



RECENT TRENDS AND FUTURE OF PHARMACEUTICAL PACKAGING TECHNOLOGY: AN OVERVIEW

Shubam Sehgal*, Tanvay Jaithliya, Mohd Shabaz Khan, Abujam Nganthoi Devi, Jahan Banoo and Atul Tiwari¹

*Faculty of Pharmaceutical Sciences, Mewar University, Chittorgarh, 312901, India.

¹Assistant Professor, Faculty of Pharmaceutical Sciences, Mewar University, Chittorgarh.

***Corresponding Author: Shubam Sehgal**

Faculty of Pharmaceutical Sciences, Mewar University, Chittorgarh, 312901, India.

Article Received on 19/03/2018

Article Revised on 09/04/2018

Article Accepted on 30/04/2018

ABSTRACT

Packaging pharmaceutical products is a broad, encompassing, and multi-faceted task. Generally packaging plays several important roles like Containment, Protection, Presentation and information, Identification, Convenience. Packaging is the science, art and technology of enclosing or protecting products for distribution, storage, sale and use. Packaging is responsible for providing life-saving drugs, medical devices, medical treatments, and new products like medical nutritionals (nutraceuticals) in every imaginable dosage form to deliver every type of supplement, poultice, liquid, solid, powder, suspension, or drop to people the world over. There are several materials which are used to pack pharma products like glass, plastic, polymers, papers, etc. nowadays there is a latest technologies which plays important role in packaging are Blow-Fill-Seal (BFS) Technology and Anti-Counterfeit Packaging Technologies. This project focus on packaging, material uses and latest technology infield of packaging.

KEYWORDS: Packaging, Blow-Fill-Seal, Anti-Counterfeit Packaging Technologies, polymers, etc.

INTRODUCTION

Packaging is the science, art and technology of enclosing or protecting products for distribution, storage, sale and use. Packaging is defined as the collection of different components which surround the pharmaceutical product from the time of production until its use. Packaging pharmaceutical products is a broad, encompassing, and multi-faceted task.

Packaging is responsible for providing life-saving drugs, medical devices, medical treatments, and new products like medical nutritionals (nutraceuticals) in every imaginable dosage form to deliver every type of supplement, poultice, liquid, solid, powder, suspension, or drop to people the world over. It is transparent to the end user when done well and is open to criticism from all quarters when done poorly.^[1,2]

Distribution of products is now more global than ever. Mass customization of packaging to permit its use in multiple markets is a topic that needs exposition and discussion. Environmental issues, including sustainability, will always be a subjective dimension to any packaging design. Packaging is an emerging science, an emerging engineering discipline, and a success contributor to pharmaceutical industries. Packaging can reside, or report through research and development (R and D), engineering, operations, purchasing, marketing,

or the general administrative department of a company. For the majority of products produced in pharmaceutical industries it is probably the single largest aggregate purchase made by a company of materials critical to the protection, distribution, and deal of the product.

Pharmaceutical packaging / drug packaging)

It is the packages and the packaging processes for pharmaceutical preparations. It involves all of the operations from production through distribution channels to the end consumer. Pharmaceutical packaging is highly regulated but with some variation in the details, depending on the country of origin or the region. Several common factors can include: assurance of patient safety, assurance of the efficacy of the drug through the intended shelf life, uniformity of the drug through different production lots, thorough documentation of all materials and processes, control of possible migration of packaging components into the drug, control of degradation of the drug by oxygen, moisture, heat, etc., prevention of microbial contamination, sterility, etc. Packaging is often involved in dispensing, dosing, and use of the pharmaceutical product. Communication of proper use and cautionary labels are also regulated. Packaging is an integral part of pharmaceutical product.^[3,4]

Functions of Pharmaceutical Packaging

Containment

The containment of the product is the most important function of packaging for medicinal products. The design of good packaging must take into account both the needs of the product and of the manufacturing and distribution system. This requires the packaging: not to leak, nor allow diffusion and permeation of the product, to be strong enough to hold the contents when subjected to normal handling and not be altered by the ingredients of the formulation in its final dosage form.^[5]

Product Protection

Packaging protect the contents of product from spoilage, leakage, etc.

Presentation and information

Packaging is also an essential source of information on medicinal products. Such information is provided by labels and package inserts for patients.

Product Identification

Packaging greatly helps in identification of products.

Facilitating the use of Product

Packaging should be convenient to open, handle and use for the consumers.

Categories of Pharmaceutical Packaging

Primary packaging: is the material that first envelops the product and hold it. i.e., those package components and subcomponents that actually come in contact with the product, or those that may have a direct effect on the product shelf life e.g., ampoules and vials, prefilled syringes, IV containers, etc.^[6]

Secondary packaging

is outside the primary packaging and used to group primary packages together. e.g. cartons, boxes, shipping containers, injection trays, etc.

Tertiary packaging

is used for bulk handling and shipping e.g., barrel, container, edge protectors, etc.

Table 3.1 Types of primary and secondary packaging material.^[7]

Material	Type	Example of use
Glass	Primary	Metric medical bottle, ampoule, vial
Plastic	Primary	Ampoule, vial, infusion fluid container, dropper bottle
	Secondary	Wrapper to contain primary pack
Cardboard	Secondary	Box to contain primary pack
Paper	Secondary	Labels, patient information leaflet

Materials used for Pharmaceutical Packaging

Following materials are commonly used in packaging of pharmaceutical products i.e., Glass, Rubbers, Metals, Jute, Paper / cardboard, Plastic, Wood and Bubble wrap.^[9]

Paper and Cardboards

Paper and Cardboards are suitable for small scale and bulk packaging, also suitable for all kinds of food packaging.

ADVANTAGE

1. Light weight
2. Less expensive and Easily available
3. Cardboard cartons have high shock resistant capacity Flexible and Easily molded

- #### DISADVANTAGE
1. May cause damage on transportation without external barriers
 2. Most paper packs are not reusable.

Plastic

Plastics are group of substance of nature or synthetic origin, consisting chiefly of the polymers of high molecular weight that can be molded into a shape by means of heat and pressure.

ADVANTAGE

1. Less weight than glass
2. Flexible
3. Resistant to breakage
4. Chemically inert, safe in use

DISADVANTAGE

1. Absorption permeability to moisture.

Metal

Metals are used for preparation of containers. The metals commonly used are aluminum, tin plated steel, stainless steel, tin and lead.

ADVANTAGE

1. Impermeable to light, moisture and gas
2. Rigid and Unbreakable
3. Label can be printed directly onto the surface

DISADVANTAGE

1. Expensive

Rubber

Rubber is mainly used for construction of closures for vials, transfusion fluid bottles, dropping bottles and for many other type of products.

Types of Rubbers

1. Butyl Rubber
2. Nitrile Rubber
3. Neoprene rubber
4. Silicon Rubber

Recent Packaging Technologies

Blow-fill-seal technology

Blow-Fill-Seal technology is a technique used to manufacture liquid-filled polymer containers as small volume (0.1mL to 99mL) as well as large volume (100mL and above). The technology is advanced in

Europe and has significant demand in Europe followed by North America. The technique has relatively high use in the pharmaceutical market to fill the parental preparation with comparatively less intervention of human being. The technology is considered as a superior method for aseptic filling of parental preparation by various regulatory bodies such as the U.S. Food and Drug Administration (FDA). Blow-Fill-Seal (BFS) technology is used in filling of eye drops, infusions, inhalation, and other parental preparations.^[10] Aseptic blow-fill-seal (BFS) technology is the process by which plastic containers are formed, filled with sterile filtered product and sealed in an uninterrupted sequence of operations within the controlled sterile environment of a single machine.^[11,12]

Blow-Fill-Seal (BFS) Technology Market: Dynamics

The major factor driving the market of Blow-Fill-Seal (BFS) technology is increasing the pharmaceutical market and packaging market. Other factors driving the market of Blow-Fill-Seal (BFS) technology are convenient packaging, innovation in pharmaceutical packaging, increasing demand for a qualitative technique for filling parental preparation, etc. The availability of a wide range of innovative packaging solutions is likely to have a significant influence on the demand for Blow-Fill-Seal (BFS) technology market during the forecast period. The Blow-Fill-Seal (BFS) technology require a relatively high cost for preparation which leads to increasing price of final product. Considering this factors, the final price of the product will increase, which will be a restraining factor for the Blow-Fill-Seal (BFS) technology market. The key trends in Blow-Fill-Seal (BFS) technology market are rising demand for aseptic packaging and regulations over the packaging of pharmaceutical products. The company manufacturing this technology have significantly high opportunity in regions such as Asia Pacific, Europe, and Latin America as in these regions the pharmaceutical industry and packaging industry is in its growth phase which will lead to the growth of Blow-Fill-Seal (BFS) technology market.

Blow-Fill-Seal (BFS) Technology Market: Segmentation

Basically, Blow-Fill-Seal (BFS) technology market is segmented by the specification, by application, and by region. The global Blow-Fill-Seal (BFS) technology market is segmented on the basis of application into pharmaceuticals and others. Pharmaceuticals segment has the significantly high market share with substantial growth rate. As Blow-Fill-Seal (BFS) technology is now-a-days particularly used for parental preparation filling as the technology helps to fill the preparation with minimum contamination, therefore, pharmaceutical segment occupies principal market share.

Based on specification, the global Blow-Fill-Seal (BFS) technology market is segmented into

- Small Volume (1mL-99mL)

- Large Volume (100mL and Above)

Based on application, the global Blow-Fill-Seal (BFS) technology market is segmented into

- Pharmaceuticals
- Others

Blow-Fill-Seal (BFS) Technology Market: Regional overview

On the basis of region Blow-Fill-Seal (BFS) technology market is segmented as North America's Blow-Fill-Seal (BFS) technology market, Latin America's Blow-Fill-Seal (BFS) technology market, Europe's Blow-Fill-Seal (BFS) technology market, Asia-Pacific's Blow-Fill-Seal (BFS) technology market, and Middle East & Africa's Blow-Fill-Seal (BFS) technology market. The Blow-Fill-Seal (BFS) technology market has significantly high market in Europe followed by North America. Whereas, the growth rate is relatively high in Asia-Pacific Blow-Fill-Seal (BFS) technology market, Latin America Blow-Fill-Seal (BFS) technology market, and Middle East Africa Blow-Fill-Seal (BFS) technology market.

Advantages of BFS Technology

BFS technology offers considerable advantages over conventional aseptic filling of preformed (plastic or other) containers, which are described as follows.^[13]

1. BFS technology reduces personnel intervention making it a more robust method for the aseptic preparation of sterile pharmaceuticals.
2. There is no need to purchase and stock a range of prefabricated containers and their closures. Bulk containers of plastic are required.
3. Cleaning and sterilization of prefabricated containers and closures is not required. A clean, sterile container is made within the BFS machine as it is required for filling.
4. The cost of material transport, storage and inventory control is reduced.
5. Validation requirements are reduced.
6. The technology allows the design of high-quality, custom-designed containers with tamper-evident closures in a variety of shapes and sizes.

Blow-fill-seal technology has gained much market focus in recent years due to the increased focus on biologics, proteins and other complex solutions. These important products often cannot withstand exposure to high temperatures for extended periods of time without degradation of their active components. Conventional terminal sterilization, therefore, is not an acceptable method to produce a 'sterile' product. Bulk sterilization, sterilization by gamma irradiation or filter sterilization followed by direct packaging utilizing the blow-fill-seal process are often used successfully for these types of products.

Anti-Counterfeit Packaging Technologies

Counter-feiting means producing products and packaging similar to the originals and selling the fake as authentic

products. Counterfeit is a problem of product security, with reference to packaging is not a problem in isolation; it is the part along with;

Duplication - i.e., copying labels, packaging, products, instructions and usage information.

Substitution - placing inferior products in authentic or reused packaging,

Tampering - by altering packages/labels and using spiked, pilfered, or stolen goods in place as real, Returns and Warranty frauds they are addressed as Brand Theft.

Anti-Counterfeiting Technology Solutions

The current numbers of anti-counterfeiting solutions are many and new options are introduced in the market with some variations. An attempt is made to explain the technologies for easy understanding on product packaging.

Overt (visible) features

Overt features are intended to enable end users to verify the authenticity of a pack. Such features will normally be prominently visible, and difficult or expensive to reproduce. They also require utmost security in supply, handling and disposal procedures to avoid unauthorized diversion. They are designed to be applied in such a way that they cannot be reused or removed without being defaced or causing damage to the pack for this reason an overt device might be incorporated within a tamper evident feature for added security.

Tamper evident packaging systems

Some packages are inherently tamper proof, like a tin can hermetically sealed, an aseptically packed multilayer carton or a vacuum pack. The tamper evident packaging systems are:

a) Film wrappers: A transparent film with a distinctive design is wrapped securely around a product or product container. The film must be cut or torn to open the container and remove the product. Substrates options include ultra-destructible films, voidable films that provides image when removed.
e.g. Solvent sensitive papers.

b) Shrink seals and bands: Bands or wrappers with a distinctive design are shrunk by heat or drying to seal the cap and container union. The seal must be cut or torn to remove the product.

c) Breakable caps: Such caps break when an attempt is made to open it. These caps provide external tamper evidence and can also be combined with the internal seals thereby providing double security.

d) Sealed tubes: The mouth of the tube is sealed, and the seal must be punctured to obtain the product.

Covert (hidden) features

The purpose of a covert feature is to enable the brand owner to identify counterfeited product. The general public will not be aware of its presence nor have the means to verify it. A covert feature should not be easy to detect or copy without specialist knowledge, and their details must be controlled on a “need to know” basis. If compromised or publicized, most covert features will lose some if not all of their security value [Figure 1].

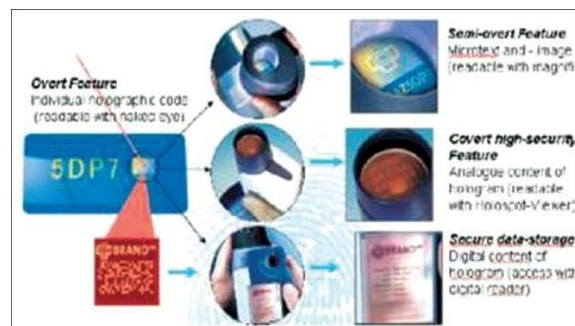


Figure 1. Covert (hidden) features.

RFID

Radio frequency identification (RFID) is hardly a new concept. For some, RFID is already a mainstream technology-it is used every day to pay tolls, secure building access, catch shop lifters etc. It allows the identification of objects through a wireless communications in a fixed frequency band. Three essential components in any RFID system are: the tag, the reader and the software. The tag is an integrated circuit containing a unique tracking identifier, called an electronic product code (EPC), which is transmitted via E.M. waves in the radio spectrum. The reader captures the transmitted signal and provides the network connectivity between tag data and the system software. The software can be tailor made for the purpose of anti-counterfeiting. For their track and trace usage, RFID tags are used [Figure 2].



Figure 2. Radio frequency identification.

a) Passive tag: When RFID tag is within the interrogation zone of the reader (i.e., interrogator) equipment; sufficient power is extracted from the interrogator to power up the tag or circuit, or a special reflective material. It then responds by transmitting data back to the interrogator.

b) Active tag: Such tags incorporate a battery to increase range for collating data, tag to tag communication, etc., But these are much more expensive.

c) Semi-active tag: In these tags batteries are used to back up the memory and data, but not to boost the range. With some active RFID tags, the batteries are only used when interrogated or when sending a homing pulse at fixed intervals to reduce cost and size.

Packaging designs: Materials/Substrates and other design options

a) Substrates: There are several variety of substrates used in the design of packages with intent to provide counterfeit and tamper evident features starting from litho paper, polystyrenes, destructive vinyl's, acetate films synthetic paper and coatings etc., There are many ways of incorporating covert markers within a substrate, such as visible or UV fluorescing fibers, or chemical reagents in carton board or paper. Watermarks can be embedded in leaflet paper, or metallic threads interwoven in the base material, possibly including an overt optically variable devices (OVD) feature. These require a dedicated supply source and large volume production, which, if affordable, results in a very effective option. Micro-encapsulated distinctive odors can be applied as an additive to an ink or coating to provide a novel covert or semi-overt feature, as well as sound chips creates special opportunities in the design.

b) Packaging designs: Packaging designs like sealed cartons, aerosol containers have inherent strength against counterfeiting.

c) Sealing systems: Special caps such as the outer tamper evident system or the foil seal as an internal tamper evident feature are commonly used for pharmaceutical products. Sealing options are lever-lidded tins, secure packaging tapes, lined cartons and tear tapes/bands.

Security labels

Tamper evident and security labels play an important role in providing some relief to the consumers against fakes. In self-adhesive labels the substrate mostly performs as a complimentary interaction of the substrate and the pressure sensitive adhesive. While passive security labels have been extensively used, today one can find a greater application of functional labels such as printing plus anti-theft. Some label options are:

a) Paper labels with security cuts: The substrate used for these labels is ordinary coated/uncoated paper. The security features are built in by the label printer at the converting stage. With the help of a special cutting die, the face material is given cuts at various angles so that by any ways one tries to remove these labels the paper will tear off. A general purpose permanent

adhesive works fine with such labels. Care is taken to ensure that the adhesive will adhere well and firmly to the surface on which the label has to be applied.

b) Destructible labels: Needs a special substrate designed for the purpose. Most of the high-end applications use a specially made cellulose acetate film. The film is very intricately designed so that it has adequate strength to undergo conversion into label stocks in roll form. It is available both in clear and opaque formats and further converted into labels using aggressive pressure sensitive adhesives. The labels can be automatically dispensed on automatic label dispensers and when attempted to be removed, break-up into very small fragmented pieces. The cost effective vinyl have replaced acetate film. A combination of various synthetic polymers can be used to impart low inherent strength to the substrate.

c) Void labels and tapes: The most important of the tamper evident security labels and have text built into them. When as a self-adhesive label they are removed, they exhibit the word VOID both in the removed film and the adhesive layer left behind. These substrates gain importance as there can be customization built into the labels produced with it. One can use polyester or biaxially oriented polypropylene (BOPP) as face materials. Variety of colors, even metallization is possible. The text VOID could be replaced by the customers brand, emblem or a message, which would normally be invisible till the label is opened. Due to the versatility of things that can be done with the product, these label substrates have found widespread usage worldwide. The substrates can even be designed to work as tapes for the final outer corrugated cartons to prevent pilferage.

d) Self destructing paper label: The labels are very similar to destructible labels as mentioned earlier. In this case, the substrate used is of very weak strength paper of low grammage. The paper is also heavily loaded with fillers creating a weak and brittle paper. Labels made from such papers fragment into pieces when attempted to be removed. However, converting it is a very tricky issue when using these substrates due to the lack of strength. The papers are very difficult to source since most of the paper mills are trying to develop papers with very high strength.

e) Holographic labels: The labels form a very large and important part of the security label market and are an ideal choice for product authentication. The holographic foil that is an optically variable device is largely made using a polyester film base. The optical interaction of the holographic image and the human eye makes it ideal for brand promotion and security. These products reveal the holographic image when tilted in light. The image so revealed can be customized to the need of the brand owners to make the maximum impact. The hologram production involves development of complex origination

process and a lot of innovation to make it difficult for counterfeiters to duplicate. Many holograms are designed such that besides offering brand authentication they also have tamper evident properties. The top polyester layer has a special coating that if the hologram is attempted to be removed, the top layer peels off leaving the hologram behind on the product [Figure 3].



Figure 3. Holographic labels.

f) Multi layered labels: The face stock of the labels is laminates of different substrates depending on the requirement of the security label, which can be film to a film or film to paper or other coatings. The layers are designed such that on separation they either exhibit tamper evidence by way of a one layer getting fiber tear or by complete separation and exhibiting a design or message. The various layers are bonded together by adhesive or heat seal coatings depending on the requirement of the design of the label. The segment of substrates can be vast and can be designed to the requirements of the user and offering variants as per the imagination of the designer or producer.

g) Transfer labels: The substrate consists of either polyester or BOPP. The film has a release coat over which the matter is printed and then adhesive coated. Such labels when applied and peeled off, the clear top layer comes off leaving the printed matter behind. This can also be designed such that some printing is subsurface and remains behind and some printed matter is on the top and comes off with the top layer.

h) UV fibers in paper: Here the substrate is paper and the security is built in at the paper mill during the paper making process. UV light sensitive fibers are incorporated into the pulp and evenly distributed in the paper. When labels made from such paper are exposed to UV light, the fibers glow indicating the genuineness of the labels. The volumes required for these substrates have to be large enough to allow the paper mill to produce a batch full of pulp that would eventually be converted into paper for security labels. The color of the fibers can be selected as per the wish or need.

i) Security threads: Thin micronic threads are introduced in the substrates either at the label stock

making stage or they are separately built into two layers of paper laminated together. The threads can also be sensitive to UV light which will glow under UV light. e.g., currency notes.

j) Water mark: The mark that can be seen as an image in the paper when held against the light. The mark can also be built into the paper at the paper making stage in a paper mill. The volume has to be large enough to justify incorporating the markings in the paper making process. However, some converters do print these with inks where security requirements are not of a very strict nature.

Coding, printing and graphics

a) Coding and marking: For a long time, regulatory compliance drove the need for coding and marking on the packaged products starting with best before date. However, with an increasing awareness and greater printing and marking options like ink jet coding, laser coding and electrolytic etching for metal marking on can decide their use to evolve an overall anti-counterfeit feature. These provide the opportunities for online coding with flexibility, programmable options, time saving and low running costs. Depending on the exact requirements one can go for the touch dry contact coding, non-contact coding or the permanent laser coding etc. Traceability and counterfeiting measures can be improved by using a variable data on the labels i.e., to create unique marking of the packages, which can be made cost effective by using digital printing technology for producing on demand short run packed products.

b) Security graphics: Fine line color printing, similar to banknote printing, incorporating a range of overt and covert design elements such as guilloches, line modulation and line emboss. They may be used as background in a discrete zone such as an overprint area, or as complete pack graphics, and can be printed by normal offset lithography or for increased security by intaglio printing. Subtle use of pastel "spot" colors makes the design more difficult to scan and reproduce, and security is further enhanced by the incorporation of a range of covert design elements, such as micro-text and latent images.

Holograms

Holograms were used first for promotional purposes during 80's and exhibited a phenomenal growth by 1996. Probably the most familiar overt feature is the "dove" hologram which has been used to protect credit cards for many years. A hologram normally incorporates an image with some illusion of 3-dimensional construction, or of apparent depth and special separation. Holograms and similar optically variable devices (OVD) can be made more effective when incorporated in a tamper evident feature, or as an integral part of the primary pack (e.g., blister foil). They can be incorporated into tear bands in over wrap films, or as threads embedded into paper substrates and hence may be usefully employed on

secondary/transport packs. Several processes can be used to incorporate holograms into packaging; flexible, folding cartons or bottles. Methods include pressure sensitive, shrink, or glue applied labels, hot stamping, web transfer and lamination. Essentially selection options for the hologram are the image and media. The right combination of the two components produces a successful anti-counterfeiting marking that meets the desired objective.

a) Image choices: In the form of Parallax, 3-D perception, switching images, animated images, dynamic color effects, micro text, fine line patterns, machine readable image, hidden image readable through special reader.

b) Media or the form of delivery: The choices available are tamper evident, frangible, paper labels, induction wads, shrink sleeves, hot stamping foils, aluminum foils, PVC films, hologram tape/thread.

c) On-product marking: On-product marking technologies allow for special images or codes to be placed on conventional oral dosage forms. The overt technologies can be difficult to replicate and offer a security technology at the pill level. The added layer of security is effective even when products are separated from the original package.

d) Invisible printing: Using special inks, invisible markings can be printed on almost any substrate, and which only appear under certain conditions, such as via UV or IR illumination. They can be formulated to show different colors with illumination at different wavelengths.

e) Embedded image: An invisible image can be embedded within the pack graphics which can only be viewed using a special filter, and cannot be reproduced by normal scanning means. The effects can be quite dramatic, and yet well hidden.

f) Digital watermarks: Invisible data can be digitally encoded within graphics elements and verified by means of a reader and special software. The data can be captured using webcam, mobile phone or other scanning equipment, but the digital information is not visible to the human eye, and attempts to replicate it will be detected by virtue of the degradation of the embedded data.

g) Hidden marks and printing: Special marks and print may be applied in such a way that escapes attention and is not easy to copy. Their effectiveness relies on a combination of secrecy and subtlety.

h) Anti-copy or Anti-scan design: Fine line background patterns appear as uniform tones, but when scanned or copied reveal a latent image which was not

previously visible. Commonly used on secure documents to prevent photocopying, they may be applied to product packaging as a background tint.

i) Laser coding: The application of batch variable details by lasers coding requires special and expensive equipment, and results in recognizable artifacts which may be difficult to simulate. Laser codes can be applied to cartons and labels, and plastic and metal components.

Forensic markers

There is a wide range of high-technology solutions which require laboratory testing or dedicated field test kits to scientifically prove authenticity. These are strictly a sub-set of covert technologies, but the difference lies in the scientific methodology required for authentication.

a) Chemical taggants: Trace chemicals which can only be detected by highly specific reagent systems, but not normally detectable by conventional analysis.

b) Biological taggants: A biological marker can be incorporated at extremely low levels (parts per million or lower) in product formulations or coatings, or invisibly applied to packaging components. At such low levels they are undetectable by normal analytical methods, and require highly specific “lock and key” reagent kits to authenticate.

c) DNA taggants: Highly specific DNA “lock and key” reagent systems can be applied to packaging by a variety of printing methods. They require a “mirror image” recombinant strand to effect the pairing, and this reaction is detectable by a dedicated device. Security is further assured by hiding the marker and reagent pair in a matrix of random DNA strands, but the test is tuned to work only with one recombinant pair.

d) Isotope ratios: Naturally occurring isotopes are highly characteristic of the source compound, and accurately be determined by laser fluorescence or magnetic resonance techniques. They can provide a “fingerprint” of one or more of the product constituents, or alternatively a specific marker added with its own unique signature. Detection requires highly specialist laboratory equipment.

e) Micro-taggants: Micro-taggants are microscopic particles containing coded information to uniquely identify each variant by examination under a microscope. It may take the form of alphanumeric data depicted on small flakes or threads, or fragments of multicolored multilayered laminates with a signature color combination. These can be embedded into adhesives, or directly applied to packaging components as spots or threads.

f) Nano-Printing: The technologies allow microscopic application onto individual tablets. UV inks allow invisible printing onto any substrate including glass vials and ampoules and provide an excellent security.

Plasma Impulse Chemical Vapor Deposition

Plasma impulse chemical vapor deposition (PICVD) was

developed by Schott more than 10 years ago. It was the first CVD - based coating technology for the mass production of optical coatings on glass components (cold light mirrors, infrared reflective coatings and others). During the last few years, a modified PICVD-process for the deposition of three different functional coatings on plastics has been developed. The functions- anti-reflective, anti-scratch and easy-to clean layers- are provided by only one technology-PICVD. This is a major progress compared for instance to the standard production line of polymer based eyeglass lenses, which uses a PVD process for anti-reflective coating, dip coating for anti-scratch and plasma polymerization for easy-to-clean coatings. Moreover, the development was extended to different kinds of plastics including optical polymers like polymethylmethacrylate (PMMA) and polycarbonate (PC). The PICVD coating technologies were not capable of depositing durable functional coatings on PMMA with a sustained adhesion to the substrate. A completely new layer system on PMMA with an adapted adhesive layer has been developed for these coatings. Durability has been proven by passing different types of functionality tests like tape test, grid test, climate tests or temperature shock tests.^[14]

Materials can be Coated Using Plasma Impulse Chemical Vapor Deposition

Although developed 20 years ago by Schott Glass, PICVD has been very successful in coating high volume glass products, such as pharmaceutical vials, ampoules, syringes. To expand the application areas of PICVD into plastics Schott HiCotec was set up as a new division. Very quickly it succeeded in modifying the original PICVD process and applying bonded homogeneous coatings - in particular glass-like SiO and TiO oxide coatings to a broad range of plastics (e.g., PET, PMMA, PC, COC, PP and HDPE). The result is that plastic can now have all the positive properties of glass. In the case of plastic lenses and display covers it is now possible to produce anti-scratch and antireflective coatings, while in the case of plastics packaging, a PICVD coating creates a barrier against the passage of gas oxygen can no longer get in, and released carbon dioxide cannot get out. Consequently, the contents have a longer shelf life with no effect on their taste.^[15]

Prefilled Syringes

The use of prefilled syringes is a modern way to apply parenteral drugs. With the achievements in science and technology in the past twenty years an increasing number of injectables apply prefilled syringes. The benefits compared with vial/disposable syringe concepts are obviously convenience and ease of handling, as well as advantages in safety and a reduction of drug overfill. The currently existing market of prefilled syringes is in the range of US\$1-2 billion. The growth rate is to be expected to remain at a high level of more than 10% annually. In the future, the pharmaceutical and biotech industries will ask for prefillable drug delivery systems for valuable potent drugs. Particularly, for biologicals the

parenteral application will remain the most important route of application. The worldwide prefilled market is estimated to be one billion units.^[16]

Prefilled syringes in the US market have been growing at a rate of 20% per year for at least five years. Studies indicate that the majority of healthcare professionals are demanding the convenience and safety that prefilled syringes provide.^[17]

The primary driving factors behind the growth of prefilled syringes includes:

1. Ease of administration; more convenient for healthcare professionals and end users; easier for home use; easier in emergency situations.
2. Reduction of medication errors, misidentification; better dose accuracy.
3. Increased assurance of sterility.
4. Better use of controlled drugs such as narcotics.
5. Lower injection costs- less preparation, fewer materials, easy storage and disposal.
6. Elimination of vial overfills for products transferred to syringes for direct injection or addition to primary diluents.
7. Removal of preservatives (i.e., thimerosal) from vaccine formulations.
8. Product differentiation.

Today, prefills can be introduced at any point during a product's lifecycle to make it more desirable. Switching from vials to prefilled syringes, syringes to a nasal spray or a self injection system, prefills can work easily for products in development and those already on the market. At the same time, drug delivery systems must evolve and adapt to meet tomorrow's demands.

BD Medical-Pharmaceutical Systems markets a broad range of customizable, prefilled solutions for parental drug delivery such as BD Hypak PhysioliS™ glass prefilled syringe, BD Accuspray™, BD Sterifill TSCF™, BD Preventis™.^[18]

Safety Ampoule Breaker

Ampoules are small glass vessels in which liquids for injections are hermetically sealed. They are opened by snapping off the glass top at the neck. The scoring at the neck does not always break where it is intended. This is due to the glass remolding to some degree at the score line. When the cap is snapped off, glass chips can fly off and a jagged or sharp edge can cut the hands of the healthcare worker. Safer products exist removes the risk of broken glass cuts when breaking off the glass top. SafeBreak™ is a safety ampoule breaker and it avoids dangerous glass filing required during breaking the ampoule. No gauze pads necessary to protect hands. SafeBreak™ prevents cross contamination.

Snapit invented by a Registered Nurse in Rockhampton, QLD, Australia. Most people who work with ampoules have suffered an injury from breaking an ampoule.

Furthermore, the very sharp edge on both the ampoule and the ampoule lid when the neck of an ampoule is snapped off can cause serious cuts. Snapit reduces the risk of sustaining a sharps injury by keeping hands out of harms away.^[19]

Snap Off Ampoules

Ampoules are small glass vessels in which liquids for injections are hermetically sealed. A typical pharmaceutical ampoule has a narrow neck between a cylindrical body and a conical tip. Ampoule is a small, hermetically sealed glass or plastic container, e.g., one containing medication for parenteral administration. Snap off ampoule enables to break a piece from a whole ampoule. Hisafe™ ampoules are manufactured with pre-fragilized systems like SafeCut™ OPC ampoules or SafeBreak™ color ampoules for easy opening by doctors without cutter or filling. SafeCut™ ampoules open safely by using a predetermined breaking point to give a clean cut. SafeBreak™ ampoules come with color ring on its constriction which is used to open the ampoules easily by hand.^[20]

Two-In-One Prefilled Vials

The innovative tamper-evident design of new EZ Fusion two-in-one prefilled vials enables consumers to easily determine authenticity of the product. Two-in-one prefilled vial consists of top and bottom chambers made of polypropylene, an insulating spacer, a stopper and tin cap. Two-in-one vials enables consumers to easily determine authenticity of the product. There is less chance of contamination, and it provides a cost-effective solution versus traditional glass vials.

Two-in-one vial is a multi-chamber dispenser, which provides a closure solution for filling and separately packing the medication and water for injection, or for the compound injection packaging in a sterile vial. The mixture forms with a simple twist after removing the safety ring and flip-flopping the insulation spacer, then gently shaking the vial prior to usage.^[21]

Unit Dose Vials

A unit dose is the amount of a medication administered to a patient in a single dose. Unit-dose packaging is the packaging of a single dose in a non reusable container. It is increasingly used in hospitals, nursing homes, etc., Medications in unitdose packaging are easily identifiable and can be returned to the pharmacy if the medication is discontinued.^[22] Twist-Tip™ unit-dose vial incorporates a plastic squeeze-bulb with an integral twist-off tab. Once opened, the vial's contents can be dispensed through the opening by squeezing or pouring.^[23] Twist-Tip™ units are manufactured and filled by modified blow-fill-seal technology.

These unit dose vials are used in medical devices, oral health care, personal care products and cosmetics and veterinary.^[24]

Child-Resistant Packaging

Child-resistant packaging or CR packaging is special packaging used to reduce the risk of children ingesting hazardous materials. This is often accomplished by the use of a special safety cap. It is required by regulation for prescription drugs, over-the-counter medications, Nicotine Containing Electronic Cigarette devices or Refill containers that can contain Nicotine EUTPD 36.7^{[25][26][27]} pesticides, and household chemicals^[28] In some jurisdictions, *unit packaging* such as blister packs is also regulated for child safety.^[29]

The U.S. Consumer Product Safety Commission has stated in a press release that "There is no such thing as child-proof packaging. So you shouldn't think of packaging as your primary line of defense. Rather, you should think of packaging, even child-resistant packaging, as your last line of defense."^[30]

It is required by regulation for prescription drugs, over-the-counter medications, pesticides, and household chemicals. In some jurisdictions, unit packaging such as blister packs is also regulated for child safety. In developed countries like UK, it has been made compulsory to pack drugs like Aspirin, Paracetamol, Elemental iron, Contraceptives and many other drugs to be packed in CRP.

CONCLUSION

In the era of globalization, it would be a challenge for the packaging industry, as the years ahead would witness the opening of the global channels, and to match the international standards and quality, it is necessary that packaging industry upgrades more in research to have a holistic approach to packaging that would go beyond functional aspect of packaging. Presently, very few pharmaceutical industries spend time and money on R and D in packaging. The conventional packages available do not serve the purpose of providing protection against counterfeiting and quality, and the industry seems to be sluggish in adopting the technical advances in the packaging, probably on account of the prohibitive cost factor. As packaging industry is directly or indirectly involved in the drug manufacturing process, it becomes ethically mandatory to understand and incorporate scientific methods in packaging. The pharmaceutical packaging trends are on the verge of innovative rapid growth provided the needs of the product, its security, cost and patient convenience is taken into consideration to build brand identity.

REFERENCES

1. Jain UK, Nayak S. 1st ed. Hyderabad: Pharma Med Press; Pharmaceutical Packaging Technology; 2008; 1–273.
2. Carter SJ. Copper and Gunn's Packaging in tutorial pharmacy. 2005; 133–41.
3. Santoro, MIRM "Pharmaceutical Packaging". In Yam, K L. Encyclopedia of Packaging Technology. Wiley. ISBN 978-0-470-08704-6. 2009; 205-216.

4. Kunal, Mehta (July 2012). "Recent Trends in Pharmaceutical Packaging: A Review" (PDF). INTERNATIONAL JOURNAL OF PHARMACEUTICAL AND CHEMICAL SCIENCES. Retrieved 24 June 2011; 1(3): 1282–1292.
5. Edward JB. 1st ed. New York: Informa Healthcare; Pharmaceutical Packaging Handbook; 2009; 387–92.
6. Nityanand Zadbuke, Sadhana Shahi, [...], and Mahesh Thube Recent trends and future of pharmaceutical packaging technology.pdf
7. Manoj, Shekhawati College of Pharmacy, Dundlod <https://www.pharmatutor.org/articles/the-pharmaceutical-packaging-article>.
8. <https://www.pharmatutor.org/articles/the-pharmaceutical-packaging-article?page=1>.
9. <http://www.preservearticles.com/2011090212748/what-are-the-materials-used-for-packaging-pharmaceutical-products.html>.
10. Blow-Fill-Seal (BFS) Technology Market - Global Industry Analysis, Size, Share, Growth, Trends and Forecast REP ID: TMRGL15362 category packaging., 2016 – 2024.
11. Reed CH. Recent technical advancements in blow-fill-seal technology. Business Briefing: Pharmagenerics. 2002.
12. Ingelheim B. Aseptic production of pharmaceuticals in boehringer ingelheim using blow-fill- seal technology. Business Briefing: Pharmatech. 2003.
13. Nityanand Zadbuke, Sadhana Shahi, [...], and Mahesh Thube Recent trends and future of pharmaceutical packaging technology.pdf.
14. Kuhr S, Bauer U, Rothhaar D, Wolff Coatings on plastics with the PICVD technology. Thin Solid Films. 2003; 442: 107–16.
15. Plasma impulse chemical vapour deposition: A coating technique for plastic substrates. Mat World. 2003; 11: 13–5.
16. Becton Dickinson promotional literature, B01/D/ENG/02/US/FL-40
17. Polin JB. The Ins and Outs of Prefilled Syringes. Pharm Med Packaging News. 2003
18. On Drug Delivery. [Last accessed on 2011 Oct 19]. Available from: <http://www.ondrugdelivery.com>.
19. Safety ampoule breaker. [Last accessed on 2011 Oct 17]. Available
20. Hisafe Ampoules. [Last accessed on 2011 Oct 17]. Available
21. Two-in-one prefilled vial design provides innovation. [Last accessed on 2011 Oct 18]. Available from: http://www.healthcarepackaging.com/archives/2010/05/two-in-one_prefilled_vial_desi.php.
22. Unit dose. [Last accessed on 2011 Oct 18]. Available from: <http://>
23. Twist-Tip [Last accessed on 2011 Oct 18]. Available from: <http://www.unicep.com/11/twist-tip>.
24. Twist-Tip Product Uses. [Last accessed on 2011 Oct 18]. Available from: <http://www.unicep.com/42/product-uses>.
25. "The Tobacco and Related Products Regulations 2016". www.legislation.gov.uk.
26. Sanbar, Shafeek S. Legal medicine. Elsevier Health Sciences. ISBN 978-0- 323-03753-2. Retrieved 6 November 2010. 2007; 393.
27. Winter, Harold (2005-05-01). Trade-offs: an introduction to economic reasoning and social issues. University of Chicago Press 98. ISBN 978-0-226-90225-8. Retrieved 6 November 2010.
28. Gaunt, Michael J. (May 2007). "Child-resistant does not mean Childproof". Pharmacy Times. Retrieved 3 March 2009.
29. Smith, G; Barone, S (16 March 2005). "PPPA, Unit Packaging" (PDF). CPSC. Retrieved 25 March 2010.
30. "New National Emergency Hotline Assessed; CPSC Joins in Launching Poison Prevention Week to Stop 30 Deaths Each Year" (Press release). CPSC. Retrieved 26 March 2009.