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Review Article

INNOVATION IN PACKAGING: A REVIEW

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ABSTRACT

Packaging is the important unit operation for providing protection, presentation, identification, information, convenience, compliance and compatible unit, which maintain the integrity and stability of the product. Many advances have been made in packaging in order to increase protection from the harmful environmental conditions and to increase patient compliance. As the packaging industry continues to develop increasingly sophisticated concepts, big pharma is starting to embrace innovations in this field to improve patient adherence to drug regimens. It's no exaggeration to say improvements in this area of pharmaceutical packaging have the potential to improve treatment outcomes and even save lives. In the realm of patient compliance-patients taking their medication when they are supposed to take.

Key words: Packaging, Container, Closure, Carton, box, vial, pouches, label, inserts, paper, foil

INTRODUCTION

Packaging is the science, art and technology of enclosing or protecting product for distribution, storage, sale, and use. It also refers to the process of design, evaluation and fabrication of the packages.

Pharmaceutical packaging is a means for providing protection, presentation, identification, information, convenience, compliance and compatible unit, which

maintain the integrity and stability of the product.[1]

Importance:

→ Protect against all adverse external influences that can alter the properties of the product.

→ Protect against biological contamination.

→ Protect against physical damage.

→ Carry the correct information and identification of the product.

→ Tamper evident / Child resistance/ Anti counterfeiting.

Objectives:

- **Physical protection:** Package may require protection from other things, shock, vibration, compression, temperature etc.
- **Barrier protection:** A barrier from oxygen, water vapor and dust is required.
- **Containment or agglomeration:** Small dosages are typically grouped together in one package for reasons of efficient packaging and physical handling.
- **Information transmission**: Information on how to use, transports, recycle or dispose of the package or product is often contained on the package or label.
- **Marketing:** The packaging and the labels are used by marketers for the purpose of encouraging potential buyers to purchase the product.
- **Security:** Packages can be made with improved tamper resistance to determine tampering and also can have tampered evident features to help indicate tampering.
- **Convenience:** Packages can have features, which add convenience in distribution, handling, display, sale, opening, reclosing, use and reuse.[2, 3]

CRITERIA FOR THE SELECTION OF PACKAGE TYPE AND PACKAGE MATERIAL:

- Stability
- Compatibility with the contents
- Strength of container and the degree of protection required
- Moisture-proofness
- Resistance to corrosion by Acids or Alkalis
- Resistance to grease
- Protection against salt
- Resistance to microorganisms
- Resistance to insects and rodents
- Resistance to differences in temperature

- Protection against light, fire and pilferage
- Odor retention and transmission
- Aesthetic effect
- Cost
- Machine suitability of packaging and the filling method
- Convenience of the packaging for the physician, pharmacist and finally the patient (size, weight, method of opening/re-closing, legibility of printing)

TYPES OF PACKAGING:

1. **Primary packaging** material is the material that first envelops the product and holds it. These are package components and subcomponents that actually come in to contact with the product or those that may have a direct effect on the product shelf life.
   e.g., Glass bottles, jars Plastic bottles, Strip packs, Blister packs etc.
2. **Secondary packaging** material used externally over the primary pack which provides physical protection to ensure safe warehousing and mechanical protection required in shipment and transport.
   e.g., Paper drums, corrugated boxes, shipping containers etc.
3. **Tertiary packaging** is used for bulk handling and shipping.[4-6]
   e.g., slip sheet, Crate, Edge protector, Pallets, Stretch wrap etc.

Type of Materials	Use
Glass	Bottles, vials, ampoules, syringes, aerosol containers.
Plastic	Bottles, syringes, tubes, bags, laminates, pouches, lids, taps, stems, aerosol containers.
Rubbers	Closures, vial wrappers, caps, plungers.
Paper\cardboards	Labels, inserts, display units, pouches, laminates, cartons, boxes, foil, gum tapes, paper drums.
Metals	Collapsible tubes, foils, needles, aerosol containers, cans.

COMPONENTS OF PACKAGING:

a) **Container:** In which the product or medicine is placed and enclosed. It remains in direct contact with the drug.

b) **Closure:** It tightly packs the container to exclude oxygen, carbon dioxide, moisture and microbes and prevents

the loss of water and other volatile substances from the product.

c) **Carton\outer:** It is the outer covering, which gives secondary protection against mechanical and other environmental hazards and also serves for display of written information. The cartons are made up of cardboard, molded wood pulp and expanded polystyrene.

d) **Box:** In the box, multiples of the products are packed. It provides primary defense against external hazards and have shock absorbing features. They are made up of thick cardboard and wood.[7]

CHANGES AND TRENDS IN PACKAGING MATERIALS:

As changes to packaging material are relatively slow, the materials which might be considered of historical value are still in wide usage. This particularly applies to the use of glass and metal, which extends back over several centuries.

A slight reduction in the use of glass has occurred in recent years, and it is likely that this will continue as a slow downward trend. However, glass is generally seen as environmentally friendly, hence this trend could reverse.

Metal containers are showing a much more serious usage drop in terms of containers for tablets, capsules, ointments, granules, powders, etc., and even survival as collapsible metal tubes is doubtful with the advent of laminated tubes. Rigid aluminum containers, other than aerosol containers, showed a rapid drop in usage some 8-10 years ago, due to high costs, compared to glass and plastic. Also the conversion of bauxite to aluminum involves high energy levels.[8]

Although it has been accepted that not a single type of plastic can offer the inertness of glass, particularly with reference to retention of certain preservatives, flavors and active ingredients, it is relatively easy to find a plastic which is suitable for a specific product- occasionally with a slightly reduced shelf life. Under this category, various grades of PETP and PETG (polyester variants) are steadily growing in use. Since under normal handling polyester is much less prone to breakage and is lighter than glass, any cost premium can be readily offset. Polyesters generally show good retention of such volatile substances as menthol, camphor, esters of salicylic acid. Coated and multi-layer plastic containers offer further potential usage for liquid products. Silicon dioxide ('glass') coated plastics (SiO_2 coatings) are also of interest. These are being closely followed by carbon 'diamond-like' coatings.

Although recognized as plastics, the thermosets play only a minor role as a packaging material and it was not until around 1953 onwards, when the first thermoplastics were used as low density polythene squeeze packs, that the real plastic revolution began. In 1996, most economical five were most widely used. These include the:

- Polyethylenes (PE)—LDPE, MDPE, HOPE, LLDPE, ULDPE, VLDPE
- Polypropylenes (PP)—homopolymers and copolymers of polypropylene
- Polystyrenes (PS)—crystal and to some extent impact modified polystyrene
- Polyvinylchloride — unplasticized PVC and plasticized PVC
- Polyesters — PETP and PETG.

These materials cover a wide range of properties, e.g. a range of densities (0.9-1.45), are clear to very hazy, hard, brittle to flexible, some virtually unbreakable; from highly permeable to ones of low permeability (with reference to moisture, gases, solvents, etc.), relatively inert to only fair inertness, etc.[9]

The pharmaceutical industry is the perfect place for the packaging industry to show off some of its advanced technology. Chris Lo discovers how packaging concepts are helping patients to make the most of their prescriptions. In most industries, product packaging is a means of protecting and preserving items contained within, as well as communicating marketing and regulatory information to consumers. In the pharmaceutical industry, perhaps above all others, effective and intelligent packaging has the potential to do so much more.

Fig.1: Wireless packaging leverages cellular networks to track patient adherence data, allowing reminders to be sent by text

As the packaging industry continues to develop increasingly sophisticated concepts, big pharma is starting to embrace innovations in this field to improve patient adherence to drug regimens. It's no exaggeration to say improvements in this area of pharmaceutical packaging have the potential to improve treatment outcomes and even save lives.

Fig.2: Removal of pills is tracked and the information can be sent to an electronic database

The issue of patient adherence

Patient adherence, also known as compliance, is the extent to which patients stick with medication they have been prescribed. For national healthcare systems, the problem of non-compliance costs lives and billions in unnecessary hospital treatment, while pharma companies lose revenue from lapsed prescriptions.

The extent of the problem is well-documented; several studies, backed up by the World Health Organization, suggest that in developed countries, only around 50% of patients with chronic diseases take their medication as prescribed. These levels generally fall even lower in the developing world, with the poor disproportionately affected in both cases.

It has been estimated that 1,25,000 people die in the US each year as a result of failure to adhere to medication regimens, as well as costing the country's health system nearly $300 billion. Meanwhile the pharmaceutical industry reportedly loses around $8 billion a year from unfilled prescriptions.

New innovations in intelligent packaging are being developed to buck this trend, and pharmaceutical companies are increasingly making use of these new concepts as the costs of patient non-compliance become clearer.[10]

Fig.3: Packaging can now connect with computers using sensor technology

Electronic compliance monitoring: Information Mediary supplies battery operated electronic devices (Med-ic) in blister packs that can be customized to record unacceptable levels of temperature and other parameters during transit. Most importantly, this system can obtain useful information regarding patient compliance, without requiring the patient to do anything new, by recording when each tablet is removed.

Fig.4: Book-type blister pack with an electronic content monitoring system

Because this system is more expensive than the ribbon, it will not be deployed in large numbers of blister packs in the near future, but it should prove invaluable in trials to determine the efficacy of new medication and customized blister packs.

The US National Pharmaceutical Council estimates that patients' non-compliance with instructions on medication costs more than $100 billion annually in the US alone. Indeed, 11% of hospital admissions in the US were also attributed to non-compliance with the instructions on medication. According to Information Mediary, patients taking HIV medication correctly for 94% of the time, actually half their chance of suppressing the virus when compared with those taking their medication 100% correctly. This illustrates, how even minor mistakes in compliance can distort the results of trials of new formulations and endanger patients taking established medicines.

Variants of Information Mediary's systems can also be used:

- to control unauthorized sales and counterfeiting
- to warn of expiration
- to record data of interest for market research
- to assist in safety studies
- During security investigations.

Talking blister packs: Scrip Talk RFID labels from Envision America (Normal, Illinois, USA) can be placed behind the printed label on certain pharmaceutical packaging in the US so that blind and partially sighted patients can use a reader that speaks the name of the patient, type, dose and timing. This customized RFID label is selectively applied to multipacks by pharmacists on an as needed basis; further developments will no doubt make it suitable for blister packs. Scrip talk employs a microchip and costs are currently not low enough for it to become standard on all pharmaceuticals.

Even with smart packaging technology, there remains a great gulf between what the blister pack offers and what many patients need. AstraZeneca has been sensitive to one aspect, which is the simplification of what to take when. The

company has customized blow packs marked with instructions regarding when to take each tablet from its blister.

However, elderly patients and those with Parkinson's disease sometimes have problems opening blister packs. These patients often require a number of different tablets, usually from different manufacturers. One possible solution could be a single container that sounds an alarm when the medication needs to be taken. Ideally, an electronic record should be kept. Electronic tablet dispensers without a recording capability are obtainable but expensive. Because many patients live alone, they do not want to be dependent on someone coming to their house and filling customized containers.

Disposable electronics: Low cost disposable electronics are currently being developed. Figure 5 shows a disposable paper timer suitable for incorporating into pharmaceutical packaging, manufactured by Power Paper Ltd (Einat, Israel). It is powered by an environmentally safe paper battery.

Looking ahead, several organizations believe the blister pack itself could be made into electronic circuits to perform a variety of functions such as those discussed earlier.

Fig.5: Paper timer set for a specific time relevant to the product that the package contains

A team at the Polymer Centre of Sheffield University (UK) believes that the aluminum foil could constitute an electrode of a thin film electronic circuit grown on its surface by oxidation and deposition. In an alternative approach, proponents of polymer electronics have already created advanced circuits on polymer film by ink jet printing at high speed. In due course, they foresee these becoming feasible with everyday films such as those in blister packs. The smart blister pack has already arrived, and any further developments will simply make it more economic and more versatile.[11]

Container/Closure Innovations:

For years, there was little change in traditional container/closure systems. There were bottles for tablets, and they evolved into various shapes and sizes. Then childproof closures were added to these bottles. Childproof closures have

evolved as well, although a lot of improvement is still needed in this area. Blister packaging has evolved into many new and innovative packages. Many of the new packages are designed for patient compliance. You read constantly that most patients do not take all of the recommended drugs prescribed for them. The new packages are designed for weekly and monthly supplies, some actually with prescription and non-prescription doses, such as Actonel® that is prescribed once a week but is supplied with calcium tablets for the other six days of the week. These blisters can be in cards, wallets, or folded boxed packages. Most blisters are produced for over-the-counter supply. Some blisters are very easy to open, but some are extremely difficult to open, requiring scissors or some sort of assistance in opening. The equipment, the equipment settings and the materials used can have an impact on the structure of the package and the ease of opening.

Some concern has been recently expressed over the repackaging done by mail order and traditional pharmacies. They repack most drugs into new bottles with new closures and do not always include patient information or desiccants that may be included with the initial packaging from the pharmaceutical company. The choice of closure is not always available from the mail order companies but it is an option from most traditional pharmacies. Traditional pharmacies do include detailed patient information. In some cases, the pharmacy will supply you with the original package from the pharmaceutical company, complete with desiccant and patient information. Where the product is produced as a monthly supply, you most always receive the original package.

Parenteral drugs were traditionally in syringes, vials, sometimes ampoules, IV bottles and bags. Although the containers are still very similar, there are many different types of administration devices. These include safety syringes, adapters for saline flush, multiple IV's. There are multi-part syringes and vials with both lyophilized and liquid products. There are auto injectors, multiple auto injectors containing two drugs, needleless injectors and a new micro-delivery system for vaccines.

Alternatives to glass for parenterals are starting to enter the market. Worldwide, many plastics are used in blow/fill/seal operations for parenteral products, but there has been a reluctance to use this technology in the U.S. for human injectables. The U.S. does use this technology for animal health injectable products. There is, however, a new

material that is being considered for use. Cyclic Olefin Copolymers (COCs) are a new family of materials suitable for high-performance optical, medical, electrical, packaging, and other applications. This material is a credible alternative to glass in the design of pharmaceutical primary packaging, including injection devices such as films, pre-filled syringes, vials, bottles and other containers.

Other innovations in production and on the horizon are many unique inhalation devices. These range from the traditional nasal sprays to powder inhalers. In some cases, the package is the device, and in others, a tablet can be placed into a device. Continuous innovation is anticipated in this area to ensure the best adsorption of the drug as possible.

Now we also have a multi-phase, multi-compartment clear capsule that can deliver incompatible compounds in a single dosage form with different release profiles. This technology could be used to deliver multiple drugs at different times to the patient.

Patches, needleless injections and many other innovative administration devices are on the market, and many more are on the horizon, such as drugs being embedded into dissolvable strips by using the same technology as oral care strips.[12]

CHANGES IN PACKAGING PROCESSES:

In the past 25 years there have many progressive changes in packaging processes, and several significant improvements are detailed below.

Form fill seal processes for liquids and semi-liquids:

The Bottle pack system (Rommelag, Germany) and a similar process by Automatic Liquid Packaging (USA)- blow fill seal - continue to be successfully used for pharmaceutical products..

In use they usually operate in a clean area but also with a laminar flow type hood over the moulding-filling stations. With these precautions the unit can produce sterile non-preserved products. Output largely depends on the pack size, special machines can also insert sterile components, e.g. rubber stoppers. Machines can handle PE, PP, PVC, PET, etc.

Aseptic Blow-Fill-Seal (BFS) technology:

The beauty and simplicity of BFS-technology is the fact that it uses plastic granules to form, fill and seal the pharmaceutical container in one unit

operation. Thus, there is no need for storage or transportation of empty containers or closures, taking up valuable warehouse space and truck transport capacity. BFS-technology is regarded in the USP as an advanced aseptic process.

The extruder process, transforming the granules into a hot plastic parison, has been shown to be an excellent tool for rendering the plastic material sterile and endotoxin-free. Since a virgin surface is continuously being formed in the parison, the risk for environmental contamination is minimized.

Once formed and cut into the correct length, the parison bottom end is closed and the container is shaped using vacuum or by blowing sterile air into the mould. To fill the formed container, the mould carriage is shuttled under the filling station, a transversal shift usually taking 1-2 seconds. Filling is taking place under a constant stream of sterile filtered air and after filling, when filling needles have been withdrawn; the upper part of the divided mould is closed to seal the container.

Clean-in-place and steam-in-place (CIP and SIP) systems make sure the entire aseptic system is sterile before production. Leak detection systems (100% in-process) are often installed downstream to exclude possible leaking units.[13]

Bilcare Research barrier films – Climate protection for your product:

Not all films are alike. Bilcare´s films are engineered to provide excellent results at lowest cost to you. Depending on your application and the processing of the film, Bilcare has the ideal films for your requirements. These will exceed even your expectations on quality and effectiveness. A combination of the wide variety of thicknesses, colors and additional properties offers the best solution to your individual requirements.

OTHER SPECIAL CONSIDERATIONS:

There are occasions when demands or considerations related to a pack conflict. This applies to some of the general observations listed below, and in certain instances an acceptable compromise may be difficult to achieve.

Child-resistance packaging:

Safety-Pak Plus uses 50-micron opaque polyester film, a peelable release adhesive, and 25-micron (0.001-in.) aluminum foil laminated together. The resulting product is a functionally reliable peelable lidding providing adult consumers a package that they can open with greater ease than

traditional paper based CR lidding materials. The product provides pharmaceutical packaging engineers with a material that will improve production efficiencies by promoting increased line speeds at lower and broader sealing temperatures to obtain package integrity. Safety-Pak Plus reaches acceptable adhesion to the PVC bottom web at lower heat seal temperatures when compared with traditional CR structures. The 0.2 sec dwell time is indicative of the sealing conditions on a rotary type thermoforming machine. The film used in the Peel-Push version of Safety-Pak Plus can be printed on both sides prior to lamination, which may provide a covert anticounterfeiting solution.[14, 20]

Anti-counterfeiting OVD:

A hot stamping company will feature Trustseal, an optical security device that makes it easier to distinguish high-value, quality items from counterfeit goods, at Interphex. Trustseal is a form of an Optically Variable Device (OVD) that it exhibits sharper image contrasts at a wider variety of viewing angles and is easily recognizable even under unfavorable conditions, such as dim or diffused light. To increase the level of security, special elements such as lenses and contrasts can be integrated into the Trustseal; these naked-eye effects are backed up with hidden features detectable with special viewing tools or under very high magnification. Trustseal can be employed as a label for identifying a product and as an effective marketing instrument.[15, 20]

Multilayer Vials:

One company is presenting Cyclic Olefin Polymer (COP) multilayer vials at Interphex, made of a highly innovative plastic development for sensitive injection substances. The new multilayer vials are glass-clear, of standard dimensions, and almost unbreakable. This heavy-metal-free plastic is suitable for the demanding field of cytostatics and biopharmaceutics having thermally and mechanically durable qualities. With the new development, the injection specialists have enhanced these barrier properties - to several times that of vials consisting of COP alone - by combining two COP outer layers with a middle layer of polyamide.[16, 20]

Security Foils:

A converter of foils and films will be displaying a patented security foil that allows for fine-line graphics, text, logos, and micro features to be applied directly to the surface of the aluminum during the rolling process. Since the images are embedded in the foil, they cannot be removed and because the high precision laser technology that created CPI Security

Foil is not readily known or available on the market, it cannot be imitated or copied by counterfeiters.[17, 20]

Oxygen Absorbers:

One company has developed a family of specialty oxygen absorbers. StabilOx significantly reduces oxygen levels within the package to decrease the rate of oxidative degradation, while maintaining relative humidity at a specified level suited for chemical or physical stability, helping to address moisture-mediated chemical degradation of drug formulations. Available in a variety of delivery formats, including packets, labels, canisters and solid forms, these products offer flexibility to a range of healthcare applications and packaging operations. StabilOx solid forms are also suited for channeled thermoform and cold blisters packs and label formats.[18, 20]

Single - Use Systems:

A designer and manufacturer of single-use systems for the pharmaceutical and biotechnology industries offers flexible containers with sizes ranging from 50 mL to 3000 L. It can produce nearly any configuration as well as porting option. More than 1000 components and more than 90 tubing varieties are available along with access to all major filter manufacturers. Capabilities include high-volume manufacturing, Class 10,000 clean rooms, sterilization, and ISO 13485:2003 and FDA registrations.[19, 20]

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