Pharmaceutical Packaging

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Pharmaceutical Packaging

- Packaging can be defined as a means of providing, presentation, protection, identification/information, containment, convenience and compliance for a product during storage, carriage, display and use.
- Selection of the right pack-product combination is important part of drug product development

Primary packaging: a package that is in direct contact with the preparation

Secondary packaging: a package that is not in direct contact with the preparation

Single dose containers: containers that hold an amount of product intended for single dose

Multidose containers: containers that hold an amount of product that will be used for two or more doses

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Primary Packaging

Direct interaction with product

Secondary Packaging

No direct interaction with product

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Pharmaceutical Packaging

The role of the pack

- The pack must:
  - Be economical
  - Provide protection against climate, biological, physical and chemical hazards
  - be sufficiently strong to withstand handling while empty, when filling, closing, sterilizing, labeling, transport, storage and use by the consumer
  - Provide an acceptable presentation which will contribute to product confidence
  - Maintain adequate identification and information
  - Contribute in terms of confidence and compliance
  - Be easy to handle (e.g. the closure must be easy to remove and replace)

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Pharmaceutical Packaging

The pack should not:

- allow loss of product
- react with the contents
- absorb substances from the content

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The pack as a protection

Protection is the most important function of the pack

This include protection from:

1) Mechanical hazards

- Shock or impact damage
- Compression
- Vibration
  - vibrations consist of two variables, frequency and amplitude
- Abrasion
- Puncture or piercing (penetration from sharp object)

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The pack as a protection

2) Climate or environmental hazards

- Moisture
  - Moisture can cause chemical (hydrolysis, effervescence..) or physical changes (softening, hardening..) in the product.
- Temperature
- Pressure
- Light
  - UV is a potential source of photochemical changes
  - Light may cause discoloration of packaging material (fading of colors, white may go yellow)
- Atmospheric gases
  - These include oxygen, carbon dioxide, nitrogen and any other airborne gases.
  - Oxygen may lead to oxidation
  - CO_2 can cause a pH shift and/or lead to precipitation of some products
- Solid airborne contamination (particulates)

The pack as a protection

3) Biological hazards

- Microbiological
  - There is a general tendency towards improved microbial control for all products
  - In the case of sterile products, the pack must maintain a 100% seal against microbial ingress
  - Ingress of yeast is critical in sugar-based products
  - Moulds may grow on cellulose based materials (i.e paper and board) if kept under humid conditions
- Other forms of infestation
  - This include attack by insects, termites, vermin, rodents or any other sources
- Pilferage and adulteration risks

The pack as a protection

4) Chemical hazards

- This include external chemicals and gases
- The pack itself may interact with product. This interaction may be associated with absorption, adsorption, corrosion, erosion, contamination, whereby ingredients may be lost or gained.
- Such changes may be identified as organoleptic changes, increase in toxicity, degradation, precipitation, turbidity, pH shift etc.

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Pack selection

Factors influencing choice of pack

1) The nature of the product itself (chemical activity, sensitivity to moisture and oxygen, compatibility with packing material)

2) The dosage form

3) Method of administering the medication

4) The type of patient (baby, child, teenager, adult, elderly etc)

5) The market
   - where the product may be used (clinic, hospital, home)?
   - By whom it is used or administered?
   - For home sale or for export?
   - The price
   - The distribution system

6) Required shelf life

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Packaging materials

Glass

- Glass containers are particularly useful for liquid preparations owing to their rigidity and superior protection properties.
- Glass can be colored to be amber or green for light protection.

Glass containers

- Bottles
- Dropper bottles
- Jars
- Containers for parenteral use

Packaging materials

Advantages of glass containers

- Transparent
- Chemically inert
- Superior protection properties
- Easily cleaned without damage
- Proper glass can be selected by changing constituents

Disadvantages

- Brittle and heavy
- They crack when subjected to sudden change in temperature

Packaging materials

Types of glass for pharmaceutical use

Various types of glass are used for pharmaceutical purposes:

Type I-Borosilicate glass (Neutral glass)

- The most inert type of pharmaceutical glass
- Lowest coefficient of thermal expansion (less danger of cracking with sudden temperature change
- Expensive
- Uses:
  - It is widely used for glass ampoules and vials
  - for package of solutions which could dissolve basic oxides in the glass

Type II- surface treated soda-lime glass

- Made by treating the hot surface of type-III glass with sulfur dioxide, ammonium sulfate or ammonium chloride. This neutralizes some of the surface of alkali radicals.
- cheaper than type I

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Packaging materials

Types of glass for pharmaceutical use

Type III-Soda lime glass

- It has the same composition as type-II but contains more leachable oxides.
- This is the most widely used type where extraction of metal ions from glass is not critical to the product.
- It is suitable for packaging nonaqueous parenteral products and powder for injection.

Type IV- glass

- This is made of soda-lime silica glass with low hydrolytic resistance and so it is not guaranteed to have the same quality as type-III glass.
- It is suitable for packaging solid and semisolid preparations

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Packaging materials

Plastics

- Past years have seen a significant expansion in the use of plastics and they became the major packaging materials.

Advantages of plastics for packaging

- release few particles into the product
- flexible and not easily broken
- light in weight
- can be heat sealed easily
- easily molded into different shapes
- suitable for use as containers closures and secondary packages
- cheap

Packaging materials

Plastics

Disadvantages

- They are not chemically inert as type I glass
- some plastics are very heat sensitive
- They are not as impermeable to gases as glass
- They may posses an electrostatic charge which may attract particles
- Additives in the plastic are easily leached into the product
- Substances such as drug and preservatives may be absorbed or adsorbed by the plastic or it is possible that volatile constituents are lost by permeation through it.

Plastic Packaging materials

The most economic four types are:

1) Polyethylene

- This is used as high (HDPE) and low (LDPE) density polyethylene
- LDPE is usually the preferred plastic for squeeze bottles because it is softer , more flexible and more easily stretched than HDPE.
- HDPE is widely used in bottles for solid dosage forms

<u>Disadvantages of polyethylene containers</u>

- They are softened by aromatic and flavoring oils
- They crack on contact with organic solvents
- They adsorb antimicrobial preservatives
- They are unsuitable for packing oxygen sensitive products due to high gas permeability

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Plastic Packaging materials

2) Polyvinyl chloride (PVC)

- This is extensively used as the main component of IV bags

3) Polypropylene

- It is used for tablet containers, IV bottles and for closures

4) Polystyrene

- It is hard with low impact resistance
- It is used in jars for ointments and creams

Less commonly used plastics include: nylon (PA), polyvinylidine chloride (PVDC), polycarbonate (PC), polytetrafluroethylene (PTFE) and polyester (PET).

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Plastic Packaging materials

Additives for plastic

Type	Purpose	Examples
Plasticizers	Enhance flexibility	Phthalates
Stabilizers	Retard degradation	Epoxy compounds
Antioxidants	Prevent oxidative degradation	Hindered phenolics (BHT)
Lubricants	Improve processability	polyethylene (PE) waxes
Antistatic agents	Minimize surface static charge	Quaternary ammonium compounds
UV absorbers	Enhance product protection	
Colorants		

Packaging materials

Paper and board

- Paper is rarely use on its own for primary packaging
- Uses of paper
  - Envelops used for dispensing powders, a few tablets or capsules on the counter.
  - leaflets
  - labels
  - Secondary packaging
  - Cartons and boxes for packing the pharmaceutical containers
- Properties of paper and board may be modified by laminating it with plastic, wax or other materials.

Packaging materials

Rubber

- The majority of rubber usage is related to the closure of sterile products
- The main types of rubber used for pharmaceutical products include:

  natural rubber, neoprene, nitrile, butyl, chlorobutyl, bromobutyl and silicone rubbers

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Packaging materials

Metals

- Metal containers are not very popular for pharmaceutical packaging because:
  - They may react with content
  - They are heavy
  - They are costly
- Collapsible tubes for creams, ointments, pastes etc. are made of tin or aluminum. They may be laminated with plastic if necessary
- Rigid metal containers made of tin or aluminum are mainly used in pressurized packs
- Aluminum foil, laminated with plastic, is used in sachets, strip and blister packaging
- Aluminum foil provides superior protection properties than plastic. However plastic layer helps better sealing

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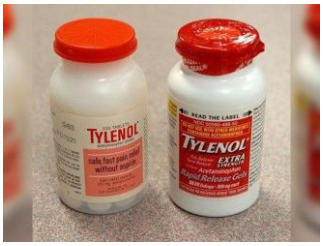
Closures

- Any closure system should provide an effective seal to retain the container contents and exclude external contaminants
- Child-resistant containers (CRCs) are provided with specially designed closure.
- Closures of tamper-evident containers indicate if the product has been opened.
- Closure can be of three types according to closing way:
  - Screw caps
  - Push over
  - Plug in

Threaded Screw cap closure



Push over

Plug in

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Closures

Requirements of closure

- To be compatible with the product
- To be readily openable and effectively sealed
- to be of suitable shape that agree with the container
- To offer additional functions as necessary- to aid in pouring, metering, administration, child resistance, tamper evidence etc.

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Determination of closure efficiency

- Closure efficiency can be determined by numerous methods:

1. placing a desiccant in a pack stored under high RH and detecting any moisture gain.

2. Putting liquid inside the pack , storing under high temperature and low RH, and then detecting any moisture loss as a reduction in weight.

3. Holding the empty pack under water (with dye), applying a vacuum and observing for leakage or liquid ingress.

4. Putting liquid in the pack, inverting and applying a vacuum.

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Materials used for the construction of closures

Cork

- It is a wood obtained from the bark of oak tree

Plastics

- They are becoming more popular

Rubber

- Either synthetic or natural
- Synthetic types are better than natural

Metals

- Tin plate and aluminum are used

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Classification of containers according to their shapes

1) Bottles
2) Dropper bottles
3) Collapsible tubes
4) Jars
5) Cardboard boxes
6) Ampoules
7) Vials
8) Plastic bags for intravenous fluids
9) Bottles for intravenous fluids
10) Aerosol containers
11) Strips
12) Blisters

Classification of containers according to their shapes

Semisolids

Collapsible tubes

Eye/ear/nose drops

Dropper bottle

Classification of containers according to their shapes

Containers for parenteral preparations

Glass bottle

Plastic bag

Vial

Ampoules

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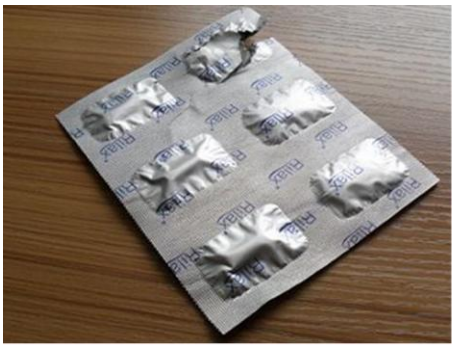
Classification of containers according to their shapes



Strip

Blister

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BLISTER PACKAGING

- This type, for solid dosage forms, involves forming a heat-softened plastic film into or around a deep-drawn, pocketed mold to make a plastic tray (thermoforming), filling with a solid dosage-form product and sealing with covering.
- The forming film, covering, and product must flow at the right rates without sticking.
- Appropriate heat and pressure must be applied to ensure that permanent sealing will be formed that will protect the product

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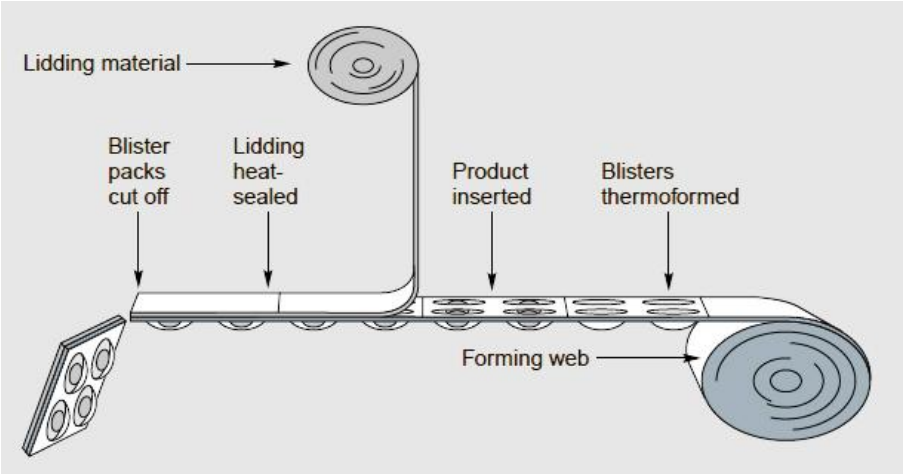

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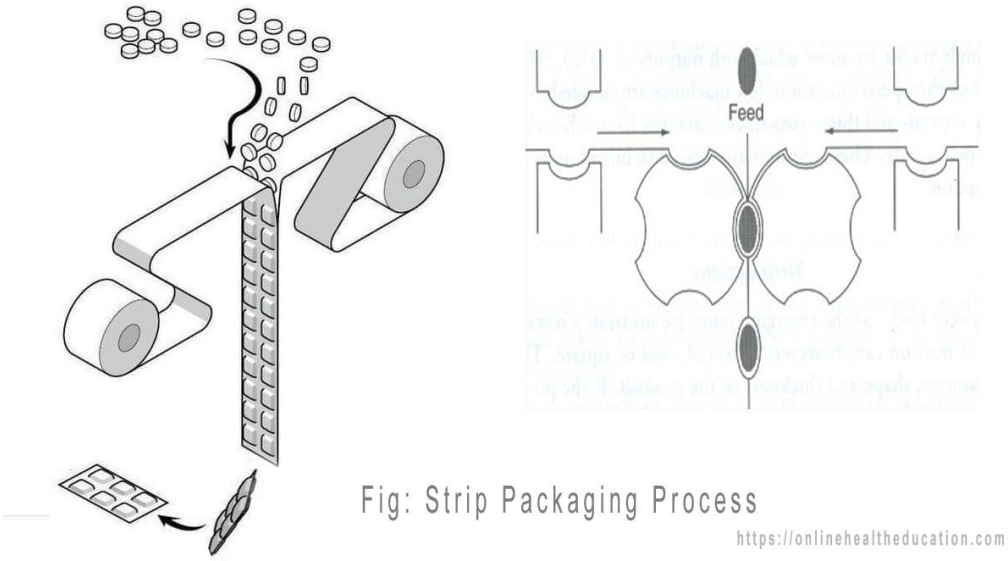

Fig: Strip Packaging Process

https://onlinehealtheducation.com

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QUALITY CONTROL OF PACKAGING

- Quality control tests are available for packaging material and containers.
- Based on these tests, the packaging material may be passed or rejected.
- **Examples on QC tests:**
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  - Physical/Mechanical tests
    - Physical inspection (color, defects, …)
    - Dimensional examination
    - Mechanical strength
  - Functional examination
    - Vapor permeability tests
    - Leakage tests
    - Adsorption tests

Analytical/Chemical tests

- Identification
- Impurities
- Glass neutrality
- light transmission of glass
- heavy metals in glass or plastics

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QUALITY CONTROL OF PACKAGING

- The principle instrumental techniques employed for applied packaging control are:
  A. Spectrophotometry
  B. Chromatography methods
  C. Thermal analysis techniques
  D. Physical test methods
  E. Gas transmission analysis: Instruments are available for measuring:
  - oxygen,
  - water vapor,
  - carbon dioxide and
  - ethylene oxide permeability

  through sheet materials and complete package.

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QUALITY CONTROL OF PACKAGING

Identification

- Identification of plastic containers is performed normally by FTIR spectroscopy.
- The spectrum of sample should exhibit major absorption bands at the same wavelengths as reference standard.

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QUALITY CONTROL OF PACKAGING

Glass neutrality (The Glass Grains Test)

1. A glass container is first crushed and sieved to get a sample of a uniform particle size.
2. A specified amount of sample is taken for further testing.
3. Crushed glass with uniform particle size is selected for the test as it will allow a constant surface area to be exposed to the solution.
4. Water is then added to the crushed glass present in a resistant glass beaker.
5. It is then autoclaved at 121 C for 30 min. The solution is then allowed to cool and filter for further processing.
6. Finally, the filtrate is titrated with standardized H_2SO_4

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QUALITY CONTROL OF PACKAGING

Light transmission

Apparatus

- UV-Vis spectrophotometer equipped with either a photodiode detector or a photomultiplier tube coupled with an integrating sphere.

Sample Preparation:

- Break or cut the container using a suitable tool.
- Select representative sections of the wall thickness and trim them appropriately for mounting in the spectrophotometer.
- Wash and dry each specimen carefully to avoid scratching the surfaces.
- Place in the holder.

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QUALITY CONTROL OF PACKAGING

Light transmission

Method:

- Measure the transmission of the specimen with reference to air in the spectral region of 290–450 nm.

Limits:

- For containers used for products for nonparenteral use, the observed spectral transmission should not exceed 10% at any wavelength in the range of 290–450 nm

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QUALITY CONTROL OF PACKAGING

Water Vapor Permeability Test

- Five containers are filled with a nominal amount of water and then sealed.
- Each container is then allowed to stand at a relative humidity of 20% at 25C for 14 days.
- Reweigh each container after 14 days.
- Calculate the loss of weight that must not be more than 0.2%.

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QUALITY CONTROL OF PACKAGING

Leakage Test Methods

- **High-Voltage Leak Detection (HVLD):**
  - Measures electrical conductance to detect leaks in nonporous packages with liquid products.
  - Requires electrically nonconductive package components and electrically conductive products.
- **Laser-Based Gas Headspace Analysis:**
  - Uses near-IR diode laser to analyze gas composition in packages.
  - Suitable for packages requiring specific gas content (e.g., low oxygen or low pressure).

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QUALITY CONTROL OF PACKAGING

Leakage Test Methods

- **Laser-Based Gas Headspace Analysis:**

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QUALITY CONTROL OF PACKAGING

Leakage Test Methods

- **Pressure Decay:**
  - Increase pressure inside the package and monitors pressure decay in the package to detect leaks.

- **Vacuum Decay Leak Test:**
  - Quantitatively detects leaks using vacuum outside the package and monitoring pressure rise.

QUALITY CONTROL OF PACKAGING

Leakage Test Methods

- **Tracer Gas Detection (Vacuum Mode):**
  - Uses tracer gases like helium to detect leaks in nonporous packages.
  - Suitable for rigid or flexible packages with tracer gas introduction before final closure.
- **Bubble Emission Leak Test:**
  - Leaks are detected as bubbles emitted from the leak site when submerged in water or coated with surfactant.
  - Two approaches are commonly used:
    - internal pressurization method
    - submersion in a vacuum chamber

QUALITY CONTROL OF PACKAGING

Leakage Test Methods

- **Microbial Challenge (Immersion Exposure):**
  - Test samples are filled with sterile, growth-supporting media, followed by incubation and visual inspection of samples to ensure sample sterility before microbial challenge.
  - Samples are then immersed in a concentrated bacterial suspension for a predetermined time.
  - Samples can be exposed during immersion to a vacuum.
  - Samples are then incubated under growth-promoting conditions, followed by examination of package contents for evidence of microbial growth.

  ➢ **Disadvantage**: Long procedure

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QUALITY CONTROL OF PACKAGING

Leakage Test Methods

- **Tracer liquid**
  - Tracer liquid tests are a method used to detect leaks in nonporous packages using a liquid with tracer elements such as dyes
  - These tracer elements help in detecting leaks by diffusing through leak paths or effusing from the package.
  - Tracer liquid tests are suitable for rigid or flexible nonporous packages that can tolerate wetting or submersion.
  - They are commonly used for laboratory or off-line testing at various stages of the product life cycle.
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QUALITY CONTROL OF PACKAGING

Leakage Test Methods

- **Tracer liquid**
- There are two main approaches to tracer liquid testing:
  - Submerging test samples in tracer liquid for visual inspection: This approach involves directly submerging the test samples in tracer liquid and visually inspecting them for tracer.
  - Submerging tracer-filled samples in tracer-free liquid for analysis outside the sample: In this approach, the test samples are filled with tracer liquid, submerged in tracer-free liquid, and then analyzed outside the sample for tracer.
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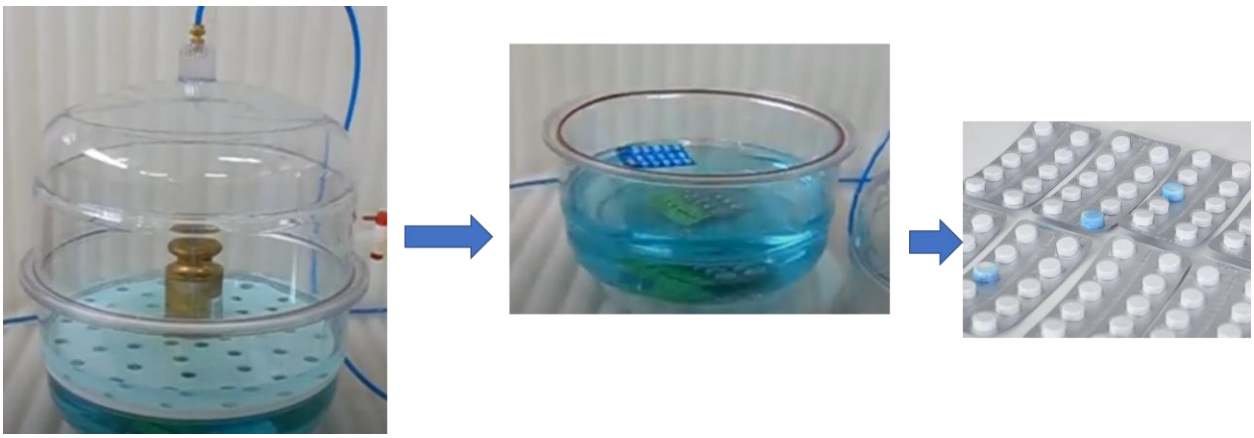
Leakage Test Methods



CODING IN PHARMACEUTICAL PACKAGING

- Coding became important in pharmaceutical packaging for regulatory compliance.
- Online coding has improved with better programming features, offering options like laser coding or inkjet coding for marking on metal surfaces.
- Coding includes one-dimensional, two-dimensional, and Quartile (QS) two-dimensional codes.

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CODING IN PHARMACEUTICAL PACKAGING

- Coding helps in anticounterfeit efforts by ensuring product authenticity and preventing unauthorized reproduction of branded products.
- Variable data on labels improves traceability and helps combat counterfeiting by creating unique markings on packaging materials, often achieved through digital printing.
- Using technology for coding is cost-effective and supports producing short-run packages on demand, enhancing efficiency in pharmaceutical packaging processes.

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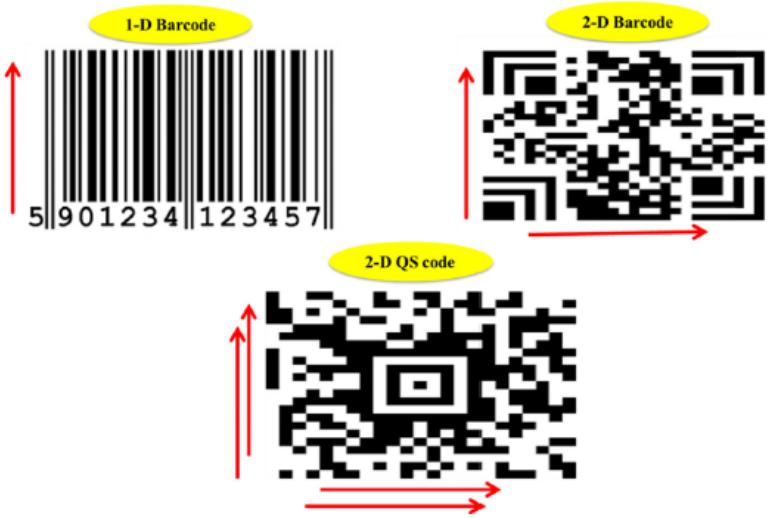

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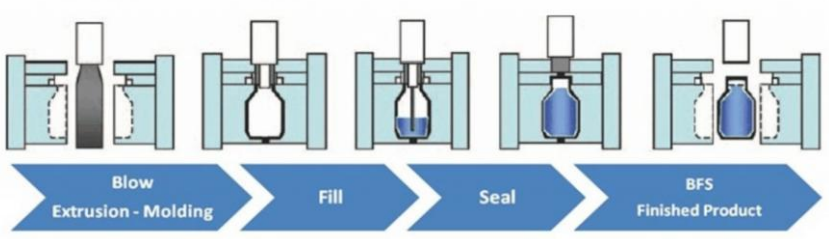
Blow-Fill-Seal (BFS) technology

- Blow-Fill-Seal (BFS) technology is an aseptic manufacturing process that integrates forming, filling, and sealing of containers in a controlled sterile environment.
- BFS technology uses a single machine to form plastic containers, fill them with sterile filtered product, and seal them in a sterile environment.
- This integrated process reduces the risk of contamination and ensures sterility.



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Blow-Fill-Seal (BFS) technology

- BFS technology is recognized and accepted by regulatory authorities globally for its robustness and advanced aseptic capabilities.
- The process provides a high degree of assurance for sterility, which is crucial in pharmaceutical and healthcare applications.
- BFS technology offers cost advantages due to its efficiency, requiring fewer personnel for operation and maintenance and minimal space requirements.
- Commonly used polymers in BFS technology include polyethylene and polypropylene of varying densities, offering versatility in container material selection.

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