondary packaging components, containers, and the packaging process are distinguished, with choices based on protection, compatibility, filling methods, cost, and user convenience [8].

Labels play a crucial role in product identification, stability preservation, batch tracking, and masking identities in clinical studies [9]. Compliance is enhanced through user-friendly designs, while protection involves tamper-evident features and child-resistant closures [10].

Containers for pharmaceuticals [11]

There are six basic primary packaging or container systems:

1. Ampoules – glass
2. Vials – glass and plastic
3. Pre-filled syringes – glass and plastic
4. Cartridges – glass
5. Bottles – glass and plastic
6. Bags – plastic

Ampoules

For decades, glass sealed ampoules were the most popular primary packaging system for small volume injectable products. Ampoules were favorable because they offer only one type of material (glass) to worry about for potential interactions with the drug product compared to other packaging systems that contain both glass or plastic and rubber [12].

Fig 1: Ampoule

Glass ampoules are Type I tubing glass (Type I and tubing glass are discussed in more detail later.) in sizes ranging from 1–50 mL. Thus the tip-sealed ampoule has a longer section above the neck while the pull-sealed ampoule has a more blunt, ‘fatter’ top. Modifications of ampoules are available, e.g. wide mouth ampoules with flat or rounded bottoms to facilitate filling with dry materials or suspensions [13].

Vials

The most common packaging for liquid and freeze-dried injectables is the glass vial. Plastic vials have made some ingress as marketed packages for cancer drugs, but may require more time before being commonplace in the injectable market. Plastic vials are made of cyclic olefin copolymer (COC). The appearance of aplastic vial looks identical to a glass vial [14].

Fig 2: Vial

Reasons why plastic vials have not become as commonplace as glass vials include: Challenges 1. in introducing pre-sterilized containers into a classified (ISO 5) aseptic environment. Challenges in handling and movement of much lighter weight containers compared to glass along conveyer systems on high-speed filling lines, with smaller vials (1–5 mL) especially difficult to process [15].
Concerns about potential interactions with the drug product (Absorption, adsorption, migration, leachables) especially over a 2–3 year shelf life.

Syringes
Syringes are very popular delivery system. Plastic syringes can be purchased or some companies have the technology to apply form-fill-finish technologies for their own use. [16]

Fig 3: Syringe

One company now has the capability to form-fillfinish glass syringes from tubing glass [17]. Other options regarding syringe size, components, formats, treatment of rubber materials, and manufacturing methods are summarized in Table 1. Most of the world's vaccines are packaged and delivered in syringes. The growth rate for products filled and packaged in pre-filled syringes increases about 13% per year.This growth is related to the top factors that influence a physician's choice of a drug delivery type, which include ease of use by patients, convenience, and comfort. [37] Primary reasons for syringe popularity include:

- The emergence of biotechnology and the need to eliminate overfill (Reduced waste) of expensive biomolecules compared to vials and other containers. Vaccines, antithrombotics, and various home healthcare products such as growth hormone and treatments for rheumatoid arthritis and multiple sclerosis are more conveniently administered using pre-filled syringes.
- Availability of enormous (millions) quantities of presterilized ready-to-fill syringes such as BD Hypak® SCF and Bunder Glas RTF.

The use of these protection devices is increasing due to the 2000 United States Federal Needle Stick Safety and Prevention Act [18]. Needle stick prevention can be manual (shield activated manually by the user although there is still the risk of accidental sticking), active (automated needle shielding activated by user), or passive (automated needle shielding without action by the user).
Items that must be addressed in selecting and qualifying components of a syringe include:

- Container/closure integrity testing;
- Plastic component extractables;
- Sterilizability, especially if needle is part of the packageto be sterilized;
- Siliconization of barrel and plunger (although silicone-free syringes now exist that provide both lubricity and inert drug-contact surfaces);
- Compatibility of product with syringe contact parts, especially the rubber plunger;
- Appropriate gauge size of needle for product and its indication. Syringe needle gauges range from 21G to32G. It is important to note some suspensions may not flow through the syringe properly if the needle gauge is not carefully considered.

The articles demonstrate that these techniques show uneven distribution of silicone oil within syringe glass barrels as potential sources of chattering and stalling of the syringe plunger during injection using auto-injectors [19].

Cartridges
Cartridges are similar to syringes with respect to having a product filled into a glass tube closed on either side by a rubber plunger and a rubber disk seal. Cartridges are inserted into delivery pens as shown schematically. Cartridge/pen delivery systems are used primarily for multiple dose proteins such as insulin and growth hormone, and, historically have been used for dental anesthesia and epinephrine emergency uses [21].

Fig 4: Cartridge

Most pens use special pen needles that can be extremely short and thin. For example, the Becton Dickinson pen uses needles that are 29G to 31G; Novo Nordisk pen needles, called NovoFine®, are 30G to 31G [22].

Bottles

Fig 5: Bottle

Bottles typically refer to containers larger than 100 mL, thus, large volume injectable solutions or emulsions are contained in bottles (or bags) rather than vials. Bottles are manufactured by the blow-molded process. Bottles can be glass or plastic, both are commonly used in hospital pharmacy practice.

Bags

Bags used for IV fluids include pre-filled or empty containers that range in size from 25 mL to greater than 1 L. Sizes that are 1 L or greater are often used in hospital settings for delivery of total parenteral nutrition. Bags of all sizes are used for ease of delivery and ease of transport. However, maintaining identification of the bags can be a problem. Printing on plastic bags is a challenge because of the flexibility of the bag material and labels adhered to the bags can become difficult to read. This was mostly resolved by the introduction of bar coding that allows traceability of bags from filling to patient use [23].

Packaging Materials and Closures in Pharmaceutical Products [24]

Pharmaceutical packaging plays a critical role in ensuring the safety, efficacy, and stability of medicinal products. The packaging materials, closures, and containers must meet diverse requirements based on the method of use and administration. This is especially crucial for novel medicinal products like those administered through transdermal delivery systems. Glass, a commonly used packaging material, possesses unique properties and variations. Understanding its composition, types, physical properties, manufacturing processes, and potential issues such as extractables is essential for maintaining product quality.

Testing methods

Glass extractables are always the primary concern and this is reflected in the compendial test requirements. Test requirements vary depending on the compendia (USP vs. EP vs. JP). All require light transmission, arsenic, and the alkalinity tests (powdered glass or water attack). Other tests include hydrofluoric acid testing (EP), soluble iron (JP) and appearance (JP). The USP and EP require either a crushed-glass test that determines the bulk composition of the glass or a surface test to examine the composition and durability of the glass as a result of the forming process.

Glass syringes present an interesting case where an additional extractable did not directly originate from the glass. The inner needle channel in glass syringes is oftenformed using a tungsten pin [25-28].

Rubber

In the injectable drug product business, rubber is used for many applications - closures for vials and bottles, seals and plungers for syringes and cartridges, gaskets in manufacturing equipment, and ports on plastic bags and intravenous administration sets [29].

Cleaning and sterilization

Sterilization of rubber closures occurs by steam sterilization in an autoclave using a validated cycle. Rubber plungers used in pre-sterilized, ready-to-fill syringes are sterilized by gamma radiation. Examples of stopper preparation equipment are DCIB, Getinge C, and Icos D. The DCI machines clean, siliconize, and depyrogenate stoppers within the same unit and the stoppers are batched and sterilized in an autoclave [30]. The Getinge machines clean, siliconize, depyrogenate, and sterilize the stoppers within the same unit. Alternatively, stoppers may be purchased directly from the stopper manufacturer already washed, siliconized, depyrogenated, and/or sterilized. Stoppers may be purchased from the stopper manufacturers as:

- Raw stoppers – have not been processed and must bewashed, siliconized (if applicable), and sterilized.
- Ready to Sterilize (RTS) Stoppers – have been washedand siliconized (if applicable) in bags but have notbeen sterilized.
- Ready to Use (RTU) Stoppers – have been washed, siliconized (if applicable), and sterilized.

Qualification

Physico-chemical and toxicological tests for evaluating rubber closures are described in compendia such as the USP. Biological tests are both *in vitro* (USP <87>) and *in vivo* (USP <88>) tests. *In vitro* biological reactivity tests for rubber include the agar diffusion test, the direct contact test, and the elution test. *In vivo* biological reactivity tests include the systemic injection test, the intracutaneous test, and the implantation test. Physicochemical tests (USP <381> and Ph. Eur. 3.2.9) involve extractable studies using water.

Recently, polymeric coatings have been developed that are claimed to have more integral binding with the rubber matrix, but details of their function are trade secrets.

There are four general types of rubber interactionswith the drug product:

a) Adsorption of the active ingredient at the surface of the rubber. Proteins are well known to adsorb to rubber surfaces.
b) Absorption of one or more formulation components into the rubber. Components with high partition coefficients are prone to absorb into rubber.
c) Permeation of a formulation component through the rubber. Phenolic preservatives are a well-known example.
d) Leaching of rubber components into the drug product. The well-known example of 2-mercaptobenzothiazole;also aluminum, nitrosamines, and zinc are common rubber leachates.

Siliconization

Rubber closures must be ‘slippery’ in order to move easily through a rubber closure hopper and other stainless steel passages until they are fitted onto the filled vials. Traditionally, rubber materials are ‘siliconized’ (silicone oil or emulsion applied onto the rubber) in order to provide lubrication.

The practice of applying silicone to the rubber closures is acceptable as long as the silicone application process is effective (i.e. not too much or too little silicone applied to each rubber closure) and the product does not have any interactions with silicone.

Coating

Coatings are utilized for one or two main purposes.

a) As a barrier between the stopper and the drug product to reduce leachables and extractables;
b) To eliminate the requirement of silicone for processing.

These coated stoppers offer the following advantages compared with stoppers that must be siliconized:

- Eliminates the need for adding silicone oil;
- Provides lubricity for machinability;
- Reduces rubber stopper clumping problems;
- Decreases particulate matter levels;
- Reduces potential for formulation adsorption and absorption;
- Reduces chemical extractable levels.

Another laminated film available only to stoppers with a flat inner surface is Teflon®. Teflon®-coated stoppers require additional siliconization for processing. Recently, Teflon® has come under scrutiny as a possible carcinogen. The Environmental Protection Agency (EPA) has initiated a major investigation to determine if perfluorooctanoicacid, which is a chemical used to make Teflon®, is a possible carcinogen [30-33].

In addition, packaging must meet the following requirements:

- It must preserve the physical properties of all dosage forms and protect them against damage or breakage;
- It must not alter the identity of the product;
- It must preserve the characteristic properties of the product, so that the latter complies with its specifications;
- It must protect the product against undesirable or adulterating chemical, biological or physical entities.

Labels

Throughout manufacturing, a succession of specific outer labels are applied to the container of the medicinal product. The level of processing is indicated by the following words:

- Quarantine
- Storage
- Distribution.

Specifications for labels for finished drug products are defined in the WHO guidelines on GMP for pharmaceutical products. Written labels on the packaging:

- Permit the identification of each active ingredient by means of its INN, and also give the dosage form and the trade name/trademark. All information concerning the medicinal product, as required by national legislation, must be stated on the packaging.
- Preserve the stability of the medicinal product by giving advice on its storage [4].

After the stability of the product has been evaluated, one of the following recommendations as to storage conditions can be prominently indicated on the label:

- Store under normal storage conditions;
- Store between 2 and 8 °C (Under refrigeration, no freezing);
- Store below 8 °C (Under refrigeration)

Table 1: Examples of plastic additives

Additive type	Examples
Antioxidants	BHT, thioesters, phosphates
Heat stabilizers	Metallic stearates, epoxidized soybean oil, barium benzoate
Lubricants	Fatty acid amides, polyethylene waxes, silicones, fluorocarbon, zinc stearate
Plasticizers	Phthalates (30–40% added to polyvinyl chloride)
Colorants	Dyes, ultramarine blue, other pigments

Table 2: Plastic polymer applications in injectable drug delivery

Material	Components
Plastic vials	Polycyclopentane, cyclic olefin copolymer
Containers for blood products	Polyvinyl chloride, polyolefin, others
Disposable syringes	Polycarbonate, polyethylene, polypropylene
Irrigating solution container	Polyethylene, polypropylene, polyolefin
Intravenous infusion container	Polyvinyl chloride, polyester, polyolefin
Administration set	Acrylonitrile butadiene
Administration set spike	Nylon
Administration tubing	Polyvinylchloride, other
Needle adapter	Polymethylmethacrylate
Clamp	Polypropylene
Catheter	Teflon, polypropylene

For parenteral preparations, the combination of glass containers and elastomeric closures, usually secured by an aluminium cap, is widely used. Typical examples are infusion bottles, injection vials and prefilled syringes. The rubber closures used within such a system must be carefully selected in accordance with the intended.

Quality Assurance aspects of packaging [34]

The essential part of quality control is performed by the manufacturer during the development, production, release and post-marketing surveillance of the entire medicinal product, i.e. the finished dosage form in its primary and secondary packaging. As pointed out by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its thirty-second meeting [35].

The basic requirements for quality control are as follows [35]:

a) Adequate facilities, trained personnel and approved procedures must be available for sampling, inspecting and testing starting materials, packaging materials, and intermediate, bulk and finished products, and where appropriate for monitoring environmental conditions for GMP purposes.
b) Samples of starting materials, packaging materials, intermediate products, bulk products and finished products must be taken by methods and personnel approved of by the quality control department.
c) Test methods must be validated.
d) Records must be made (Manually and/or by recording

instruments) demonstrating that all the required sampling, inspecting and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated.

e) The finished products must contain ingredients complying with the qualitative and quantitative composition of the product described in the marketing authorization; the ingredients must be of the required purity, in their proper container, and correctly labeled.
f) Records must be made of the results of inspecting and testing materials and intermediate, bulk and finished products against specifications; product assessment must include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures.

Sampling

Sampling is used to check the correctness of the label, packaging material or container reference, as well as in the acceptance of consignments, detecting adulteration of the medicinal product, obtaining a sample for retention, etc. The sampling procedure should be described in a written protocol. Further details are given in "Sampling procedure for industrially manufactured pharmaceuticals

Package testing procedures

The testing procedures may be divided into two groups according to whether the test is applied to the packaging material in isolation or to the entire package.

Testing material: Tests applied to packaging materials may be:

a) Chemical - The pH value of materials chloride and sulphate in paper or board, alkalinity of glass, compatibility test with chemicals or medicaments are typical of the chemical tests.
b) Mechanical-Standard tests are available for the effect of creasing, folding and so on.
c) Environmental-Materials may be tested by standard methods for absorption of water, permeability to water vapour, gases, oils, odours etc. and for characteristics such as light transmission.

Testing, Packages

a) Mechanical – Mechanical tests are applied mainly to outer packaging for protection from transportation hazards. They consist of the use of a standardized test procedure to compare the effect of different protective materials to prevent damage to the contents.
b) Environmental- Packages are subjected to conditions that reproduce the environment and some evaluation is made at suitable intervals. Such procedures may be applied to testing closures for water vapour transmission.

Hazards encountered by a package

a) Mechanical hazards – shock, compression, puncture, vibration etc.
b) Environmental Hazards-temperature, pressure, moisture, gases, light, contamination etc.

There are various tests to ensure that the resultant product will comply with its specification. Tests applied to the environment or to equipment, as well as to products in process, may also be regarded as a part of in-process control.

Principle instrumental techniques for packaging control

a) Spectrophotometry
b) Chromatographic Methods
c) Thermal analysis techniques
d) Gas transmission analysis
e) Leak detection
f) Physical test methods
g) X-ray Fluorescence Analysis

Ideal requirements of good packaging

a) They should be able to hold the product without loss on account of leakage, spoilage or permeation.
b) They should afford protect against environmental conditions like light, air and moisture during storage.
c) They should not have any permeability for gases.
d) They should possess sufficient strength to withstand shocks of handling, transportation etc.
e) They should facilitate efficient safe and convenient use of contents.
f) The material must not interact with the contents.
g) The containers should afford protection from moulds, bacteria etc.
h) The cost of material should be as low as possible without compromising the quality.
i) They should facilitate easy identification.
j) They should afford protection from moulds, bacteria etc.
k) The container should not absorb or adsorb any material containing.
l) The closure should provide air tight closing to the container.

QC for containers

- **Airtight container:** A container that is impermeable to solids, liquids and gases under ordinary conditions of handling, storage and transport. If the container is intended to be opened on more than once, it must be so designed that it remains airtight after re-closure.
- **Hermetically Sealed container:** A container that is impervious to air or any other gas under normal conditions of handling, shipment, storage and distribution, e.g. sealed glass ampoule, gas cylinder etc.
- **Light-resistant container:** A container that protects the contents from the effects of actinic light by virtue of the specific properties of the material of which it is made.
- **Multidose container:** A container that holds a quantity of the preparation suitable for two or more doses.
- **Sealed container:** A container closed by fusion of the material of the container.
- **Single-dose container:** A container that holds a quantity of the preparation intended for total or partial use as a single administration.
- **Tamper-evident container:** A container fitted with a device or mechanism that reveals irreversibly whether the container has been opened.
- **Tightly-closed container:** A tightly-closed container protects the contents from contamination by extraneous liquids, solids or vapours, from loss or deterioration of the article from effervescence, deliquescence or evaporation under normal conditions of handling, shipment, storage and distribution. A tightly-closed container must be capable of being tightly re- closed after use.
- **Well-closed container:** A well-closed container protects

the contents from extraneous solids and liquids and from loss of the article under normal conditions of handling, shipment, storage and distribution.

QC for Glass containers

Crushed – glass test

This test is official in USP. The container is crushed and sieved to produce uniform particles of which a definite weight of taken. The control of the particle size and weight of powder ensures that a constant surface area is exposed to the solution.[87] Because all of the glass (not just the surface layer) is examined and extraction is enhanced by the rough surfaces of the particles, this is a severe test, and, if a glass passes, it is unlikely that containers made from it will give trouble while is use. Nevertheless, the technique is tedious and is not applicable to surface treated containers (Sulphured or siliconed) because crushing would expose the alkaline glass below the surface. This test can be used for determining the nature of a glass or for distinguish between two types of glasses, such as neutral or surface – treated.

Whole-Container test

This test is official in European, British and International Pharmacopoeias. It is used in the USP for treated soda-lime containers only. The containers are simply filled with the test solution and exposed to the test conditions. Glassware may pass the whole container test more easily because the surface layer of a container is smooth and less reactive.

Table 3: Surface area which supplies alkali to each milliliter of the solution

Container	Surface area which supplies alkali to each milliliter of the solution.
Ampoule (1 ml.)	5.9 cm^2
Ampoule (10 ml.)	2.9 cm^2
Bottle (1000 ml)	0.5 cm^2

Chemical resistance of test

USP and IP provide two tests to determine the chemical resistance of glass containers.

Table 4: Limits of alkalinity for glass containers:

Tests	Containers	Limits ml of 0.02 N H_2SO_4
1. Powdered Glass Test	Type I	1.0
	Type III	8.5
	Type NP	15.0
2. Water Attack Test	type II (100 ml of less)	0.7
	type II (over 100ml)	0.2

Powdered Glass Test

From the glass containers, alkaline constituents (Oxides of sodium, potassium, calcium, aluminum, etc.) are leached into purified water under conditions of elevated temperatures. When the glass is powdered the leaching of alkali can be enhanced in the powdered is critical.

The principle involved in the powdered glass test in estimate the amount of alkali leached form the glass powder. The amount of acid that is necessary to neutralize the released alkali (A specified limit) is specified in the pharmacopoeia. The basic analysis is acid-base titration using methyl red indicator.

Water Attack Test

This test is used only with containers that have been exposed to sulphur dioxide fumes under controlled humidity conditions. Such a treatment neutralizes the surface alkali. Now the glass becomes chemically more resistant. The principle involved in the water attack test is to determine whether the alkali leached form the surface of a container is within the specified limits or not. Since the inner surface is under test entire container (Ampoule) has to be used. The amount of acid that is necessary to neutralize the released alkali from the surface is estimated, the leaching of alkali is accelerated using elevated temperature for a specified time. Methyl red indicator is used to determine the end point. The basic is acid-base titration.

Considerations for Drug Plastic

Permeation

- Concerns the transmission of gases, vapors, or liquids through plastic packaging.
- Influenced by temperature and humidity.

Leaching

- Possible migration of container ingredients into the drug.
- Especially critical when coloring agents are used.

Sorption

Bonding of solutes to plastic, potentially impacting drug product constituents.

Chemical Reactivity

Ingredients in plastic formulations may react with drug components.

Physiochemical Tests

1. Appearance
2. Light Absorption
3. pH
4. Non-volatile Matter
5. Residue on Ignition
6. Heavy Metals
7. Buffering Capacity
8. Oxidizable Substances

Biological Tests

Implantation Test

Placing small plastic pieces intramuscularly in rabbits.

Systemic Injection Test

Injecting eluates intravenously or intraperitoneally in mice.

Intracutaneous Test

Subcutaneous injection of eluates in rabbits.

Tests for Parenteral and Non-parenteral Preparations
Leakage Test
Checking for signs of leakage after inverting containers.

Collapsibility Test
Ensuring containers yield at least 90% of nominal contents during use.

Clarity of Aqueous Extract
Testing clarity of extracts from containers.

Transparency Test
Assessing cloudiness of diluted suspension in containers.

Water Vapour Permeability Test
Checking weight loss in containers over 14 days at specified conditions.

Tests for Plastic Containers for Ophthalmic Preparations:
1. Leakage Test
2. Systemic Injection Test
3. Eye Irritation Test:

Evaluating responses to instillation of extracts in the rabbit's eye.

QC for Closures
Penetrability
Measuring force required for needle penetration.

Fragmentation Test
Checking for closure fragments after needle penetration.

Self Sealability Test
Testing closure integrity after multiple piercings and exposure to a colored solution.

Extractive Test
Boiling closures with water and ensuring residue does not exceed limits.

Compatibility Test
Checking for interactions between closure and bottle contents.

Light Absorption
Measuring light absorbance of filtrate within a specified range.
These tests and considerations help ensure the quality, safety, and efficacy of pharmaceutical products by assessing the suitability of plastic containers and closures for drug packaging.

WHO Guidelines for Packaging Materials
- Containers and closures for use must comply with pharmacopoeial and specified requirements.
- Sample sizes, specifications, test methods, cleansing, and sterilization procedures must align with packaging material suitability.
- Plastic granules should meet pharmacopeial requirements, including physio-chemical and biological tests.
- Containers and closures must be rinsed with water for injection before sterilization.
- Design must facilitate an airtight seal, and chosen containers and closures must not adversely affect the product.
- For glass bottles, a written cleansing schedule must be followed, and individual containers must be examined for foreign matters against a background with diffused light.

Glass Bottles
- Rational and standardized shape and design.
- Use of USP Type-I and Type-II glass bottles. Type-III for non-parenteral sterile products.

Plastic Containers
- Preformed plastic containers for large volume parenterals molded in-house through an automatic machine.
- Blowing, filling, and sealing operations conducted in rooms conforming to requirements.

Rubber Stoppers
Rubber stoppers for large volume parenterals must comply with specifications in the Indian Pharmacopeia.

Conclusion
Pharmaceutical packaging serves a multifaceted role, providing protection, identification, information, convenience, and compliance throughout the product's lifecycle. Factors like child safety, dosage accuracy, patient traceability, and prevention of tampering and diversion are critical considerations. In the current landscape, concerns around drug counterfeiting and terrorism underscore the urgency for traceability in medical packaging.
Ensuring the authenticity of pharmaceuticals from manufacturing plants to the end-user is increasingly achievable through technologies like barcodes and Radio Frequency Identification (RFID). RFID, embedded in pharmaceutical packaging, enhances traceability, authenticity, and overall efficiency in the drug supply chain. As the pharmaceutical industry continues to evolve, maintaining high-quality packaging standards remains paramount to ensure the safety and efficacy of medicinal products.

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