Innovations in Pharma Packaging Technologies

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ABSTRACT

"Need is an auspicious element of all Inventions", this phrase describes ongoing technology towards pharmaceutical packaging. Packaging in a pharmaceutical company is an intensive, comprehensive work consisting of various tasks right from containment of products to its protection followed by checking and delivering the product. Henceforth the responsibility of packaging within the market cannot be underestimated. Flow for packaging is the protection and preservation of items, with market communication and regulatory information to consumers. A few years back packaging industries relied on preserving the standard and quality of the enclosed product, where nowadays they are focussing on stability, shelf life, and convenience of the product, also prevention from tampering and counterfeiting of product and ensure its safety. Hence In the future product designing gives a restful impact to the users, so its packaging should complement its features as well. The packaging industries are on the path of developing newer and sophisticated concepts and thus industries are on the verge of astonishing innovations in this field to improve patient adherence to drug regimens.

Key words: Convenience, Counterfeiting, Drug regimens, Pharmaceutical packaging, Recent trends, Tampering.

INTRODUCTION

Wordings like protection, production, storage, distribution, supply, display, and lastly consumed by consumers or patients with maintaining the integrity and stability of product complete the whole definition of packaging. Containment is the foremost and primary function of packaging. This ensures that packaging designs are in a manner such that it does not allow any leakage, diffusion, or permeation of the product, and also hold its contents during normal handling. It remains unaltered by ingredients of the dosage form. Packaging also provides protection against factors like light, oxygen, moisture, biological contamination, adulteration, and mechanical damage can change its quality or potency. Packaging serves to provide correct identification and information through labels and package inserts for the patients. Packaging is designed to be convenient during use.[1]

The envelope that holds the product consists if components that are in direct contact with the product is called primary packaging. It may have the tendency to affect the products quality or shelf life. Examples of primary packaging are glass bottles, strip packs, blister packs. Secondary packaging: It is used externally over the primary pack and provides physical protection to ensure safe warehousing and mechanical protection required for shipment and transport e.g. Paper drums, corrugated boxes, shipping containers. Tertiary packaging: It provides shipping and handling of bulk materials from one place to another e.g. Slip sheet, Crate, Edge protector, Pallets.[1]

Need for innovation: In India, pharmaceutical packaging covers a major portion of the overall drug market. Previously, it was focused on protecting the quality of enclosed medication. Now, current concern includes; fighting with counterfeiting, promoting patient adherence, ensuring the safety and efficacy of pharmaceuticals, and child-resistance.

APPROACHES TOWARDS INNOVATION

Prevention of counterfeiting

Counterfeiting includes products and packaging materials that look like the originals and involves the selling of fake products as original products. Counterfeit is associated with product security. Counterfeit medicines can contain either the same amount of API as that of an authentic brand or insufficient or at times no API. It can also include medicines with a post expiry date. Medicines that don't have the manufacturer's name and address are considered counterfeit too.

"Many anti-Counterfeiting technologies are in use". Some of them are mentioned below;

Overt features: It enables the end-users to confirm the realness of the pack and includes avoidance of any unauthorized diversion, the requirement for the highest level of security in the supply, handling, and hazardous materials. It can't be reused or removed without causing damage to the product. Additional security can be achieved by incorporating an overt device within a tamper-evident feature.

Covert features: This feature will help the brand owner in identifying counterfeit products. Common people don't know their presence and will have no means to verify the same and it is difficult to detect or duplicate.

Forensic markers: This includes solutions that require dedicated filed test kits or testing in laboratories to prove genuineness. These are a subset of covert technologies. It includes Chemical taggants, biological taggants, DNA taggants, isotope ratios, micro-taggants.

Trace and track technologies: These technologies provide a distinct identity to every stock unit in the process of manufacturing and this stays with it throughout the process until it is consumed. This identity includes product information, such as name and strength, as well as a lot number and expiration date.

RFID (Radio Frequency Identification) is a technology that uses tiny computer chips to track items that are located at a distance. This tiny chip is connected to an antenna that detects electromagnetic energy emitted by a reader device. When the energy is picked up, the reader device receives the chip's unique identification number. This allows remote identification of the item. This technology provides efficient inventory management, helping manage costs, and delivering on patient

safety initiatives. It makes use of wireless communications for the identification of objects. The tag, the reader and the software are three most important components of the RFID system. An integrated circuit with an electronic product code (EPC), a unique tracking identifier, makes up the tag. This code is transmitted over the radio spectrum using electromagnetic radiation waves. This transmitted signal is captured by the reader, which aids in the establishment of connectivity between tag data and the system software. Anti-counterfeiting software can be added to the software.

A passive tag is a type of RFID tag present within the interrogator. Enough power is taken from it to start the tag, circuit, or any exceptional reflective material. The response is sent back to the interrogator in the form of data. Active tags have a battery to extend their range for data collection or tag-to-tag communication. However, they are found to be costly. Batteries are used to back up the memory and data in semi- active tags, but they do not extend the range. To save money and space, some active RFID tags only use their batteries when they are interrogated or when they send a homing pulse at predetermined intervals (Figure 1).

RFID technology is used for detection of counterfeit medicines in many ways. Equipment that encodes and prints tag-equipped labels verifies the tag before and after encoding and high- quality labels are encoded and rechecked. When tags are read properly, labels are printed and their barcodes are verified. For automated applications, an encoded, print and apply unit is available. It performs all the checks of the RFID printer and applies the labels at a maximum rate of 100/min. RFID can be combined with cryptography to enable on- or off-network authentication. This helps in the simplification of various processes of shipping, receiving, and inventory location. Collection of data occurs during the time of tracing a product through the supply chain to avoid counterfeiting and diversion coupled with sensors to monitor the conditions during shipping and storage and provide alerts if parameters are exceeded.[2]

Encouraging patient compliance

Industries are continuously exploring various packaging solutions that will help consumers in identifying the correct medicine to be used and the correct dosage to be taken. Pack design can consist of different color coding which can help consumers in identifying the dosage of medicines. However, the greatest opportunity now is for packaging designers to use new technologies to help consumers remember to take the appropriate dose at the appropriate schedule. The talking packaging is one such advancements. There are two innovations in talking packaging, the Talk Pack and NFC tags.

Talk Pack is a packaging system from Wipak Walsrode. It can be linked either to any printed image or to any of the packaging material. It contains a special type of pen-shaped reader. It's used to recover data that's been saved but isn't accessible such as audio files that further help in rendering speech, music, or sounds audible. This can help customers to obtain information about different manufacturers, various brands, shelf life, or additional information. This technology does not encompass the use of any microchips or RFID. A special varnish is used for printing dot code on the apex of text and images. This kind of technology can be used for all types of printing technologies and all the package types used.

NFC (Near Field Communication) tags can be included in any packaging. A consumer can make use of mobile phones with NFC tags to download text, audio, or web page product information. It will be played back on that particular handset by simply touching the code present on the packaging. It provides instructions verbally about dosing from pharmacy staff which helps visually impaired patients. The technology can be put to use display detailed information and instructions in a small area.[3]
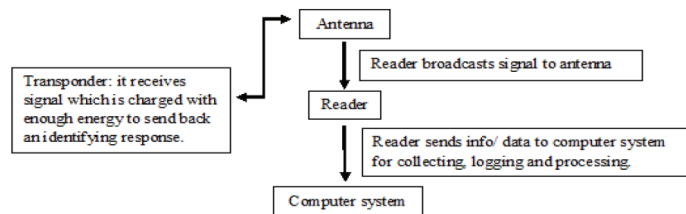
WORKING OF RFID

Figure 1: Schematic representation of the RFID system.

The *"Helidac Therapy Kit"* is from Procter and Gamble Pharmaceuticals. It is used for treating *Helicobacter pylori* infections (responsible for most stomach ulcers) by simplifying its complex, multipill, frequent-cycle regimen. This kit contains three antimicrobial agents: bismuth subsalicylate, metronidazole, and tetracycline hydrochloride. The kit organizes the regimen into 14 daily-dose blister cards, each divided into four-pill dos-ing units for breakfast, lunch, dinner, and bedtime.[4] Each dose contains four pills: two bismuth subsalicylate tablets, one metronidazole tab-let, and one tetracycline hydrochloride black and yellow capsule. The therapy also has an information booklet for patient reminders. Clinical trials have shown that in up to eighty two percent of patients with duodenal ulcers, the treatment is effective. To analyze patient behavior Helidac development team created design development which is based on packaging, education, reminders, and motivation concept.

REMIND-A-CAP™ is a patented pill bottle cap. It helps patients to manage their medication. This prescription cap schedule simplifies and regulates patient's medication intake thus promoting better health outcomes. A simple turning of a knob enables individuals to set the next date of intake[5] (Figure 2).

The features in this packaging include; S-shaped dial is designed for ease of use and comfort, a child-proof safety cap that can be added to existing bottle packaging. The product information, a marketing slogan and/or quick facts. The caps are available in three different sizes: 45, 38, and 33 mm and the dial can be customised to treatment instructions and the look can be customised to match branding. Advantages are there is no need to set up anything, no electronic liability, Compliance is improved and Enhancement of the Rx brand.

Rx Timer Cap is the pharma product helps with patient dosing. These bottles contain prescription-based lids with built-in-timers which re-sets itself like a stop watch. This built-in digital timer displays the amount of time it has been since the pills were last taken. It functions as a reminder irrespective of whether the patient is taking multiple medicines at different times or just one medicine once a day. The packaging helps to manage medications simply and effectively in the bottle they are dispensed in. This makes safety information handy to use in emergencies. It has a built-in stopwatch and activation mechanism making it tamper-resistant. It has been reported that this simple solution has increased the compliance by up to 33%. It is an easy, reliable, and accurate way for patients to safely take their medicines in the bottles they are dispensed and provides safety by detecting and deterring unwanted use.[6]

The features of this packaging includes a digital timer on each cap that shows how long it has been since the last pill was taken. Each pack contains one large vial whose dimensions are 4" x 2.25" x 2.25"and one small vial whose dimensions are 3" x 1.5" x 1.5", as well as a cap and their overall weight 1.2 ounces. Rx TimerCap has a built-in LCD timer that is activated when the cap is put on a container and it works in the following manner, first a cap is applied on the bottle and the TimerCap is applied on it. After the timer starts, it counts the minutes and the hours since it was last closed and stops once the cap is reopened. It resets and

restarts when put back on the bottle. This type of packaging can be used to provide safety precautions when opioids or other dangerous medication have been prescribed. The challenge in effectively using this packaging is in educating and training the patients in securing the cap correctly in place and using a unique code that is not known to everyone.

Stora Enso has developed a new package called Pharma DDSi (Discrete Dosage Slider intelligent). This package is conductive ink-based applied on a blister inlay made of carton board, which is, in turn, linked to a cellular module that is built into the package.[7] On removal from the blister, this device allows tracking of one pill whose data is sent to the cellular module and further forwarded wirelessly by connecting electronic health record systems to GSM or GPRS cellular networks. This allows a physician to monitor and intervene in real time, as well as make timely changes to the system which is a patient medication history document. The blister inlay on the pharma DDSi wireless is linked to the cellular module (chargeable battery works for several months without recharging) and has no metal components.

Amcor Opening feature launched by Amcor Flexibles Push-Through Blister Lidding that is Child- resistant. As compared to the usual peel or peel-push method which is generally opted for child resistance, blister contents can be easily accessed with a targeted push-through motion with AOF. The result is an improvement in senior friendliness, child resistance, and sustainability.

Instead of using standard 3-ply, AOF makes use of a 2-ply structure. It does not require peel tabs resulting in a reduction of total package size to up to 40%. However, it does not compromise the barrier layer or seal integrity of the contents of the package and thus maintains product stability. A study was performed by Amcor Flexibles on Dec 2014 to meet the criteria of 16 CFR part 1700. This study confirmed qualities of child resistant and senior-friendliness of AOF blister lidding. AOF blister lidding was used to produce blisters and this package met the test criteria of F=1 (which means only 2 children out of 50 were able to access one cavity). Also, in contrast to the normal target of a minimum of 90%, the Senior Use Effectiveness (SAUE) score was found to be 98%. This package helps in providing product protection, is child-resistant and senior-friendly, and has a reduced environmental footprint.[8]

Ensuring drug integrity

All Pharmaceutical industries and manufacturers assume that perfect packaging gives desired drug integrity and success. Biodose is the only monitored dosage system on the market to accommodate medications; both liquid and solid. It has been voted by 85% of pharmacies in U.K.as much as better than any other monitored dosage system.[9]

Biodose pharmacy receives prescriptions and fills the trays electronically by the computer to create personalised trays, medication administration records sheets that contain patient's medicine, dose times, and quantities. All types of dosage forms solid and liquid measured and put into Biodose pods at the appropriate dosage times for each patient. Before the Biodose trays are sealed, heat is applied to the tray then it delivers to each individual pod finally the pharmacist double-checks for correctness. For Check-In resident's pre-measured medication is delivered to the home with MAR sheets. Medication is checked in and placed into Biodose trolleys or cabinets provided, ready for the drugs round. From POD to patient, photos on each tray mean it's easy to identify the right medication during the round. Just pop it out of the securely sealed monthly or weekly tray. Final checks having cross checked against the residents 'MAR sheets, the patient and drug names printed on every single pod offer an extra safeguard before opening the Biodose pod. Administer with accuracy the pre-portioned pod is passed to the patient, thus removing the need of handling multiple packs or getting fingers sticky while handling liquid medicines from the bottle. To aid patients to abide by complicated medication schedules, Biodose contains a removable
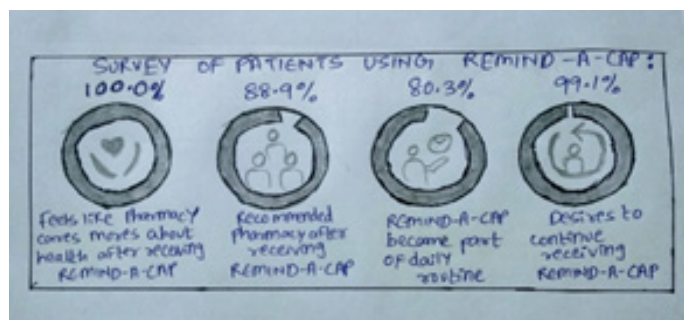
Figure 2: The positive impact of Remind-A-Cap on Adherence.

tray which is divided into 28 sections (or pods) with each pod having a capacity of holding up to 10 ml of the liquid medications as well as seven solid dose medications.

Pre-measured medications can be stored and organized for seven days in this tray on a daily basis with four pods. The pods on each tray are individually labeled and are removable which can help users to recognize the right medication easily and makes managing multiple medications trouble-free. To reduce the possibility of missed doses, the dispensing pharmacy can set up a tailored program of alerts based on the needs of each individual patient. When the due date arises, then the light sparks so that there are customizable alarms, and voice messages under each pod are set up to indicate the same thing. Further, as per the patient preference, the Biodose Connect database can be used to programme and store emails and text messages.

It has the advantage of storing liquid and solid medications in a Biodose tray, which is a removable container. In a secure and timely manner, the pharmacy seals and dispenses the medication. For seven days, there are 28 compartments with dosages of up to four times per day. Each tray's pods are individually labelled and removable, allowing users to quickly identify the correct medication. Remotely programmable visual and audible alerts, as well as customizable reminders. Selected caregivers are contacted via email, text messages, and other means during real-time monitoring. The benefits include real-time monitoring, which sends a customized message to either relatives or telecare centres if the medication is not removed from the tray after a predetermined amount of time. Compliance data at your fingertips, which increases patient compliance by providing compliance data in a user-friendly manner, which includes highlighting when particular doses are not removed or removed incorrectly, or alternatively, if they are taken late or early. Enabling independence for users allows for the re-ordering of empty trays via the chosen pharmacy while allowing the device to maintain contact with the user.

Child resistance

This packaging can minimize the risk of poisoning in children that can happen through the ingestion of hazardous items such as prescription products, over-the-counter medicines, pesticides and household chemicals. There are two types of packaging Locked4kids and Eco-friendly pharma packaging (Ecoslide-rx).

Locked4Kids is a recloseable, child-resistant folding carton for packaging (CRSF) pharmaceuticals launched by Ecobliss. It is certified according to US16 CFR 1700.20 and ISO 8317. It consists of tear-resistant laminated paperboard and features a polyethylene terephthalate blister tray that locks in place. The US and European standards not only specify child-resistant but also senior friendliness.[10] The packaging is made up of a carton and a plastic tray that hold the medications in blister strips. To access the product, the tray has to be pulled out; it contains small hooks that are placed diagonally towards one another, thus ensuring that the tray is locked securely when it is pushed in. To take out the tray, both

hooks have to be released at that time. It works by pressing the box evenly and firmly at the marked points with the assistance of the thumb and forefinger. This makes it unworkable for children, since their hands are very small. The boxes have a tear-resistant laminate on both sides, which places additional restrictions on the children.

Eco-friendly pharma packaging (Ecoslide-rx)[11]

Packaging industries are nowadays under constant pressure to develop eco-friendly and sustainable products. This has started affecting pharmaceutical packaging, which is among the industry's most complex sectors. A major challenge to be taken into consideration while developing sustainable packaging is that environmental considerations must not in any way lead to compromising on a package's safety or accessibility. Keystone Folding Box Company, in association with Legacy Pharmaceutical Packaging, introduced a sustainable compliance packaging, Ecoslide-RX. This pack is prepared from 100% recycled material and contains a minimum amount of unfeasible film and foil. It also reduces costs and energy usage by removing the necessity of heat sealing in the manufacturing process.

It's a type of secondary package that isn't made of plastic. It is made entirely of recyclable materials, ensuring a long-term design. When compared to other paperboard compliance packs, it uses the least amount of film and foil. It is inexpensive and can be automated at high speeds, as seen on bottling lines. F=1 (Maximum CR rating). The locking mechanism of the Ecoslide-RX is opened by pressing the thumb on a release button located on the corner of the carton. This process assures top-level child resistance along with senior friendliness. A film/foil is present inside the outer carton which acts as a push-through blister card that slides out when the CR lock is released and remains connected to the carton at all times. There is no requirement for heat sealing of the paperboard during the assessment process. While opening the pack, directions are given. Users have to simply unlock the pack by applying a little force with a thumb press on a release button. Also, the pack offers easier pill access as compared to the usual push-through process. Ecoslide-RX offers a full array of compliance and safety benefits to consumers. There will be a low risk of contamination that occurs from dropping or spilling or through moisture. It also increases compliance by providing a pill reminder/weekly calendar. It also has additional space for package printing that enables large and bold labeling which is of critical importance for visually impaired consumers. Ecosilde-RX is found to be more stackable in medicine cabinets. It is also convenient for users to be carried in handbags and suitcases during transport as compared to amber vials.

EFFECT OF NOVEL CORONAVIRUS PANDEMIC ON PACKAGING INDUSTRY

Pharmaceutical packaging is a topic few people ever think about. A vial or syringe usually costs just a few cents. The vaccine, on the other hand, could cost tens or hundreds of dollars. Yet packaging is an integral part of the drug product.

Borosilicate glass has been used for packaging drugs for over 100 years. More than 50 billion containers are made of it per annum. Every single day, more than 135 million injections are administered inside a borosilicate glass container. SCHOTT alone is escalating its manufacturing of borosilicate glass tubing by 40,000 tons providing enough raw material

to produce an extra 6.8 billion standard vials. Such vials will be the preferred type of packaging for the initial release of the vaccine.[12]

CONCLUSION

The packaging industry is linked to the drug manufacturing process. So it has become a necessary step to incorporate ethical and scientific methods in the packaging. Pharmaceutical packaging trends are undergoing rapid expansion. This can happen if the needs of the product, its cost, security, and patient handiness are taken into consideration to build a brand identity. The packaging designers, as well as in the frameworks, were brimming with ideas. There are numerous hurdles that the packaging industry has to overcome because of the regulations imposed on them. These regulations are important to ensure consumers that the products which they are consuming are completely safe and they exhibit all the necessary properties and are of standard quality. Industries will develop innovative packaging that will increase consumer acceptability while also influencing consumer and patient adherence to the product.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

CR: Child resistant, **CFR:** Code of federal regulations, **MAR:** Medication Administration Record.

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